Lilly Critical Care Europe

Attn: Chief Pharmacist
Mater Misericordiae Hospital
Eccles Street
Dublin
Ireland

Geneva, 23 March 06

Xigris® (drotrecogin alfa (activated),
Powder for solution for infusion

Dear Doctor,

There have been several significant changes to the Xigris® SPC (Summary of Product Characteristics) over the course of 2005.

In order to ensure that Xigris® is used safely following the approved SPC, we are writing to you to outline the key features you should take into consideration when prescribing Xigris®.

This communication does not provide a complete list of contraindications or precautions/warnings, but emphasises changes that occurred over the last 12 months and that we would like to remind you of.

Xigris® should only be used in severe sepsis patients with multiple organ dysfunction.

SPC changes during 2005
• Xigris® is not indicated for children and any use in such patients is not recommended (SPC 4.2) • Xigris® treatment should be considered mainly if treatment can start within 24 hours of organ failure onset. In general, treatment should start within 48 hours - if possible within 24 hours - of first documented sepsis induced organ dysfunction (SPC 4.1 + 4.2) • It should be used by experienced doctors in institutions experienced in the care of patients with severe sepsis (SPC 4.2) • Xigris® should not be given in patients with single organ dysfunction, especially if they had surgery within the previous 30 days (SPC 4.4)

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Answers That Matter.

Because of its importance we would also like to remind you of the following aspect of the Xigris® SPC (this wording has not been revised in 2005):

> Xigris® must not be used in patients who had major surgery within the previous 12 hours (SPC 4.3).
>
> Additionally:
> For procedures with an inherent bleeding risk, discontinue Xigris® 2 hours prior to the start of the procedure. Xigris® may be restarted 12 hours after major invasive procedures or surgery if adequate haemostasis has been achieved. Xigris® may be restarted immediately after uncomplicated, less invasive procedures if adequate haemostasis has been achieved (SPC 4.4).

You can find the exact wording of the changes in the SPC enclosed.

Please ensure that all of these important points of the Xigris® SPC are reflected in your hospital protocol for Xigris® treatment.

If you would like to have a SPC in your local language, please contact the Customer Service Center. You will receive it as soon as it will be available.

For further information, please contact our Medical Information Centre/Customer Service Centre at your local number [☎ 01 407 32 77] or by e-mail info_xigris@lilly.com

Sincerely yours,

Dr.med. Jörg Rustige
Medical Director

Lilly Critical Care Europe
16, Chemin des Coquelicots
P.O. Box 580
CH-1214 Vernier/Geneva
Switzerland

Lilly Critical Care Europe

Attn: Chief Pharmacist
Our Lady's Hospital for Sick Children
Crumlin
Dublin 12
Ireland

Geneva, 23 March 06

Xigris® (drotrecogin alfa (activated),
Powder for solution for infusion

Dear Doctor,

In order to ensure that Xigris® is used safely following the approved SPC, we are writing to you to remind you that Xigris® is not recommended in children below the age of 18 and therefore it should not be used in children.

Following the RESOLVE study in paediatric patients with severe sepsis the outcome of this study has been included in the Xigris® SPC (Summary of Product Characteristics) in November 2005. Another clarification to the SPC has been added in February 2006.

This information can be found in section 4.2 and 4.4 of the SPC and the information from section 4.4 is provided again below for your reference.

In summary,

Xigris® should only be used in adult patients with severe sepsis patients with multiple organ dysfunction.

SPC change in November 2005
• Xigris® is not indicated for children and any use in such patients is not recommended (from SPC 4.2)

SPC change in November 2005 and February 2006
From SPC 4.4: **Paediatric patients** Xigris® is not recommended in children below the age of 18 and therefore it should not be used in children. Data from a placebo-controlled clinical trial did not establish efficacy of Xigris in paediatric patients suffering from severe sepsis, acute infection, systemic

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inflammation and respiratory and cardiovascular organ dysfunction. This trial was stopped for futility after 477 patients had received the study drug (out of 600 patients intended).

A planned interim analysis (with 400 patients enrolled) showed a low likelihood of demonstrating a significant difference in the primary endpoint of "Composite Complete Organ Failure Resolution" (CTCOFR score of 9.8 versus 9.7 mean days over 14 days). There was also no difference in 28-day mortality (17.1% versus 17.3% in the Xigris® and placebo groups, respectively).

Investigators attributed 2 deaths in the Xigris® group and 5 deaths in the placebo group to bleeding events. There was a higher rate of central nervous system (CNS) bleeding in the drotrecogin alfa (activated) versus the placebo group. Over the infusion period (study days 0-6) the number of patients experiencing CNS bleeding was 5 versus 1 (2.1% versus 0.4%) for the overall population (drotrecogin alfa (activated) versus placebo), with 4 of the 5 events in the drotrecogin alfa (activated) group occurring in patients ≤ 60 days old or ≤ 3.5 kg bodyweight. 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.

You can find the exact wording of the changes in the SPC enclosed.

Please ensure that all of these important points of the Xigris® SPC are reflected in your hospital protocol for Xigris® treatment.

If you would like to have a SPC in your local language, please contact the Customer Service Center. You will receive it as soon as it will be available.

For further information, please contact our Medical Information Centre/Customer Service Centre at your local number [☎ 01 407 32 77] or by e-mail info_xigris@lilly.com.

Sincerely yours,

Dr.med. Jörg Rustige,
Medical Director

Lilly Critical Care Europe
16, Chemin des Coquelicots
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Switzerland

Please note that this is the SPC (Summary of Product Characteristics) adopted by the CHMP in February 2006 pending the European Commission Decision

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xigris 20 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Drotrecogin alfa (activated): 2 mg per ml after reconstitution.

A vial contains 20 mg of drotrecogin alfa (activated) to be reconstituted with 10 ml of Sterile Water for Injection.

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

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xigris is indicated for the treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care. The use of Xigris should be considered mainly in situations when therapy can be started within 24 hours after the onset of organ failure (for further information see Section 5.1).

4.2 Posology and method of administration

Xigris should be used by experienced doctors in institutions skilled in the care of patients with severe sepsis.

Treatment should be started within 48 hours, and preferably within 24 hours, of onset of the first documented sepsis-induced organ dysfunction (see Section 5.1).

The recommended dose of Xigris is 24 µg/kg/hr given as a continuous intravenous infusion for a total duration of 96 hours. It is recommended that Xigris be infused with an infusion pump to accurately control the infusion rate. 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 full recommended 96 hours of dosing administration. Dose escalation or bolus doses of Xigris are not necessary to account for the interruption in the infusion.

No dose adjustments are required in adult patients with severe sepsis with regard to age, gender, hepatic function (as measured by transaminase levels) or renal function. The pharmacokinetics of drotrecogin alfa (activated) have not been studied in patients with severe sepsis and preexisting endstage renal disease and chronic hepatic disease.

Paediatrics: Data from a placebo-controlled clinical trial which was stopped for futility after 477 patients 0 to 17 years-old had received the study drug did not establish efficacy of Xigris in paediatric

patients and showed a higher rate of central nervous system bleeding in the Xigris versus placebo group. Therefore no dosage recommendation can be made and the use of Xigris is not recommended in children below the age of 18 (see Section 4.4).

4.3 Contraindications

Because drotrecogin alfa (activated) may increase the risk of bleeding, Xigris is contraindicated in the following situations:

- Active internal bleeding
- Patients with intracranial pathology; neoplasm or evidence of cerebral herniation
- Concurrent heparin therapy ≥ 15 International Units/kg/hr
- Known bleeding diathesis except for acute coagulopathy related to sepsis
- Chronic severe hepatic disease
- Platelet count < 30,000 x 10^6/l, even if the platelet count is increased after transfusions
- Patients at increased risk for bleeding (for example):
  - a) any major surgery, defined as surgery that requires general or spinal anesthesia, performed within the 12-hour period immediately preceding drug infusion, or any postoperative patient who demonstrates evidence of active bleeding, or any patient with planned or anticipated surgery during the drug infusion period.
  - b) history of severe head trauma that required hospitalization, intracranial or intraspinal surgery, or haemorrhagic stroke within the previous 3 months, or any history of intracerebral arteriovenous malformation, cerebral aneurysm, or central nervous system mass lesion; patients with an epidural catheter or who are anticipated to receive an epidural catheter during drug infusion
  - c) history of congenital bleeding diatheses
  - d) gastrointestinal bleeding within the last 6 weeks that has required medical intervention unless definitive surgery has been performed
  - e) trauma patients at increased risk of bleeding

Xigris is also contraindicated in patients with known hypersensitivity to drotrecogin alfa (activated), to any of the formulation excipients, or to bovine thrombin (a trace residue from the manufacturing process).

4.4 Special warnings and special precautions for use

Patients with single organ dysfunction and recent surgery
Xigris is not approved for the treatment of patients with single organ dysfunction and should not be used in this particular subgroup of patients, especially if they had recent surgery (within 30 days). In each of two randomised, placebo-controlled trials, PROWESS and ADDRESS (see Section 5.1), 28-day and in-hospital mortality were higher in patients treated with drotrecogin alfa (activated) compared to placebo for the sub-population of patients with single organ dysfunction and recent surgery (n=98 in PROWESS and n=636 in ADDRESS).

Bleeding
Drotrecogin alfa (activated) increases the risk of bleeding. In the following conditions, the risks of the administration of Xigris should be weighed against the anticipated benefits:

- Recent administration (within 3 days) of thrombolytic therapy
- Recent administration (within 7 days) of oral anticoagulants
- Recent administration (within 7 days) of aspirin or other platelet inhibitors
- Recent (within 3 months) ischaemic stroke
- Any other condition in which the physician considers significant bleeding is likely

For procedures with an inherent bleeding risk, discontinue Xigris for 2 hours prior to the start of the procedure. Xigris may be restarted 12 hours after major invasive procedures or surgery if adequate haemostasis has been achieved. Xigris may be restarted immediately after uncomplicated less invasive procedures if adequate haemostasis has been achieved.

As a component of routine care, measures of haemostasis (e.g., activated partial thromboplastin time (APTT), prothrombin time (PT) and platelet count) should be obtained during the infusion of Xigris. If sequential tests of haemostasis 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.

Laboratory tests
Drotrecogin alfa (activated) 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 drotrecogin alfa (activated), and/or the effect of other concurrent medications. The pharmacodynamic effect of drotrecogin alfa (activated) 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. Drotrecogin alfa (activated) that is present in a blood or plasma sample drawn from a patient who is being infused with the drug will be gradually neutralized by endogenous plasma protease inhibitors present in the sample. Virtually no measurable activity of drotrecogin alfa (activated) 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 drotrecogin alfa (activated). In addition, approximately 2 hours after terminating the infusion of the drug, there is virtually no measurable activity of drotrecogin alfa (activated) 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 determinations of the PT and/or APTT should take these variables into consideration.

Because drotrecogin alfa (activated) may affect the APTT assays, drotrecogin alfa (activated) present in plasma samples may interfere with one-stage coagulation assays based on the APTT (such as factor VIII, IX, and XI assays). Drotrecogin alfa (activated) present in plasma samples does not interfere with one-stage factor assays based on the PT (such as Factors II, V, VII and X assays).

If sequential measures of coagulopathy (including platelet count) indicate severe or worsening coagulopathy, the risk of continuing the infusion should be weighed against the expected benefit.

Immunogenicity
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 Activated Protein C on the APTT assay. However, the possibility of allergic reactions to constituents of the preparation cannot be completely excluded in certain predisposed patients. If allergic or anaphylactic reactions occur, treatment should be discontinued immediately and appropriate therapy initiated. Xigris has not been readministered to patients with severe sepsis. If Xigris is readministered to patients, caution should be employed. No anti-activated Protein C antibody formation was detected in healthy subjects, even after repeat administration.

Paediatric patients
Xigris is not recommended in children below the age of 18 and therefore it should not be used in children.
Data from a placebo-controlled clinical trial did not establish efficacy of Xigris in paediatric patients suffering from severe sepsis, acute infection, systemic inflammation and respiratory and cardiovascular organ dysfunction. This trial was stopped for futility after 477 patients had received the study drug (out of 600 patients intended).
A planned interim analysis (with 400 patients enrolled) showed a low likelihood of demonstrating a significant difference in the primary endpoint of "Composite Time to Complete Organ Failure

Resolution" (CTCOFR score of 9.8 versus 9.7 mean days over 14 days). There was also no difference in 28-day mortality (17.1% versus 17.3% in the Xigris and placebo groups, respectively). Investigators attributed 2 deaths in the Xigris group and 5 deaths in the placebo group to bleeding events. There was a higher rate of central nervous system (CNS) bleeding in the drotrecogin alfa (activated) versus the placebo group. Over the infusion period (study days 0-6) the number of patients experiencing CNS bleeding was 5 versus 1 (2.1% versus 0.4%) for the overall population (drotrecogin alfa (activated) versus placebo), with 4 of the 5 events in the drotrecogin alfa (activated) group occurring in patients = 60 days old or = 3.5 kg bodyweight. 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.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions with Xigris have not been studied in patients with sepsis.

Caution should be employed when Xigris is used with other drugs that affect haemostasis (see Sections 4.3 and 4.4) including Protein C, thrombolytics (e.g. streptokinase, tPA, rPA and urokinase), oral anticoagulants (e.g. warfarin), hirudins, antithrombin, aspirin and other anti platelets agents, e.g. non-steroidal anti-inflammatory drugs, ticlopidine and clopidogrel, glycoprotein IIb/IIIa antagonists (such as abciximab, eptifibatide, tirofiban) and prostacyclins such as iloprost.

Heparin
Two-thirds of patients in the phase 3 trial received prophylactic doses of unfractionated or low molecular weight heparin. There was no observed increase in the risk of bleeding events reported as serious adverse events in drotrecogin alfa (activated) patients receiving heparin. The effects of prophylactic low dose heparin and other coagulation-active medications on the efficacy of drotrecogin alfa (activated) have not been evaluated in a randomised controlled clinical trial.

4.6 Pregnancy and lactation

Animal studies with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development have not been conducted with Xigris. Therefore, the potential risk for humans is unknown. Xigris should not be used during pregnancy unless clearly necessary.

It is not known whether Xigris is excreted in human milk or if there is a potential effect on the nursed infant. Therefore, the patient should not breast feed whilst treated with Xigris.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Xigris increases the risk of bleeding.

The Phase 3 international, multi-centre, randomised, double-blind, placebo-controlled clinical trial (PROWESS) involved 850 drotrecogin alfa (activated)-treated and 840 placebo-treated patients. The percentage of patients experiencing at least one bleeding event in the two treatment groups was 24.9% and 17.7%, respectively. In both treatment groups, the majority of bleeding events were ecchymosis or gastrointestinal tract bleeding. The difference in the incidence of serious bleeding events between the two treatment groups occurred primarily during study drug administration.

A total of 2378 adult patients with severe sepsis received drotrecogin alfa (activated) in a Phase 3b, international, single-arm, open-label clinical trial (ENHANCE).

The incidence of serious bleeding events in the PROWESS and ENHANCE studies is provided below. In these studies serious bleeding events included any intracranial haemorrhage, 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.

A Phase 3b international, multi-centre, randomised, double-blind, placebo-controlled clinical trial (ADDRESS) of adult severe sepsis patients at low risk of death, involved 1317 drotrecogin alfa (activated)-treated and 1293 placebo-treated patients. The percentage of patients experiencing at least one bleeding event in the two treatment groups was 10.9% and 6.4%, respectively ($p<0.001$). Bleeding events included serious bleeding events, 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. In the ADDRESS trial, serious bleeding events included any fatal bleed, any life-threatening bleed, any CNS bleed, or any bleeding event assessed as serious by the investigator.

Serious bleeding events during the infusion period
The following table lists the percent of patients in PROWESS and ENHANCE experiencing serious bleeding events by site of haemorrhage during the study drug infusion period (defined as the duration of infusion plus the next full calendar day following the end of the infusion).

Site of haemorrhage	Drotrecogin alfa (activated) [PROWESS] N=850	Placebo [PROWESS] N=840	Drotrecogin alfa (activated) [ENHANCE] N=2378
Gastrointestinal	5 (0.6%)	4(0.5%)	19 (0.8%)
Intra-abdominal	2 (0.2%)	3 (0.4%)	18 (0.8%)
Intra-thoracic	4 (0.5%)	0	11 (0.5%)
Retroperitoneal	3 (0.4%)	0	4 (0.2%)
Central Nervous System (CNS)[1]	2 (0.2%)	0	15 (0.6%)
Genitourinary	2 (0.2%)	0	0
Skin/soft tissue	1 (0.1%)	0	16 (0.7%)
Nasopharyngeal	0	0	4 (0.2%)
Joint/Bone	0	0	1 (0.04%)
Site unknown[2]	1 (0.1%)	1 (0.1%)	6 (0.3%)
Total	20 (2.4%)	8 (1.0%)	85[3] (3.6%)

[1] CNS bleeding is defined as any bleed in the central nervous system including the following types of haemorrhage: Petechial, parenchymal, subarachnoid, subdural, and stroke with haemorrhagic transformation.
[2]Patients requiring the administration of ≥ 3 units of packed red blood cells per day for 2 consecutive days without an identified site of bleeding
[3] In ENHANCE six patients experienced multiple serious bleeding events during the study drug infusion period (94 events observed in 85 patients).

In ADDRESS, the percent of treated patients experiencing a serious bleeding event by site of haemorrhage was similar to that observed in PROWESS. The incidence of serious bleeding events during infusion (defined as study Day 0 through study Day 6) was 31 (2.4%) and 15 (1.2%) in drotrecogin alfa (activated)-treated and placebo-treated patients, respectively ($p=0.02$). The incidence of CNS bleeds during infusion was 4 (0.3%) and 3 (0.2%) for drotrecogin alfa (activated)-treated and placebo-treated patients, respectively. Recent surgery (within 30 days prior to study entry) was associated with a numerically higher risk of serious bleeding during infusion in both the Xigris-treated and the placebo-treated patients (Xigris: 3.6% in patients with recent surgery versus 1.6% in patients without recent surgery; placebo: 1.6% versus 0.9% respectively).

Serious bleeding events during the 28-day study period
In PROWESS, the incidence of serious bleeding events during the 28-day study period was 3.5% and 2.0% in drotrecogin alfa (activated)-treated and placebo-treated patients, respectively. The incidence of CNS bleeds during the 28-day study period was 0.2% and 0.1% for drotrecogin alfa (activated)-treated and placebo-treated patients, respectively. The risk of CNS bleeding may increase with severe coagulopathy and severe thrombocytopenia (see sections 4.3 and 4.4).

In the open-label ENHANCE study, the incidence of serious bleeding events during the 28-day study period was 6.5%, and the incidence of CNS bleeds during the 28-day study period was 1.5%.

In the placebo-controlled ADDRESS study, the incidence of serious bleeding events during the 28-day study period was 51 (3.9%) and 28 (2.2%) in drotrecogin alfa (activated)-treated and placebo-treated patients, respectively (p=0.01). The incidence of CNS bleeds during the 28-day study period was 6 (0.5%) and 5 (0.4%) for drotrecogin alfa (activated)-treated and placebo-treated patients, respectively.

In the phase 1 studies, adverse events with a frequency of ≥ 5% included headache (30.9%), ecchymosis (23.0%), and pain (5.8%).

4.9 Overdose

In clinical trials, there has been one reported overdose of drotrecogin alfa (activated). This patient with severe sepsis received a dose of 181 μg/kg/hr for 2 hours. There were no serious adverse events associated with the overdose.

Post-marketing experience: There have been reports of accidental overdosing. In the majority of cases, no reactions have been observed. For the other reports, the observed events were consistent with known undesirable effects of the drug (see section 4.8), effects of the drug on laboratory tests (see section 4.4), or consequences of the underlying condition of sepsis.

There is no known antidote for drotrecogin alfa (activated). In case of overdose, immediately stop the infusion (see Section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, enzymes, ATC code: B01AD10

Mechanism of Action
Xigris is a recombinant version of the natural plasma-derived activated Protein C, from which it differs only by unique oligosaccharides in the carbohydrate portion of the molecule. Activated Protein C is a crucial coagulation regulator. It limits thrombin formation by inactivating factors Va and VIIIa, thereby providing negative feedback regulation of coagulation. Excessive coagulation activation in the microcirculatory bed plays a significant part in the pathophysiology of severe sepsis. Furthermore, Activated Protein C is an important modulator of the systemic response to infection and has antithrombotic and profibrinolytic properties. Xigris has similar properties to those of endogenous human Activated Protein C.

Pharmacodynamic Effects
In placebo-controlled clinical trials in patients with severe sepsis, Xigris 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. Xigris 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. Xigris also restored endogenous

fibrinolytic potential, as evidenced by a more rapid trend toward normalisation in plasminogen levels and a more rapid decline in plasminogen activator inhibitor-1 levels. Additionally, patients with severe sepsis treated with Xigris had a more rapid decline in interleukin-6 levels, a global marker of inflammation, consistent with a reduction in the inflammatory response.

Clinical Efficacy
Xigris was studied in one Phase 3 international, multi-centre, randomised, double-blind, placebo-controlled trial (PROWESS) in 1690 patients with severe sepsis. Severe sepsis is defined as sepsis associated with acute organ dysfunction. Patients meeting the clinical diagnosis of severe sepsis had a) known or suspected infection, b) clinical evidence of systemic response to infection including fever or hypothermia, leucopenia or leucocytosis, tachycardia and tachypnoea, and c) acute organ dysfunction. Organ dysfunction was defined as shock, hypotension or the need for vasopressor support despite adequate fluid resuscitation, relative hypoxemia (ratio of partial pressure of oxygen in arterial blood in mmHg to the percentage of oxygen in the inspired air expressed as a decimal (PaO_2/FiO_2 ratio) < 250), oliguria despite adequate fluid resuscitation, marked reduction in blood platelet counts, and/or elevated lactic acid concentrations.

Exclusion criteria encompassed patients at high risk of bleeding (see Sections 4.3 and 4.4), patients who were not expected to survive for 28 days due to a pre-existing, non-sepsis related medical condition, HIV positive patients whose most recent CD_4 count was ≤ 50/mm^3, patients on chronic dialysis, and patients who had undergone bone marrow, lung, liver, pancreas or small bowel transplantation, and patients with acute clinical pancreatitis without a proven source of infection.

In the PROWESS trial, treatment was initiated within 48 hours of onset of the first sepsis-induced organ dysfunction. The median duration of organ dysfunction prior to treatment was 18 hours. Patients were given a 96-hour constant rate infusion of Xigris at 24 µg/kg/hr (n=850) or placebo (n=840). Xigris was added to best standard care. Best standard care includes adequate antibiotics, source control and supportive treatment (fluids, inotropes, vasopressors and support of failing organs, as required).

Patients treated with Xigris 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 (p=0.005).

Significant absolute death reduction was limited to the subgroup of patients with greater disease severity i.e. baseline APACHE II score =25 or at least 2 acute organ dysfunctions at baseline. (The APACHE II score is designed to assess the risk of mortality based on acute physiology and chronic health evaluation). In the subgroup of patients with an APACHE II score =25 at baseline, the mortality was 31% in the Xigris group (128 out of 414) and 44% in the placebo group (176 out of 403). No death reduction was observed in the subgroup of patients with lower disease severity. 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 death reduction was observed in the subgroup of patients with less than 2 acute organ dysfunctions at baseline.

A consistent treatment effect on mortality with Xigris administration was observed across patient subgroups defined by age, gender and infection type.

Heparin
Approximately 2/3 of the patients received prophylactic low dose heparin during the course of study. The mortality rate in patients receiving Xigris and concomitant prophylactic low dose heparin was 24.9% and the mortality rate in patients receiving placebo and concomitant prophylactic low dose heparin was 28.1% (p=0.20). There is uncertainty if heparin could interfere with the activity of Xigris. The effect of low dose heparin on the efficacy of Xigris has not been evaluated in specific randomised controlled clinical trials.

PROWESS Follow-up Study
Survival status was assessed in a follow-up study of PROWESS survivors. In-hospital and 3 month survival status was reported for 98% and 94% of the 1690 PROWESS subjects respectively. In the overall population, the in-hospital mortality was significantly lower in patients on Xigris than in patients on placebo (29.4% vs. 34.6%; p=0.023). Survival through 3 months was also better in the Xigris group compared to placebo (log rank p=0.048). These data confirmed that the benefit of Xigris is limited to the more severely affected sepsis patients such as patients with multiple organ failure and shock.

Further Clinical Experience
In a Phase 3b international, single-arm, open-label clinical trial (ENHANCE), 2378 adult patients with severe sepsis received drotrecogin alfa (activated). The entry criteria were similar to those employed in PROWESS. Patients received drotrecogin alfa (activated) within 48 hours of onset of the first sepsis-induced organ dysfunction. The median duration of organ dysfunction prior to treatment was 25 hours. At 28 days, the mortality rate in the Phase 3b study was 25.3%. The mortality rate was lower for patients treated within 24 hours of organ dysfunction compared to those treated after 24 hours, even after adjustment for differences in disease severity.

A total of 2640 adult patients with severe sepsis who were at low risk of death (e.g. patients with APACHE II<25 or with only one sepsis-induced organ failure) were enrolled in a randomised, double-blind, placebo-controlled trial (ADDRESS). The trial was stopped after an interim analysis due to a low likelihood of demonstrating a significant difference in 28-day mortality by the end of the trial.
The ADDRESS trial did enrol 872 patients with multiple organ dysfunction. Compared to multiple organ dysfunction patients in PROWESS, those in ADDRESS had organ dysfunction for longer prior to receiving study drug (median 25 vs. 18 hours), had lower APACHE II scores (median 20 vs. 25) and were more likely to have two organ dysfunctions (76% vs. 43%). At 28 days, the mortality rates for multiple organ dysfunction patients in ADDRESS were 20.7% versus 21.9% for drotrecogin alfa (activated)-treated and placebo-treated patients, respectively. In-hospital mortality rates were 23.1% and 25.3% respectively. In the subgroup with two organ dysfunctions, the results were similar to those seen in the PROWESS trial.

In placebo controlled clinical trials, the treatment effect was most evident at sites enrolling larger numbers of patients.

5.2 Pharmacokinetic properties

Drotrecogin alfa (activated) and endogenous human Activated Protein C are inactivated in plasma by endogenous protease inhibitors but the mechanism by which they are cleared from plasma is unknown. Plasma concentrations of endogenous Activated Protein C in healthy subjects and patients with severe sepsis are usually below detection limits (< 5 ng/ml) and do not significantly influence the pharmacokinetic properties of drotrecogin alfa (activated).

In healthy subjects, greater than 90% of the steady state condition is attained within 2 hours following the start of a constant-rate intravenous infusion of Xigris. Following the completion of an infusion, the decline in plasma drotrecogin alfa (activated) concentrations is biphasic and is comprised of a rapid initial phase ($t_{1/2\,a}$=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 drotrecogin alfa (activated) concentrations towards the steady-state. Plasma drotrecogin alfa (activated) steady-state concentrations 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, infusion of drotrecogin alfa (activated) from 12 µg/kg/hr to 30 µg/kg/hr rapidly produced steady-state plasma concentrations that were proportional to infusion rates. In the Phase 3 trial, the pharmacokinetics of drotrecogin alfa (activated) were evaluated in 342 patients with severe sepsis administered a 96-hour continuous infusion at 24 µg/kg/hr. The pharmacokinetics of drotrecogin alfa (activated) were characterised by attainment of 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, suggesting rapid elimination of drotrecogin alfa (activated) from the systemic circulation. The plasma clearance of drotrecogin alfa (activated) is approximately 41.8 l/hr in sepsis patients as compared with 28.1 l/hr in healthy subjects.

In patients with severe sepsis, the plasma clearance of drotrecogin alfa (activated) was significantly decreased by renal impairment and hepatic dysfunction, but the magnitude of the differences in clearance (< 30 %) does not warrant any dosage adjustment.

5.3 Preclinical safety data

Changes observed in monkeys at, or in small excess of, the maximum human exposure during repeated dose studies, were all related to the pharmacological effect of Xigris and include beside the expected prolongation of APTT, decreases in haemoglobin, erythrocytes and haematocrit, and increases in reticulocyte count and PT.

Drotrecogin alfa (activated) 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.

Carcinogenicity studies and animal reproduction studies have not been conducted with Xigris. However, with respect to the latter, the potential risk for humans being unknown, Xigris should not be used during pregnancy unless clearly necessary (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, sodium chloride, sodium citrate, citric acid, hydrochloric acid and sodium hydroxide.

6.2 Incompatibilities

After reconstitution, Xigris should be compounded ONLY with 0.9% Sodium Chloride Injection. The ONLY other solutions that can be administered through the same intravenous line are 0.9% Sodium Chloride Injection, Lactated Ringer's Injection, Dextrose or Dextrose and Saline mixtures.

When administering drotrecogin alfa (activated) at low concentrations (less than approximately 200 µg/ml) at low flow rates (less than approximately 5 ml/hr), the infusion set must be primed for approximately 15 minutes at a flow rate of approximately 5 ml/hr.

6.3 Shelf life

3 years

After reconstitution, immediate use is recommended. However, the reconstituted solution in the vial may be held for up to 3 hours at room temperature (15 to 30°C).
After preparation, the intravenous infusion solution can be used at room temperature (15 to 30°C) for a period up to 14 hours.

6.4 Special precautions for storage

Store at 2°C – 8°C (in a refrigerator). Keep the vial in the outer carton in order to protect it from light.

6.5 Nature and contents of container

20 mg of powder in vial (type I glass)- pack of 1.

6.6 Instructions for use and handling

1. Use appropriate aseptic technique during the preparation of Xigris for intravenous administration.

2. Calculate the dose and the number of Xigris vials needed.

   Each Xigris vial contains 20 mg of drotrecogin alfa (activated).

   The vial contains an excess of drotrecogin alfa (activated) to facilitate delivery of the label amount.

3. Prior to administration, 20 mg vials of Xigris must be reconstituted with 10 ml of Sterile Water for Injection, resulting in a solution with a concentration of approximately 2 mg/ml drotrecogin alfa (activated).

   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 drotrecogin alfa (activated) solution from the vial. Add the reconstituted drotrecogin alfa (activated) into a prepared infusion bag of sterile 0.9% Sodium Chloride Injection. When adding the reconstituted drotrecogin alfa (activated) into the infusion bag, direct the stream to the side of the bag to minimise the agitation of the solution. Gently invert the infusion bag to obtain a homogeneous solution. Do not transport the infusion bag between locations using mechanical delivery systems.

5. After reconstitution, immediate use is recommended. However, the reconstituted solution in the vial may be held for up to 3 hours at room temperature (15 to 30°C).
   After preparation, the intravenous infusion solution can be used at room temperature (15 to 30°C) for a period up to 14 hours.

6. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

7. **It is recommended that Xigris be infused with an infusion pump to accurately control the infusion rate.** The solution of reconstituted Xigris is typically diluted into an infusion bag containing sterile 0.9% Sodium Chloride Injection to a final concentration of between 100 µg/ml and 200 µg/ml.

8. When administering drotrecogin alfa (activated) at low concentrations (less than approximately 200 µg/ml) at low flow rates (less than approximately 5 ml/hr), the infusion set must be primed for approximately 15 minutes at a flow rate of approximately 5 ml/hr.

9. Xigris should be administered via a dedicated intravenous line or a dedicated lumen of a multilumen central venous catheter. The ONLY other solutions that can be administered through the same line are 0.9% Sodium Chloride Injection, Lactated Ringer's Injection, Dextrose or Dextrose and Saline mixtures.

10. Avoid exposing drotrecogin alfa (activated) solutions to heat and/or direct sunlight. No incompatibilities have been observed between drotrecogin alfa (activated) and glass infusion bottles or infusion bags made of polyvinylchloride, polyethylene, polypropylene, or polyolefin. The use of other types of infusion sets could have a negative impact on the amount and potency of drotrecogin alfa (activated) administered.

11. Care should be taken to administer Xigris at the appropriate rate, calculated based on kg of bodyweight and infused for the correct duration. It is recommended that the bag be labelled accordingly.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Grootslag 1-5, 3991 RA, Houten, The Netherlands

8. MARKETING AUTHORISATION NUMBER (S)

EU/1/02/225/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 August 2002

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Xigris 5 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Drotrecogin alfa (activated): 2 mg per ml after reconstitution.

A vial contains 5 mg of drotrecogin alfa (activated) to be reconstituted with 2.5 ml of Sterile Water for Injection.

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

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xigris is indicated for the treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care. The use of Xigris should be considered mainly in situations when therapy can be started within 24 hours after the onset of organ failure (for further information see Section 5.1).

4.2 Posology and method of administration

Xigris should be used by experienced doctors in institutions skilled in the care of patients with severe sepsis.

Treatment should be started within 48 hours, and preferably within 24 hours, of onset of the first documented sepsis-induced organ dysfunction (see Section 5.1).

The recommended dose of Xigris is 24 μg/kg/hr given as a continuous intravenous infusion for a total duration of 96 hours. It is recommended that Xigris be infused with an infusion pump to accurately control the infusion rate. 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 full recommended 96 hours of dosing administration. Dose escalation or bolus doses of Xigris are not necessary to account for the interruption in the infusion.

No dose adjustments are required in adult patients with severe sepsis with regard to age, gender, hepatic function (as measured by transaminase levels) or renal function. The pharmacokinetics of drotrecogin alfa (activated) have not been studied in patients with severe sepsis and preexisting endstage renal disease and chronic hepatic disease.

Paediatrics: Data from a placebo-controlled clinical trial which was stopped for futility after 477 patients 0 to 17 years-old had received the study drug did not establish efficacy of Xigris in paediatric

patients and showed a higher rate of central nervous system bleeding in the Xigris versus placebo group. Therefore no dosage recommendation can be made and the use of Xigris is not recommended in children below the age of 18 (see Section 4.4).

4.3 Contraindications

Because drotrecogin alfa (activated) may increase the risk of bleeding, Xigris is contraindicated in the following situations:

- Active internal bleeding
- Patients with intracranial pathology; neoplasm or evidence of cerebral herniation
- Concurrent heparin therapy ≥ 15 International Units/kg/hr
- Known bleeding diathesis except for acute coagulopathy related to sepsis
- Chronic severe hepatic disease
- Platelet count < 30,000 x 10^6/l, even if the platelet count is increased after transfusions
- Patients at increased risk for bleeding (for example):
  - a) any major surgery, defined as surgery that requires general or spinal anesthesia, performed within the 12-hour period immediately preceding drug infusion, or any postoperative patient who demonstrates evidence of active bleeding, or any patient with planned or anticipated surgery during the drug infusion period.
  - b) history of severe head trauma that required hospitalization, intracranial or intraspinal surgery, or haemorrhagic stroke within the previous 3 months, or any history of intracerebral arteriovenous malformation, cerebral aneurysm, or central nervous system mass lesion; patients with an epidural catheter or who are anticipated to receive an epidural catheter during drug infusion
  - c) history of congenital bleeding diatheses
  - d) gastrointestinal bleeding within the last 6 weeks that has required medical intervention unless definitive surgery has been performed
  - e) trauma patients at increased risk of bleeding

Xigris is also contraindicated in patients with known hypersensitivity to drotrecogin alfa (activated), to any of the formulation excipients, or to bovine thrombin (a trace residue from the manufacturing process).

4.4 Special warnings and special precautions for use

Patients with single organ dysfunction and recent surgery
Xigris is not approved for the treatment of patients with single organ dysfunction and should not be used in this particular subgroup of patients, especially if they had recent surgery (within 30 days). In each of two randomised, placebo-controlled trials, PROWESS and ADDRESS (see Section 5.1), 28-day and in-hospital mortality were higher in patients treated with drotrecogin alfa (activated) compared to placebo for the sub-population of patients with single organ dysfunction and recent surgery (n=98 in PROWESS and n=636 in ADDRESS).

Bleeding
Drotrecogin alfa (activated) increases the risk of bleeding. In the following conditions, the risks of the administration of Xigris should be weighed against the anticipated benefits:

- Recent administration (within 3 days) of thrombolytic therapy
- Recent administration (within 7 days) of oral anticoagulants
- Recent administration (within 7 days) of aspirin or other platelet inhibitors
- Recent (within 3 months) ischaemic stroke
- Any other condition in which the physician considers significant bleeding is likely

For procedures with an inherent bleeding risk, discontinue Xigris for 2 hours prior to the start of the procedure. Xigris may be restarted 12 hours after major invasive procedures or surgery if adequate haemostasis has been achieved. Xigris may be restarted immediately after uncomplicated less invasive procedures if adequate haemostasis has been achieved.

As a component of routine care, measures of haemostasis (e.g., activated partial thromboplastin time (APTT), prothrombin time (PT) and platelet count) should be obtained during the infusion of Xigris. If sequential tests of haemostasis 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.

Laboratory tests
Drotrecogin alfa (activated) 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 drotrecogin alfa (activated), and/or the effect of other concurrent medications. The pharmacodynamic effect of drotrecogin alfa (activated) 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. Drotrecogin alfa (activated) that is present in a blood or plasma sample drawn from a patient who is being infused with the drug will be gradually neutralized by endogenous plasma protease inhibitors present in the sample. Virtually no measurable activity of drotrecogin alfa (activated) 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 drotrecogin alfa (activated). In addition, approximately 2 hours after terminating the infusion of the drug, there is virtually no measurable activity of drotrecogin alfa (activated) 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 determinations of the PT and/or APTT should take these variables into consideration.

Because drotrecogin alfa (activated) may affect the APTT assays, drotrecogin alfa (activated) present in plasma samples may interfere with one-stage coagulation assays based on the APTT (such as factor VIII, IX, and XI assays). Drotrecogin alfa (activated) present in plasma samples does not interfere with one-stage factor assays based on the PT (such as Factors II, V, VII and X assays).

If sequential measures of coagulopathy (including platelet count) indicate severe or worsening coagulopathy, the risk of continuing the infusion should be weighed against the expected benefit.

Immunogenicity
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 Activated Protein C on the APTT assay. However, the possibility of allergic reactions to constituents of the preparation cannot be completely excluded in certain predisposed patients. If allergic or anaphylactic reactions occur, treatment should be discontinued immediately and appropriate therapy initiated. Xigris has not been readministered to patients with severe sepsis. If Xigris is readministered to patients, caution should be employed. No anti-activated Protein C antibody formation was detected in healthy subjects, even after repeat administration.

Paediatric patients
Xigris is not recommended in children below the age of 18 and therefore it should not be used in children. Data from a placebo-controlled clinical trial did not establish efficacy of Xigris in paediatric patients suffering from severe sepsis, acute infection, systemic inflammation and respiratory and cardiovascular organ dysfunction. This trial was stopped for futility after 477 patients had received the study drug (out of 600 patients intended).
A planned interim analysis (with 400 patients enrolled) showed a low likelihood of demonstrating a significant difference in the primary endpoint of "Composite Time to Complete Organ Failure

Resolution" (CTCOFR score of 9.8 versus 9.7 mean days over 14 days). There was also no difference in 28-day mortality (17.1% versus 17.3% in the Xigris and placebo groups, respectively). Investigators attributed 2 deaths in the Xigris group and 5 deaths in the placebo group to bleeding events. There was a higher rate of central nervous system (CNS) bleeding in the drotrecogin alfa (activated) versus the placebo group. Over the infusion period (study days 0-6) the number of patients experiencing CNS bleeding was 5 versus 1 (2.1% versus 0.4%) for the overall population (drotrecogin alfa (activated) versus placebo), with 4 of the 5 events in the drotrecogin alfa (activated) group occurring in patients = 60 days old or = 3.5 kg bodyweight. 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.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions with Xigris have not been studied in patients with sepsis.

Caution should be employed when Xigris is used with other drugs that affect haemostasis (see Sections 4.3 and 4.4) including Protein C, thrombolytics (e.g. streptokinase, tPA, rPA and urokinase), oral anticoagulants (e.g. warfarin), hirudins, antithrombin, aspirin and other anti platelets agents, e.g. non-steroidal anti-inflammatory drugs, ticlopidine and clopidogrel, glycoprotein IIb/IIIa antagonists (such as abciximab, eptifibatide, tirofiban) and prostacyclins such as iloprost.

Heparin
Two-thirds of patients in the phase 3 trial received prophylactic doses of unfractionated or low molecular weight heparin. There was no observed increase in the risk of bleeding events reported as serious adverse events in drotrecogin alfa (activated) patients receiving heparin. The effects of prophylactic low dose heparin and other coagulation-active medications on the efficacy of drotrecogin alfa (activated) have not been evaluated in a randomised controlled clinical trial.

4.6 Pregnancy and lactation

Animal studies with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development have not been conducted with Xigris. Therefore, the potential risk for humans is unknown. Xigris should not be used during pregnancy unless clearly necessary.

It is not known whether Xigris is excreted in human milk or if there is a potential effect on the nursed infant. Therefore, the patient should not breast feed whilst treated with Xigris.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Xigris increases the risk of bleeding.

The Phase 3 international, multi-centre, randomised, double-blind, placebo-controlled clinical trial (PROWESS) involved 850 drotrecogin alfa (activated)-treated and 840 placebo-treated patients. The percentage of patients experiencing at least one bleeding event in the two treatment groups was 24.9% and 17.7%, respectively. In both treatment groups, the majority of bleeding events were ecchymosis or gastrointestinal tract bleeding. The difference in the incidence of serious bleeding events between the two treatment groups occurred primarily during study drug administration.

A total of 2378 adult patients with severe sepsis received drotrecogin alfa (activated) in a Phase 3b, international, single-arm, open-label clinical trial (ENHANCE).

The incidence of serious bleeding events in the PROWESS and ENHANCE studies is provided below. In these studies serious bleeding events included any intracranial haemorrhage, 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.

A Phase 3b international, multi-centre, randomised, double-blind, placebo-controlled clinical trial (ADDRESS) of adult severe sepsis patients at low risk of death, involved 1317 drotrecogin alfa (activated)-treated and 1293 placebo-treated patients. The percentage of patients experiencing at least one bleeding event in the two treatment groups was 10.9% and 6.4%, respectively ($p<0.001$). Bleeding events included serious bleeding events, 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. In the ADDRESS trial, serious bleeding events included any fatal bleed, any life-threatening bleed, any CNS bleed, or any bleeding event assessed as serious by the investigator.

Serious bleeding events during the infusion period
The following table lists the percent of patients in PROWESS and ENHANCE experiencing serious bleeding events by site of haemorrhage during the study drug infusion period (defined as the duration of infusion plus the next full calendar day following the end of the infusion).

Site of haemorrhage	Drotrecogin alfa (activated) [PROWESS] N=850	Placebo [PROWESS] N=840	Drotrecogin alfa (activated) [ENHANCE] N=2378
Gastrointestinal	5 (0.6%)	4(0.5%)	19 (0.8%)
Intra-abdominal	2 (0.2%)	3 (0.4%)	18 (0.8%)
Intra-thoracic	4 (0.5%)	0	11 (0.5%)
Retroperitoneal	3 (0.4%)	0	4 (0.2%)
Central Nervous System (CNS)[1]	2 (0.2%)	0	15 (0.6%)
Genitourinary	2 (0.2%)	0	0
Skin/soft tissue	1 (0.1%)	0	16 (0.7%)
Nasopharyngeal	0	0	4 (0.2%)
Joint/Bone	0	0	1 (0.04%)
Site unknown[2]	1 (0.1%)	1 (0.1%)	6 (0.3%)
Total	20 (2.4%)	8 (1.0%)	85[3] (3.6%)

[1] CNS bleeding is defined as any bleed in the central nervous system including the following types of haemorrhage: Petechial, parenchymal, subarachnoid, subdural, and stroke with haemorrhagic transformation.
[2] Patients requiring the administration of ≥ 3 units of packed red blood cells per day for 2 consecutive days without an identified site of bleeding
[3] In ENHANCE six patients experienced multiple serious bleeding events during the study drug infusion period (94 events observed in 85 patients).

In ADDRESS, the percent of treated patients experiencing a serious bleeding event by site of haemorrhage was similar to that observed in PROWESS. The incidence of serious bleeding events during infusion (defined as study Day 0 through study Day 6) was 31 (2.4%) and 15 (1.2%) in drotrecogin alfa (activated)-treated and placebo-treated patients, respectively ($p=0.02$). The incidence of CNS bleeds during infusion was 4 (0.3%) and 3 (0.2%) for drotrecogin alfa (activated)-treated and placebo-treated patients, respectively. Recent surgery (within 30 days prior to study entry) was associated with a numerically higher risk of serious bleeding during infusion in both the Xigris-treated and the placebo-treated patients (Xigris: 3.6% in patients with recent surgery versus 1.6% in patients without recent surgery; placebo: 1.6% versus 0.9% respectively).

Serious bleeding events during the 28-day study period
In PROWESS, the incidence of serious bleeding events during the 28-day study period was 3.5% and 2.0% in drotrecogin alfa (activated)-treated and placebo-treated patients, respectively. The incidence of CNS bleeds during the 28-day study period was 0.2% and 0.1% for drotrecogin alfa (activated)-treated and placebo-treated patients, respectively. The risk of CNS bleeding may increase with severe coagulopathy and severe thrombocytopenia (see sections 4.3 and 4.4).

In the open-label ENHANCE study, the incidence of serious bleeding events during the 28-day study period was 6.5%, and the incidence of CNS bleeds during the 28-day study period was 1.5%.

In the placebo-controlled ADDRESS study, the incidence of serious bleeding events during the 28-day study period was 51 (3.9%) and 28 (2.2%) in drotrecogin alfa (activated)-treated and placebo-treated patients, respectively (p=0.01). The incidence of CNS bleeds during the 28-day study period was 6 (0.5%) and 5 (0.4%) for drotrecogin alfa (activated)-treated and placebo-treated patients, respectively.

In the phase 1 studies, adverse events with a frequency of ≥ 5% included headache (30.9%), ecchymosis (23.0%), and pain (5.8%).

4.9 Overdose

In clinical trials, there has been one reported overdose of drotrecogin alfa (activated). This patient with severe sepsis received a dose of 181 µg/kg/hr for 2 hours. There were no serious adverse events associated with the overdose.

Post-marketing experience: There have been reports of accidental overdosing. In the majority of cases, no reactions have been observed. For the other reports, the observed events were consistent with known undesirable effects of the drug (see section 4.8), effects of the drug on laboratory tests (see section 4.4), or consequences of the underlying condition of sepsis.

There is no known antidote for drotrecogin alfa (activated). In case of overdose, immediately stop the infusion (see Section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, enzymes, ATC code: B01AD10

Mechanism of Action
Xigris is a recombinant version of the natural plasma-derived activated Protein C, from which it differs only by unique oligosaccharides in the carbohydrate portion of the molecule. Activated Protein C is a crucial coagulation regulator. It limits thrombin formation by inactivating factors Va and VIIIa, thereby providing negative feedback regulation of coagulation. Excessive coagulation activation in the microcirculatory bed plays a significant part in the pathophysiology of severe sepsis. Furthermore, Activated Protein C is an important modulator of the systemic response to infection and has antithrombotic and profibrinolytic properties. Xigris has similar properties to those of endogenous human Activated Protein C.

Pharmacodynamic Effects
In placebo-controlled clinical trials in patients with severe sepsis, Xigris 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. Xigris 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. Xigris also restored endogenous

fibrinolytic potential, as evidenced by a more rapid trend toward normalisation in plasminogen levels and a more rapid decline in plasminogen activator inhibitor-1 levels. Additionally, patients with severe sepsis treated with Xigris had a more rapid decline in interleukin-6 levels, a global marker of inflammation, consistent with a reduction in the inflammatory response.

Clinical Efficacy
Xigris was studied in one Phase 3 international, multi-centre, randomised, double-blind, placebo-controlled trial (PROWESS) in 1690 patients with severe sepsis. Severe sepsis is defined as sepsis associated with acute organ dysfunction. Patients meeting the clinical diagnosis of severe sepsis had a) known or suspected infection, b) clinical evidence of systemic response to infection including fever or hypothermia, leucopenia or leucocytosis, tachycardia and tachypnoea, and c) acute organ dysfunction. Organ dysfunction was defined as shock, hypotension or the need for vasopressor support despite adequate fluid resuscitation, relative hypoxemia (ratio of partial pressure of oxygen in arterial blood in mmHg to the percentage of oxygen in the inspired air expressed as a decimal (PaO_2/FiO_2 ratio) < 250), oliguria despite adequate fluid resuscitation, marked reduction in blood platelet counts, and/or elevated lactic acid concentrations.

Exclusion criteria encompassed patients at high risk of bleeding (see Sections 4.3 and 4.4), patients who were not expected to survive for 28 days due to a pre-existing, non-sepsis related medical condition, HIV positive patients whose most recent CD_4 count was ≤ 50/mm^3, patients on chronic dialysis, and patients who had undergone bone marrow, lung, liver, pancreas or small bowel transplantation, and patients with acute clinical pancreatitis without a proven source of infection.

In the PROWESS trial, treatment was initiated within 48 hours of onset of the first sepsis-induced organ dysfunction. The median duration of organ dysfunction prior to treatment was 18 hours. Patients were given a 96-hour constant rate infusion of Xigris at 24 µg/kg/hr (n=850) or placebo (n=840). Xigris was added to best standard care. Best standard care includes adequate antibiotics, source control and supportive treatment (fluids, inotropes, vasopressors and support of failing organs, as required).

Patients treated with Xigris 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 (p=0.005).

Significant absolute death reduction was limited to the subgroup of patients with greater disease severity i.e. baseline APACHE II score =25 or at least 2 acute organ dysfunctions at baseline. (The APACHE II score is designed to assess the risk of mortality based on acute physiology and chronic health evaluation). In the subgroup of patients with an APACHE II score =25 at baseline, the mortality was 31% in the Xigris group (128 out of 414) and 44% in the placebo group (176 out of 403). No death reduction was observed in the subgroup of patients with lower disease severity. 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 death reduction was observed in the subgroup of patients with less than 2 acute organ dysfunctions at baseline.

A consistent treatment effect on mortality with Xigris administration was observed across patient subgroups defined by age, gender and infection type.

Heparin
Approximately 2/3 of the patients received prophylactic low dose heparin during the course of study. The mortality rate in patients receiving Xigris and concomitant prophylactic low dose heparin was 24.9% and the mortality rate in patients receiving placebo and concomitant prophylactic low dose heparin was 28.1% (p=0.20). There is uncertainty if heparin could interfere with the activity of Xigris. The effect of low dose heparin on the efficacy of Xigris has not been evaluated in specific randomised controlled clinical trials.

PROWESS Follow-up Study
Survival status was assessed in a follow-up study of PROWESS survivors. In-hospital and 3 month survival status was reported for 98% and 94% of the 1690 PROWESS subjects respectively. In the overall population, the in-hospital mortality was significantly lower in patients on Xigris than in patients on placebo (29.4% vs. 34.6%; p=0.023). Survival through 3 months was also better in the Xigris group compared to placebo (log rank p=0.048). These data confirmed that the benefit of Xigris is limited to the more severely affected sepsis patients such as patients with multiple organ failure and shock.

Further Clinical Experience
In a Phase 3b international, single-arm, open-label clinical trial (ENHANCE), 2378 adult patients with severe sepsis received drotrecogin alfa (activated). The entry criteria were similar to those employed in PROWESS. Patients received drotrecogin alfa (activated) within 48 hours of onset of the first sepsis-induced organ dysfunction. The median duration of organ dysfunction prior to treatment was 25 hours. At 28 days, the mortality rate in the Phase 3b study was 25.3%. The mortality rate was lower for patients treated within 24 hours of organ dysfunction compared to those treated after 24 hours, even after adjustment for differences in disease severity.

A total of 2640 adult patients with severe sepsis who were at low risk of death (e.g. patients with APACHE II<25 or with only one sepsis-induced organ failure) were enrolled in a randomised, double-blind, placebo-controlled trial (ADDRESS). The trial was stopped after an interim analysis due to a low likelihood of demonstrating a significant difference in 28-day mortality by the end of the trial.
The ADDRESS trial did enrol 872 patients with multiple organ dysfunction. Compared to multiple organ dysfunction patients in PROWESS, those in ADDRESS had organ dysfunction for longer prior to receiving study drug (median 25 vs. 18 hours), had lower APACHE II scores (median 20 vs. 25) and were more likely to have two organ dysfunctions (76% vs. 43%). At 28 days, the mortality rates for multiple organ dysfunction patients in ADDRESS were 20.7% versus 21.9% for drotrecogin alfa (activated)-treated and placebo-treated patients, respectively. In-hospital mortality rates were 23.1% and 25.3% respectively. In the subgroup with two organ dysfunctions, the results were similar to those seen in the PROWESS trial.

In placebo controlled clinical trials, the treatment effect was most evident at sites enrolling larger numbers of patients.

5.2 Pharmacokinetic properties

Drotrecogin alfa (activated) and endogenous human Activated Protein C are inactivated in plasma by endogenous protease inhibitors but the mechanism by which they are cleared from plasma is unknown. Plasma concentrations of endogenous Activated Protein C in healthy subjects and patients with severe sepsis are usually below detection limits (< 5 ng/ml) and do not significantly influence the pharmacokinetic properties of drotrecogin alfa (activated).

In healthy subjects, greater than 90% of the steady state condition is attained within 2 hours following the start of a constant-rate intravenous infusion of Xigris. Following the completion of an infusion, the decline in plasma drotrecogin alfa (activated) concentrations is biphasic and is comprised of a rapid initial phase ($t_{1/2\,a}$=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 drotrecogin alfa (activated) concentrations towards the steady-state. Plasma drotrecogin alfa (activated) steady-state concentrations 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, infusion of drotrecogin alfa (activated) from 12 µg/kg/hr to 30 µg/kg/hr rapidly produced steady-state plasma concentrations that were proportional to infusion rates. In the Phase 3 trial, the pharmacokinetics of drotrecogin alfa (activated) were evaluated in 342 patients with severe sepsis administered a 96-hour continuous infusion at 24 µg/kg/hr. The pharmacokinetics of drotrecogin alfa (activated) were characterised by attainment of 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, suggesting rapid elimination of drotrecogin alfa (activated) from the systemic circulation. The plasma clearance of drotrecogin alfa (activated) is approximately 41.8 l/hr in sepsis patients as compared with 28.1 l/hr in healthy subjects.

In patients with severe sepsis, the plasma clearance of drotrecogin alfa (activated) was significantly decreased by renal impairment and hepatic dysfunction, but the magnitude of the differences in clearance (< 30 %) does not warrant any dosage adjustment.

5.3 Preclinical safety data

Changes observed in monkeys at, or in small excess of, the maximum human exposure during repeated dose studies, were all related to the pharmacological effect of Xigris and include beside the expected prolongation of APTT, decreases in haemoglobin, erythrocytes and haematocrit, and increases in reticulocyte count and PT.

Drotrecogin alfa (activated) 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.

Carcinogenicity studies and animal reproduction studies have not been conducted with Xigris. However, with respect to the latter, the potential risk for humans being unknown, Xigris should not be used during pregnancy unless clearly necessary (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, sodium chloride, sodium citrate, citric acid, hydrochloric acid and sodium hydroxide.

6.2 Incompatibilities

After reconstitution, Xigris should be compounded ONLY with 0.9% Sodium Chloride Injection. The ONLY other solutions that can be administered through the same intravenous line are 0.9% Sodium Chloride Injection, Lactated Ringer's Injection, Dextrose or Dextrose and Saline mixtures.

When administering drotrecogin alfa (activated) at low concentrations (less than approximately 200 µg/ml) at low flow rates (less than approximately 5 ml/hr), the infusion set must be primed for approximately 15 minutes at a flow rate of approximately 5 ml/hr.

6.3 Shelf life

3 years

After reconstitution, immediate use is recommended. However, the reconstituted solution in the vial may be held for up to 3 hours at room temperature (15 to 30°C).
After preparation, the intravenous infusion solution can be used at room temperature (15 to 30°C) for a period up to 14 hours.

6.4 Special precautions for storage

Store at 2°C – 8°C (in a refrigerator). Keep the vial in the outer carton in order to protect it from light.

6.5 Nature and contents of container

5 mg of powder in vial (type I glass)- pack of 1.

6.6 Instructions for use and handling

1. Use appropriate aseptic technique during the preparation of Xigris for intravenous administration.

2. Calculate the dose and the number of Xigris vials needed.

   Each Xigris vial contains 5 mg of drotrecogin alfa (activated).

   The vial contains an excess of drotrecogin alfa (activated) to facilitate delivery of the label amount.

3. Prior to administration, 5 mg vials of Xigris must be reconstituted with 2.5 ml of Sterile Water for Injection, resulting in a solution with a concentration of approximately 2 mg/ml drotrecogin alfa (activated).

   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 drotrecogin alfa (activated) solution from the vial. Add the reconstituted drotrecogin alfa (activated) into a prepared infusion bag of sterile 0.9% Sodium Chloride Injection. When adding the reconstituted drotrecogin alfa (activated) into the infusion bag, direct the stream to the side of the bag to minimise the agitation of the solution. Gently invert the infusion bag to obtain a homogeneous solution. Do not transport the infusion bag between locations using mechanical delivery systems.

5. After reconstitution, immediate use is recommended. However, the reconstituted solution in the vial may be held for up to 3 hours at room temperature (15 to 30°C).
   After preparation, the intravenous infusion solution can be used at room temperature (15 to 30°C) for a period up to 14 hours.

6. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

7. **It is recommended that Xigris be infused with an infusion pump to accurately control the infusion rate.** The solution of reconstituted Xigris is typically diluted into an infusion bag containing sterile 0.9% Sodium Chloride Injection to a final concentration of between 100 µg/ml and 200 µg/ml.

8. When administering drotrecogin alfa (activated) at low concentrations (less than approximately 200 µg/ml) at low flow rates (less than approximately 5 ml/hr), the infusion set must be primed for approximately 15 minutes at a flow rate of approximately 5 ml/hr.

9. Xigris should be administered via a dedicated intravenous line or a dedicated lumen of a multilumen central venous catheter. The ONLY other solutions that can be administered through the same line are 0.9% Sodium Chloride Injection, Lactated Ringer's Injection, Dextrose or Dextrose and Saline mixtures.

10. Avoid exposing drotrecogin alfa (activated) solutions to heat and/or direct sunlight. No incompatibilities have been observed between drotrecogin alfa (activated) and glass infusion bottles or infusion bags made of polyvinylchloride, polyethylene, polypropylene, or polyolefin. The use of other types of infusion sets could have a negative impact on the amount and potency of drotrecogin alfa (activated) administered.

11. Care should be taken to administer Xigris at the appropriate rate, calculated based on kg of bodyweight and infused for the correct duration. It is recommended that the bag be labelled accordingly.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER (S)

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10. DATE OF REVISION OF THE TEXT