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 20 mg of Drotrecogin alfa (activated).

After reconstitution with 10 ml of Water for Injection each ml contains 2 mg of Drotrecogin alfa (activated).

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.

Excipient: Each vial contains approximately 68 mg sodium.
For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion. Xigris is supplied as a lyophilised, white to off-white powder.

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 (based on actual body weight) 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), renal function, obesity or co-administration of prophylactic heparin. The pharmacokinetics of drotrecogin alfa (activated) have not been studied in patients with severe sepsis and pre-existing end stage 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 treatment 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. Xigris is contraindicated in children below the age of 18 (see section 4.3 and 5.1).

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients or to bovine thrombin (a trace residue from the manufacturing process).

Drotrecogin alfa (activated) is contraindicated in children below the age of 18 years (see section 5.1).

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

4.4 Special warnings and precautions for use

No further study has confirmed the efficacy results of the single pivotal trial.

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. The incidence of serious bleeding events with Xigris was higher in patients with recent [within 30 days] surgery than in "medical" patients without surgery (see section 4.8). Bleeding risk should be taken into account when considering the risk benefit for individual patients. 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 medicinal products. 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 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. In patients developing antibodies adverse events were not more frequent in drotrecogin alfa (activated) than in placebo patients. There was no evidence that the antibodies detected represented a specific immune response to drotrecogin alfa (activated) therapy. There have been no clinical trials in severe sepsis specifically studying drotrecogin alfa (activated) re-administration. However, a small number of patients in severe sepsis controlled clinical trials received a prior course of drotrecogin alfa (activated). No hypersensitivity reactions were reported in these patients. Samples available were subsequently tested and all were negative for anti-human Activated Protein C antibody. No anti-activated Protein C antibody formation was detected in healthy subjects, even after repeat administration.

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. If Xigris is readministered to patients, caution should be employed.

This medicinal product contains approximately 68 mg sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Co-administration of low-dose heparin for prophylaxis of venous thrombotic events (VTE)
Low-dose heparin for VTE prophylaxis may be co-administered with drotrecogin alfa (activated). In a randomised study of heparin versus placebo (XPRESS) in 1935 adult severe sepsis patients, all treated with drotrecogin alfa (activated), prophylactic heparin did not adversely affect mortality (heparin 28.3% versus placebo 31.9% in the overall ITT population, and heparin 30.3% versus placebo 26.9% in patients with multiple organ dysfunction treated within 24 hours of their first sepsis-induced organ dysfunction (n=890)). In the subgroup of 885 patients who were already receiving prophylactic heparin at study entry, mortality was 26.9% in the group randomised to continue heparin versus 35.6% in the group whose randomisation (to placebo) led to the discontinuation of heparin. However the reasons for this difference are unknown and could be related to other factors.
Additionally there was no increased risk of serious bleeding, including central nervous system (CNS) bleeding. Prophylactic heparin increased the risk of non-serious bleeding (see section 4.8).
There was no statistical difference in the rates of VTE between study arms.

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 breast-fed infant. Therefore, the patient should not breast feed whilst treated with Xigris.

4.7 Effects on ability to drive and use machines

Not relevant.

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).

During the infusion period in PROWESS and ENHANCE the incidence of serious bleeding events with Xigris was numerically higher in patients with recent [within 30 days] surgery than in patients without surgery (PROWESS: 3.3% vs 2.0%; ENHANCE: 5.0% vs 3.1% respectively. Placebo rates in PROWESS 0.4% vs 1.2% respectively).

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).

In XPRESS, a randomised study of prophylactic heparin versus placebo in adult severe sepsis patients, all treated with drotrecogin alfa (activated), serious bleeding rates were consistent with those observed in previous studies over the treatment period of 0-6 days, and prophylactic heparin did not increase the risk of serious bleeding compared to placebo (2.3% vs 2.5%, respectively), including CNS bleeding (0.3% on both arms). However prophylactic heparin increased the risk of non-serious bleeding compared with placebo (8.7% vs 5.7%, respectively; p= 0.0116).

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 XPRESS serious bleeding rates were consistent with those observed in previous studies during the 28-day study period (days 0-28). Prophylactic heparin did not increase the risk of serious bleeding compared to placebo (3.9% vs 5.2%, respectively), including CNS bleeding (1.0% vs 0.7%, 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 and in 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

This medicinal product has been authorised under "Exceptional Circumstances". This means that for scientific reasons it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMEA) will review any new information which may become available every year and this SPC will be updated as necessary.

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.

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 for futility after an interim analysis. No benefit of drotrecogin alfa (activated) was observed in the subgroup of 872 patients at low risk of death with multiple organ dysfunction, so ADDRESS did not confirm the efficacy results of the PROWESS study. In the multiple organ dysfunction subgroup of ADDRESS the 28-day placebo mortality was 21.9%, similar to the single organ dysfunction subgroup of PROWESS (21.2%), confirming the lack of efficacy in patients with severe sepsis who are at low risk of death.

Paediatric patients

Xigris is contraindicated in children below the age of 18 years (see also sections 4.2 and 4.3).
Data from a placebo-controlled clinical trial (RESOLVE) 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.

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 ($t_{1/2\ \alpha}$=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 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
Sodium hydroxide

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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 (15ºC-30ºC).
After preparation, the intravenous infusion solution can be used at room temperature (15ºC-30ºC) for a period up to 14 hours.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Powder in Type I glass vial. Pack of 1 vial.

6.6 Special precautions for disposal and other 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 to a final concentration of between 100 μg/ml and 200 μg/ml. 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 30ºC).
After preparation, the intravenous infusion solution can be used at room temperature (15 to 30ºC) 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 should be 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 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

Date of first authorisation: 22 August 2002.
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA): http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Xigris 5 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 5 mg of Drotrecogin alfa (activated).

After reconstitution with 2.5 ml of Water for Injection each ml contains 2 mg of Drotrecogin alfa (activated).

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.

Excipient: Each vial contains approximately 17 mg sodium.
For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion. Xigris is supplied as a lyophilised, white to off-white powder.

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 (based on actual body weight) 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), renal function, obesity or co-administration of prophylactic heparin. The pharmacokinetics of drotrecogin alfa (activated) have not been studied in patients with severe sepsis and pre-existing end stage 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 treatment 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. Xigris is contraindicated in children below the age of 18 (see section 4.3 and 5.1).

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients or to bovine thrombin (a trace residue from the manufacturing process).

Drotrecogin alfa (activated) is contraindicated in children below the age of 18 (see section 5.1).

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

4.4 Special warnings and precautions for use

No further study has confirmed the efficacy results of the single pivotal trial.

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. The incidence of serious bleeding events with Xigris was higher in patients with recent [within 30 days] surgery than in "medical" patients without surgery (see section 4.8). Bleeding risk should be taken into account when considering the risk benefit for individual patients. 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 medicinal products. 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 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. In patients developing antibodies adverse events were not more frequent in drotrecogin alfa (activated) than in placebo patients. There was no evidence that the antibodies detected represented a specific immune response to drotrecogin alfa (activated) therapy. There have been no clinical trials in severe sepsis specifically studying drotrecogin alfa (activated) re-administration. However, a small number of patients in severe sepsis controlled clinical trials received a prior course of drotrecogin alfa (activated). No hypersensitivity reactions were reported in these patients. Samples available were subsequently tested and all were negative for anti-human Activated Protein C antibody. No anti-activated Protein C antibody formation was detected in healthy subjects, even after repeat administration.

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.
If Xigris is readministered to patients, caution should be employed.

This medicinal product contains approximately 17 mg sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Co-administration of low-dose heparin for prophylaxis of venous thrombotic events (VTE)
Low-dose heparin for VTE prophylaxis may be co-administered with drotrecogin alfa (activated). In a randomised study of heparin versus placebo (XPRESS) in 1935 adult severe sepsis patients, all treated with drotrecogin alfa (activated), prophylactic heparin did not adversely affect mortality (heparin 28.3% versus placebo 31.9% in the overall ITT population, and heparin 30.3% versus placebo 26.9% in patients with multiple organ dysfunction treated within 24 hours of their first sepsis-induced organ dysfunction (n=890)). In the subgroup of 885 patients who were already receiving prophylactic heparin at study entry, mortality was 26.9% in the group randomised to continue heparin versus 35.6% in the group whose randomisation (to placebo) led to the discontinuation of heparin. However the reasons for this difference are unknown and could be related to other factors.
Additionally there was no increased risk of serious bleeding, including central nervous system (CNS) bleeding. Prophylactic heparin increased the risk of non-serious bleeding (see section 4.8).
There was no statistical difference in the rates of VTE between study arms.

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 breast-fed infant. Therefore, the patient should not breast feed whilst treated with Xigris.

4.7 Effects on ability to drive and use machines

Not relevant.

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).

During the infusion period in PROWESS and ENHANCE the incidence of serious bleeding events with Xigris was numerically higher in patients with recent [within 30 days] surgery than in patients without surgery (PROWESS: 3.3% vs 2.0%; ENHANCE: 5.0% vs 3.1% respectively. Placebo rates in PROWESS 0.4% vs 1.2% respectively).

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).

In XPRESS, a randomised study of prophylactic heparin versus placebo in adult severe sepsis patients, all treated with drotrecogin alfa (activated), serious bleeding rates were consistent with those observed in previous studies over the treatment period of 0-6 days, and prophylactic heparin did not increase the risk of serious bleeding compared to placebo (2.3% vs 2.5%, respectively), including CNS bleeding (0.3% on both arms). However prophylactic heparin increased the risk of non-serious bleeding compared with placebo (8.7% vs 5.7%, respectively; p= 0.0116).

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 XPRESS serious bleeding rates were consistent with those observed in previous studies during the 28-day study period (days 0-28). Prophylactic heparin did not increase the risk of serious bleeding compared to placebo (3.9% vs 5.2%, respectively), including CNS bleeding (1.0% vs 0.7%, 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 and in 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

This medicinal product has been authorised under "Exceptional Circumstances". This means that for scientific reasons it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMEA) will review any new information which may become available every year and this SPC will be updated as necessary.

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.

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 for futility after an interim analysis. No benefit of drotrecogin alfa (activated) was observed in the subgroup of 872 patients at low risk of death with multiple organ dysfunction, so ADDRESS did not confirm the efficacy results of the PROWESS study. In the multiple organ dysfunction subgroup of ADDRESS the 28-day placebo mortality was 21.9%, similar to the single organ dysfunction subgroup of PROWESS (21.2%), confirming the lack of efficacy in patients with severe sepsis who are at low risk of death.

Paediatric patients

Xigris is contraindicated in children below the age of 18 years (see also sections 4.2 and 4.3).

Data from a placebo-controlled clinical trial (RESOLVE) 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.

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 ($t_{1/2\ \alpha}$=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 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
Sodium hydroxide

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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 (15ºC - 30ºC).
After preparation, the intravenous infusion solution can be used at room temperature (15ºC - 30ºC) for a period up to 14 hours.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Powder in Type I glass vial. Pack of 1 vial.

6.6 Special precautions for disposal and other 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 to a final concentration of between 100 μg/ml and 200 μg/ml. 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 30ºC).

After preparation, the intravenous infusion solution can be used at room temperature (15 to 30ºC) 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 should be 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 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/1/02/225/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 August 2002.
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA): http://www.emea.europa.eu/

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Lonza Biologicals Inc.
101 International Drive
Portsmouth
New Hampshire
03801-2815 USA

Name and address of the manufacturer responsible for batch release

Lilly Pharma Fertigung und Distribution GmbH & Co. KG
Teichweg 3
D-35396 Giessen
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the version dated 18 April 2006 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

The Marketing Authorisation Holder will continue to submit yearly PSURs.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

Clinical aspects

1. "Further to uncertain conclusions of the XPRESS study investigating the possible interaction between Xigris and heparin, additional clarifications on the benefit/risk balance of Xigris are required. Therefore the MAH has committed to performing a placebo-controlled study in patients (who were either on low-dose prophylactic heparin or not receiving any thrombosis prophylaxis) with severe sepsis and documented organ failure (e.g. MOD or vasopressor dependent septic shock) when treated within a strictly defined time window, to assert the benefit/risk profile of Xigris."

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

Xigris 20 mg powder for solution for infusion
drotrecogin alfa (activated)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 20 mg of Drotrecogin alfa (activated).
After reconstitution with 10 ml of Water for Injection each ml contains 2 mg of Drotrecogin alfa (activated).

3. LIST OF EXCIPIENTS

Excipients: sucrose, sodium chloride, sodium citrate, citric acid, hydrochloric acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial, powder for solution for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion after reconstitution and dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/225/002

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL TEXT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Xigris 20 mg powder for infusion
For intravenous infusion after reconstitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

Xigris 5 mg powder for solution for infusion
drotrecogin alfa (activated)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 5 mg of Drotrecogin alfa (activated).
After reconstitution with 2.5 ml of Water for Injection each ml contains 2 mg of Drotrecogin alfa (activated).

3. LIST OF EXCIPIENTS

Excipients: sucrose, sodium chloride, sodium citrate, citric acid, hydrochloric acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial, powder for solution for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion after reconstitution and dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/225/001

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL TEXT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Xigris 5 mg powder for infusion
For intravenous infusion after reconstitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mg

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Xigris 20 mg powder for solution for infusion
Drotrecogin alfa (activated)

Please read all of this leaflet carefully. Please remember that you cannot take Xigris by yourself because both your illness and the use of this medicine need constant medical care.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT XIGRIS IS AND WHAT IT IS USED FOR

Xigris is very similar to a protein that occurs naturally in your blood. This protein helps to control blood clotting and inflammation. When your body has a severe infection, clots can form in your blood. These can block the blood supply to important parts of your body such as the kidneys and lungs. This causes an illness called severe sepsis which can make you very ill. Some people will die from this illness. Xigris helps your body to get rid of the clots and also reduces the inflammation caused by the infection.

Xigris is used to treat adults with severe sepsis.

2. BEFORE YOU ARE GIVEN XIGRIS

You should not be given Xigris:
- if you are allergic (hypersensitive) to drotrecogin alfa (activated) or any of the other ingredients of Xigris, or bovine (cattle-derived) thrombin (protein)
- if you are a child below the age of 18
- if you have internal bleeding
- if you have a brain tumour, or pressure on the brain
- if you are being given heparin at the same time (≥ 15 International Units/kg/hr)
- if you have a bleeding tendency which is not related to sepsis
- if you have a long-standing, severe problem with your liver
- if your platelet (a type of cell in your blood) count is low, even if this has been increased by a transfusion
- if you are at high risk of bleeding (for example):
  a) you have had surgery within the last twelve hours before you receive Xigris, or you are bleeding from a previous surgery, or you might have surgery while you receive Xigris
  b) you have been in hospital with a severe injury to your head, or you have had surgery on your brain or spine, or you have had a bleed in your brain (haemorrhagic stroke) within

the past three months, or you have abnormal blood vessels in your brain, or a mass in your head; you have an epidural catheter (a tube in your spine)

c) you have been born with bleeding tendencies
d) you have bled from your bowels within the last six weeks, unless treated adequately
e) you have had a major accident and are at increased risk of bleeding

Special care should be taken with Xigris if you are at risk of bleeding, for example:
- if you are taking other medicines which affect how your blood clots (for example medicines that dissolve blood clots, thin the blood, or medicines that inhibit platelets such as aspirin)
- if within the last three months, you have had a stroke caused by a blood clot
- if you have a known problem with bleeding

Xigris should not be used if you have a less severe form of sepsis (only one organ failure) and have recently had a surgical operation.

Using other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Caution should be employed when Xigris is used with other medicines that affect how your blood clots (for example medicines that dissolve blood clots, thin the blood, or medicines that inhibit platelets such as aspirin, non-steroidal anti-inflammatory medicines, or clopidogrel).

Pregnancy and breast-feeding
It is not known whether drotrecogin alfa (activated) causes damage to an unborn child or affects your ability to have babies. If you are pregnant your doctor will only give you Xigris if necessary.
It is not known whether drotrecogin alfa (activated) appears in human milk and therefore you should not breast-feed whilst treated with Xigris.

Important information about some of the ingredients of Xigris
This medicinal product contains approximately 68 mg sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

3. HOW XIGRIS IS USED

The recommended dose of Xigris is 24 micrograms (μg) per kilogram (kg) of body weight each hour for 96 hours.

A hospital pharmacist, nurse or doctor will have dissolved the Xigris powder in water for injection and sodium chloride solution. This liquid is then passed from a bag through a tube into one of your veins for a period of 96 hours.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Xigris can cause side effects, although not everybody gets them. Xigris increases the risk of bleeding which can be serious or life-threatening. Serious bleeding during the infusion period occurred in 1% (1 in 100) of patient with severe sepsis and in 2.4% (roughly 1 in 40) of patients treated with Xigris, with most bleeding in both groups occurring in the stomach and bowel. Bleeding into the brain was uncommon, occurring in 0.2% (1 in 500) of patients treated with Xigris.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. STORING XIGRIS

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the label.

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

6. FURTHER INFORMATION

What Xigris contains
- The active substance is 20 mg of drotrecogin alfa (activated) in each vial. Drotrecogin alfa (activated) is a version of a natural protein in the blood called Activated Protein C and it is produced by recombinant technology.
- The other ingredients are sucrose, sodium chloride, sodium citrate, citric acid, hydrochloric acid and sodium hydroxide.

What Xigris looks like and contents of the pack
Xigris is presented as a powder for solution for infusion in a vial.

A vial contains 20 mg of drotrecogin alfa (activated). After reconstitution with 10 ml of Water for Injection each ml contains 2 mg of Drotrecogin alfa (activated).

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Eli Lilly Nederland B.V., Grootslag 1-5, 3991 RA, Houten, The Netherlands
Manufacturer: Lilly Pharma Fertigung und Distribution GmbH & Co. KG, Teichweg 3, D- 35396 Giessen, Germany.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on {date}

This medicine has been authorised under "Exceptional Circumstances". This means that for scientific reasons it has been impossible to get complete information on this medicine. The European Medicines Agency (EMEA) will review any new information on the medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu

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The following information is intended for medical or healthcare professionals only:

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 30ºC).
   After preparation, the intravenous infusion solution can be used at room temperature (15 to 30ºC) 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 should be 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 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.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Xigris 5 mg powder for solution for infusion
Drotrecogin alfa (activated)

Please read all of this leaflet carefully. Please remember that you cannot take Xigris by yourself because both your illness and the use of this medicine need constant medical care.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT XIGRIS IS AND WHAT IT IS USED FOR

Xigris is very similar to a protein that occurs naturally in your blood. This protein helps to control blood clotting and inflammation. When your body has a severe infection, clots can form in your blood. These can block the blood supply to important parts of your body such as the kidneys and lungs. This causes an illness called severe sepsis which can make you very ill. Some people will die from this illness. Xigris helps your body to get rid of the clots and also reduces the inflammation caused by the infection.

Xigris is used to treat adults with severe sepsis.

2. BEFORE YOU ARE GIVEN XIGRIS

You should not be given :
- if you are allergic (hypersensitive) to drotrecogin alfa (activated) or any of the other ingredients of Xigris, or bovine (cattle-derived) thrombin (protein)
- if you are a child below the age of 18
- if you have internal bleeding
- if you have a brain tumour, or pressure on the brain
- if you are being given heparin at the same time (≥ 15 International Units/kg/hr)
- if you have a bleeding tendency which is not related to sepsis
- if you have a long-standing, severe problem with your liver
- if your platelet (a type of cell in your blood) count is low, even if this has been increased by a transfusion
- if you are at high risk of bleeding (for example):
  a) you have had surgery within the last twelve hours before you receive Xigris, or you are bleeding from a previous surgery, or you might have surgery while you receive Xigris
  b) you have been in hospital with a severe injury to your head, or you have had surgery on your brain or spine, or you have had a bleed in your brain (haemorrhagic stroke) within

the past three months, or you have abnormal blood vessels in your brain, or a mass in your head; you have an epidural catheter (a tube in your spine)

c) you have been born with bleeding tendencies
d) you have bled from your bowels within the last six weeks, unless treated adequately
e) you have had a major accident and are at increased risk of bleeding

Special care should be taken with Xigris if you are at risk of bleeding, for example:
- if you are taking other medicines which affect how your blood clots (for example medicines that dissolve blood clots, thin the blood, or medicines that inhibit platelets such as aspirin)
- if within the last three months, you have had a stroke caused by a blood clot
- if you have a known problem with bleeding

Xigris should not be used if you have a less severe form of sepsis (only one organ failure) and have recently had a surgical operation.

Using other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Caution should be employed when Xigris is used with other medicines that affect how your blood clots (for example medicines that dissolve blood clots, thin the blood, or medicines that inhibit platelets such as aspirin, non-steroidal anti-inflammatory medicines, or clopidogrel).

Pregnancy and breast-feeding
It is not known whether drotrecogin alfa (activated) causes damage to an unborn child or affects your ability to have babies. If you are pregnant your doctor will only give you Xigris if necessary.
It is not known whether drotrecogin alfa (activated) appears in human milk and therefore you should not breast-feed whilst treated with Xigris.

Important information about some of the ingredients of Xigris
This medicinal product contains approximately 17 mg sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

3. HOW XIGRIS IS USED

The recommended dose of Xigris is 24 micrograms (μg) per kilogram (kg) of body weight each hour for 96 hours.

A hospital pharmacist, nurse or doctor will have dissolved the Xigris powder in water for injection and sodium chloride solution. This liquid is then passed from a bag through a tube into one of your veins for a period of 96 hours.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Xigris can cause side effects, although not everybody gets them. Xigris increases the risk of bleeding which can be serious or life-threatening. Serious bleeding during the infusion period occurred in 1% (1 in 100) of patient with severe sepsis and in 2.4% (roughly 1 in 40) of patients treated with Xigris, with most bleeding in both groups occurring in the stomach and bowel. Bleeding into the brain was uncommon, occurring in 0.2% (1 in 500) of patients treated with Xigris.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. STORING XIGRIS

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the label.

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

6. FURTHER INFORMATION

What Xigris contains
- The active substance is 5 mg of drotrecogin alfa (activated) in each vial. Drotrecogin alfa (activated) is a version of a natural protein in the blood called Activated Protein C and it is produced by recombinant technology.
- The other ingredients are sucrose, sodium chloride, sodium citrate, citric acid, hydrochloric acid and sodium hydroxide.

What Xigris looks like and contents of the pack
Xigris is presented as a powder for solution for infusion in a vial.

A vial contains 5 mg of drotrecogin alfa (activated). After reconstitution with 2.5 ml of Water for Injection each ml contains 2 mg of Drotrecogin alfa (activated).

Marketing Authorisation Holder and Manufacturer
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Manufacturer: Lilly Pharma Fertigung und Distribution GmbH & Co. KG, Teichweg 3, D- 35396 Giessen, Germany.

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This leaflet was last approved on {date}

This medicine has been authorised under "Exceptional Circumstances". This means that for scientific reasons it has been impossible to get complete information on this medicine. The European Medicines Agency (EMEA) will review any new information on the medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu

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The following information is intended for medical or healthcare professionals only:

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 30ºC).
   After preparation, the intravenous infusion solution can be used at room temperature (15 to 30ºC) 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 should be 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 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.