European Medicines Agency

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ASSESSMENT REPORT
FOR
Xigris

International Nonproprietary Name:
drotrecogin alfa (activated)

Procedure No. EMEA/H/C/396/S/28

Marketing Authorisation Holder/Applicant: Eli Lilly Nederland B.V.

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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I. SCIENTIFIC DATA PROVIDED BY THE MARKETING AUTHORISATION HOLDER

1.1 Chemical and pharmaceutical aspects

No additional data have been provided with this submission.

1.2 Preclinical aspects

No additional data have been provided with this submission.

1.3 Clinical aspects

The MAH has submitted the following documents to support the 6th annual re-assessment of Xigris:

- data from completed and ongoing clinical studies that have become available during the past 12 months
- update related to the current specific obligation
- publications occurring during the reporting period
- update on spontaneous safety data from the market
- Protocol Amendment Summary – Study F1K-MC-EVDK
- additional Safety Information received since the last PSUR (22 November 2007 - 21 July 2008)

1.3.1 Update on clinical trials during the past annual re-assessment

As of 21 July 2008, a total of up to 7243 adult patients have been exposed to Xigris in completed and ongoing clinical trials. Studies EXTEND, RESPOND, and APEX are finalised. Study PROWESS-SHOCK (new Specific Obligation) has started. Last year, 7190 adult patients had been exposed in clinical trials. Thus, 53 new patients have been exposed during the last 12 months.

EXTEND (F1K-MC-EVBQ)
The results of **EXTEND** "a placebo-controlled Phase IIIb study to determine the efficacy and safety of extended Xigris therapy in patients with persistent requirement for vasopressor support after a 96-h infusion with commercial Xigris", have been submitted in April 2008 (FUM 056) and assessed. The primary objective is to investigate whether continued administration of Xigris for up to 72 additional hours results in more rapid resolution of vasopressor-dependent hypotension versus placebo.

The main conclusion of this study is that the primary outcome of vasopressor-dependency was not significantly affected by a 72-h extended infusion of DAA after a 96-h infusion of the commercial product. The baseline difference with regard to cardiovascular sequential organ failure assessment (SOFA) score may have partly influenced these results. In addition, the reduction of the sample size may have resulted in an underpowered trial, because the treatment effect was less than anticipated. However, there was not the smallest trend for a benefit of extended treatment with Xigris beyond 72 h.

Since the primary outcome parameter of this study is not influenced by the treatment, it has no impact on the current indication.
The MAH was asked by the CHMP to indicate when they plan to publish, or otherwise make public, the results of this study and to discuss the potential description of these results in section 5.1 of the SPC and/or the addition of a warning that any prolongation of treatment beyond 4 days in patients with severe sepsis and at least 2 organ failures is futile. The MAH answerd (FU2 056.1) that actions have been taken to make these results readily available to those in the intensive care community. The MAH also mentioned that, given that EXTEND was a relatively small exploratory study that neither proves or disproves the utility of infusions of drotrecogin alfa (activated) longer than 96 hours and that the soon to be completed RESPOND study will generate additional data in this regard, it would be appropriate to await the results of the RESPOND study before deciding on what information may be

relevant to provide in the SPC related to longer (or shorter) infusions of drotrecogin alfa (activated). These responses are currently under assessment (FU2 056.1).

APEX (F1K-MC-O014) This is a Phase II exploratory study of adjuvant treatment of pulmonary embolism with Xigris. The main objective is to assess the safety of a short (12-h) infusion of Xigris combined with therapeutic doses of low molecular weight heparin versus low molecular weight heparin alone in treatment of acute submassive pulmonary embolism. Warfarin therapy is initiated on or after Study Day 3.
First patient visit was in September 2004. In November 2007, the 47th of 48 planned patients was reported to have a small subdural haematoma 4 days following administration of the study drug. This event was the only serious adverse event reported during this reporting period. As per the predefined protocol guidelines, this event prompted a review of safety by the study data safety monitoring board (DSMB) who recommended: "In consideration of the low recruitment rate of the other three participants in the APEX study, the completion of the trial should be envisaged in order to prevent further delays to obtaining final results". Their final conclusion was: "The DSMB recommends to stop recruitment of further patients and to finish the trial at this stage. The adverse events listed above do not reveal major safety problems arising within the study and can be considered to be associated in patients with high co-morbidity in the elderly patient suffering pulmonary embolism under the given antithrombotic medication".
The MAH has accepted the DSMB's recommendation and has ceased further recruitment into the study. Data lock for the study took place on 08 August 2008. The abbreviated study report for the APEX study was submitted to the CHMP in January 2009 and is currently under assessment (FUM 058).

RESPOND (F1K-MC-EVDK)
This is a Phase II exploratory study investigating the potential role of protein C levels as a biomarker to help guide therapy with Xigris, specifically comparing higher doses and longer (or shorter) infusion of Xigris with standard therapy (24 µg/kg/h for 96 hours). The first patient was entered into the study in November 2006, which is currently being conducted at sites in the following European countries: Belgium, France, Germany, Finland, Sweden, Italy and the United Kingdom, with additional sites in Canada and the United States.

The power calculation for the study was based on including a total of 422 ITT patients, comparing all patients receiving alternative therapy to those receiving standard therapy. Three interim analyses conducted by an internal data monitoring committee (DMC) were planned, one before each dose increase in the alternative therapy-higher dose/variable duration group. The activities of this internal DMC are defined within the DMC charter and function in a similar fashion as would an external DMC.

Patients potentially receiving a higher dose of Xigris are those that remain severely protein C deficient after the "common therapy lead-in period" where all patients receive standard dose Xigris for 24 hours. Based on assumptions made from the pattern of protein C results from PROWESS, it was predicted that approximately 40% of patients would have severe protein C deficiency at this time point. However, in the current RESPOND study, this number is rather ~20%. Thus when the first interim analysis occurred on 7 May 2008, although there were approximately 20 patients who had received Xigris at a dose of 30 µg/kg/h as planned, ITT patients totalled 200 rather than ~100 as initially predicted. If this pattern is maintained, the total planned sample size of 422 ITT patients will be achieved and the study will complete before the 2 highest dose groups (42 and 48 µg/kg/h) are reached.
Following the first DMC meeting the following information was sent to sites on May 13th 2008: "The DMC for this trial met on 7 May 2008 to conduct a scheduled interim analysis on a locked database of 190 patients receiving randomized therapy. After receiving additional analyses, the DMC recommended that Lilly suspend enrolment in the study until the protocol can be amended due to a safety signal (higher mortality) in the alternative therapy arm of the moderate protein C deficiency subgroup. The specific recommendation is to suspend enrolment of all patients and amend the protocol so that all patients receive a minimum of 96 hours of Xigris. As per the protocol, the DMC agreed to a future dose increase in the severe protein C deficiency alternative therapy group. Lilly has decided to accept the DMC recommendation.

The amended protocol was internally approved on 23 May 2008, and submitted for regulatory and ERB approval as appropriate. As recommended by the DMC, the primary change to the protocol was the

removal of the option for infusions shorter than the standard therapy of 96 h. A few minor errors that had been previously noted in the protocol were also corrected. The first patient was enrolled under the amended protocol on 23 July 2008. The RESPOND study team as well as all study sites remain blinded to the interim analysis data.
As of 21 July 2008, 240 patients have received any Xigris infusion, including 211 ITT patients. Although a number of sites are actively screening for patients, it is anticipated that recruitment will not get back to pre-amendment levels until late September 2008, and it is now predicted that recruitment will not be completed until towards the end of Q3 2009. This delay will also move the predicted completion of the study report into Q2 2010.

As of 21 July 2008, based on blinded serious adverse event reports, out of 240 patients treated, 57 patients have reported at least one serious adverse event, of which 14 (5.8%) reported having serious bleeding event, of which 3 were CNS bleeds. These rates are higher than those reported from Xigris patients in PROWESS; however, they are more similar to the reported serious adverse event rates for the Phase 2 study to determine the safety, pharmacokinetics and effective dose range and dosing duration for rhAPC in severe sepsis (EVAA), and the serious bleeding event and CNS bleeding event rates from the open-label study ENHANCE (6.6%). These events were included in the DMC's assessment of safety during the interim analysis, where it was recommended to continue with the next highest dose of Xigris and also with the possibility of longer infusions.

The CHMP was of the opinion that the explanations on the changes in protocol and in timelines of study RESPOND are acceptable. The CHMP noted that the completion of the study report is planned for Q2 2010, except if the DMC stops the study for futility or safety after 300 ITT patients have been treated. It is expected that the MAH will inform the CHMP should that occur. From the preliminary (blinded) information disclosed so far, it appears that infusions of Xigris shorter than 96 h are not recommendable. This does not impact the SPC or the benefit/risk balance of Xigris under the current conditions of use.

Study F1K-US-EVDA
This is a prospective, nonrandomised, multicentre, open-label clinical trial of Xigris in patients with septic shock. Although this study has been included in previous safety updates, because it was a relatively small, nonrandomised, exploratory study being performed at US sites only, it has not been reviewed in previous clinical overviews. The study evaluated the vasopressor requirement, haemodynamic response, and measures of tissue perfusion with the administration of Xigris as part of physician-directed therapy in patients with septic shock as compared to a control cohort of patients with septic shock in which the physician chose not to treat with Xigris. A total of 43 patients were entered into the study. Two nonfatal treatment-related serious bleeding events were reported in patients receiving Xigris: a haemothorax during study drug infusion and a peritoneal haemorrhage post study drug infusion. No serious bleeding events were reported in control cohort patients not receiving Xigris.

The MAH will provide the clinical study summary in the forthcoming annual reassessment application which will be submitted in October 2009.

PROWESS-SHOCK (F1K-MC-EVDP)
This is the new placebo-controlled study in fulfilment of the current Specific Obligation for Xigris. This study is run 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.

The CHMP has requested that the MAH provide yearly updates on the following in each Annual Reassessment with the following information

(1) the names of centres recruiting patients for that study,
(2) their worldwide allocation,
(3) the prescriptions (and recommendations concerning the use of Xigris at each participating centre,
(4) the number of patients included,
(5) the blinded opt-out rate.

This study is discussed in section 2.1.1 of this report.

1.3.2 Publications occurring during the reporting period

The CHMP has previously requested that the annual licence reassessment should include a discussion of publications related to Xigris during the reporting period. The MAH has provided a list of publications based upon the MEDLINE database (July 2007 through July 2008) using the search terms: Xigris, drotrecogin alfa (activated), recombinant human activated protein C, and activated protein C. Below is a review of a selection of those that appear to have some clinical relevance to the use of Xigris.

Nonclinical Studies

Research has focused on activated protein C's (APC) activity at the microvascular and endothelial levels, and particularly how its activity may be mediated though signalling pathways (endothelial protein C receptor [EPCR], protease-activated receptor 1 [PAR 1], and sphingosine-1-phosphate receptor 1) independent of its anticoagulant and antfibrinolytic effects. This research has been facilitated by the recent development of APC variants with predominantly PAR 1 or anticoagulant effects. In addition, the use of animal models has expanded in recent years with the realisation that species specificity may be less important than initially thought when investigating the nonanticoagulant properties of APC and, also, through the availability of rat and mouse rAPC. Yet, as was also highlighted in last year's report, some of the *in vitro* experiments have used very much higher concentrations of APC than plasma levels found in septic patients treated with 24 μg/kg/h Xigris so may not be relevant to severe sepsis treatment. For instance, opposing effects of APC on barrier protection of endothelial cells have been reported independently by at least 3 laboratories in the previous years (Zeng et al. 2004; Feistritzer et al. 2005; Bae et al. 2007). At therapeutic concentrations of APC (1 nM or less), APC reversed endothelial leakage induced by thrombin or other cytokines, such as IL-1β. At high concentrations of APC (10 nM or higher depending on the type of endothelial cell used), APC induced endothelial leakage. These data illustrate that some of the effects of APC at very high concentrations may differ from those at pharmacologic levels.

The CHMP noted that there is a tremendous increase in non-clinical research activity regarding APC. Multiple effects of APC, in particular on microvascular and endothelial structures, are being reported beyond the simple anticoagulant action. Some of these effects could partly explain the beneficial effects of Xigris. The suggestion, made last year, that APC could facilitate some oncogenic processes, including angiogenesis, has not been supported based by recent literature. Overall, these non-clinical developments are important as they may point to potential ways of improving the selection of patients who should receive Xigris.

Clinical Studies/Case Series/Case Reports

- The Surviving Sepsis Campaign (Dellinger et al. 2008) published updated guidelines for management of severe sepsis and septic shock. The following are the recommendations related to Xigris:

"We suggest that adult patients with sepsis-induced organ dysfunction associated with a clinical assessment of high risk of death, most of whom will have APACHE II ≥25 or multiple organ failure, receive rhAPC if there are no contraindications (weak recommendation). Relative contraindications should also be considered in decision making. We recommend that adult patients with severe sepsis and low risk of death, most of whom will have APACHE II <20 or one organ failure, do not receive rhAPC (strong recommendation)".

The MAH was requested to discuss why the Surviving Sepsis Campaign has downgraded the level of evidence for Xigris in its 2008 guideline and whether PROWESS pivotal trial is now considered as a largely suboptimal trial.

The MAH in its response was of the opinion that above mentioned recommendations may reflect uncertainty related to the findings of several studies following PROWESS (ADDRESS, RESOLVE, and XPRESS) rather than reconsiderations concerning PROWESS. For example, the ADDRESS study found no benefit in low risk patients and, particularly, the finding of higher mortality in single organ dysfunction patients with recent surgery. The recommendations are also in keeping with the general level of equipoise within the critical care community. The MAH noted however, that within the original sepsis "bundle" concept, which was provided as a tool to help implement the original guidelines and to audit process

improvements related to implementation of the Surviving Sepsis Campaign guidelines, compliance with the Xigris component of the bundle was deemed to have been fulfilled by the presence of a written policy in the ICU defining the use of Xigris, even if this policy was not to use or to restrict the use of Xigris beyond the SPC. Thus, hospitals only needed a policy as to how to use Xigris and did not have to use it at all to be measured as being "compliant with the guidelines". Thus, the original guideline was not as favourable to Xigris as it may have appeared. The MAH was not of the opinion that the new Surviving Sepsis Campaign guidelines represent a specific "downgrading" of the PROWESS study, but a reflection of a new grading system and new clinical trial data.

The involvement of an Ad Hoc Expert Group was deemed necessary to discuss amongst other, whether the downgrading of the "evidence grade" for a recommendation for the use of Xigris by the Surviving Sepsis Campaign (guideline published in January 2008) to a "weak recommendation" changed the use of Xigris in clinical practice.
There was a consensus among the experts that the downgrading of the "evidence grade" for a recommendation for the use of Xigris by the Surviving Sepsis Campaign to a "weak recommendation" has not been a driver in any way for a different clinical use of the product. The change of the guideline is a secondary event as the clinical practice is not driven by this guideline only. Some experts reminded the group that the Surviving Sepsis Campaign was not an evidence-based process but relied mostly on the opinion of experts. Several experts specified that the use of Xigris in their hospital or unit (selection of patients, timing, etc.) was controlled by strict protocols that had not been changed following the new (2008) SSC guideline.

- The *Gentry et al.* study (*Crit Care Med*, January 2009) is a retrospective medical record interview study in 73 patients in 2 tertiary care hospitals in Oklahoma City, OK, USA, showing that serious bleeding events occurred in 7 of 20 patients (35%) with any baseline "bleeding precaution" (as defined in the US label) *vs* only 2 of 53 patients (3.8%) without any bleeding precautions ($p<0.0001$). In addition, more patients with a baseline bleeding precaution died compared with patients without any bleeding precautions (65% vs. 24.5%, $p=0.0015$). Most of the baseline "bleeding precautions" are contra-indications in the EU SPC so this retrospective analysis has not been considered by the CHMP as a new serious concern in the EU.

- There has been only 1 randomised, placebo-controlled study published during this reporting period. Liu et al. (2008) tested the utility of APC versus placebo for the treatment of acute lung injury (ALI) in patients not indicated for commercial treatment because of severe sepsis. There was no difference in ventilator free days, mortality, or lung injury score. Given that there was no difference in the primary objective of ventilator free days, the data safety monitoring board chose to stop the study at 75 patients, rather than allowing enrolment to the planned sample size of 90 patients.

The results from a number of registries and audits of Xigris use in clinical practice have been published.

- Dhainaut et al. (2007) reported the findings of the PREMISS observational cost effectiveness study of adult patients recruited before and after licensure of rhAPC in France. Post-license patients were younger, had less co-morbid conditions and had failure of more organs than did pre-license patients. The incremental cost-effectiveness ratio was €33,797 per quality adjusted life-year (QALY) gained. This is higher than the previously published PROWESS-based estimates. They conclude that this is because of a lower absolute reduction in 28-day mortality (-3.3% versus -7.4% in the subgroup with multiple organ failure in PROWESS) rather than being due to hospital costs. However, Rowan et al. (2008) report effectiveness results from a UK national audit of Xigris use similar to PROWESS. Patients receiving Xigris in clinical practice were younger and more severely ill (77% of patients had three or more organs failing) than in the pivotal study but had less co-morbidity. Nonrandomised estimates for the effectiveness of Xigris were consistent with the findings of PROWESS, which appeared greatest in those treated within the first 24 h and those with greater disease severity. In the UK audit, 61% of patients were treated within 24 h of the first organ failure. One or more serious adverse events, of which 77% were serious bleeding events, occurred in 8% of patients. This is higher than what was seen in the PROWESS (3.5%) and ADDRESS (3.9%) results but closer to the ENHANCE results (6.2%).

- Also in the UK, Ridley et al. (2008) performed a retrospective review of ICU charts and medical records of patients who had received Xigris in 5 of the largest users' centres in England. Between December 2002 and November 2005, 351 patients received Xigris. They conclude that expected mortality derived from both the APACHE II score and organ dysfunctions suggests that Xigris does reduce mortality. Serious adverse incidents occurred in 5.1% patients.

- Wheeler et al. (2008) also reported observational data collected retrospectively from patients who received Xigris as part of physician-directed treatment in 5 US teaching institutions. Patients treated in clinical practice were younger, had more co-morbidities, greater severity of illness, and longer mean time from severe sepsis onset to the start of Xigris compared to PROWESS. Although overall hospital mortality in clinical practice patients was higher than PROWESS, for patients treated within 1 day of severe sepsis onset it was similar to Xigris-treated PROWESS patients with an APACHE II score ≥25. Serious bleeding events during infusion were noted in 4.0% of clinical practice patients.

- Vincent et al. (2008) used a logistic regression equation, controlling for age and the presence or absence of organ dysfunction, in non-Xigris-treated patients from Belgium in the PROGRESS registry to calculate the expected mortality rates for Xigris-treated patients in the Belgian reimbursement registry. The observed hospital mortality of the 286 Belgian registry patients was 50.7% compared to a predicted mortality of 63.5, implying an adjusted absolute mortality reduction of 12.8% with Xigris.

- Afessa et al. (2008) concluded that the introduction of multiple evidence-based protocols in the Mayo Clinic was associated with improved outcome in critically ill medical patients. The use of Xigris was 1 of 4 evidence-based protocols (lung protective strategy for acute lung injury, activated protein C for severe sepsis/septic shock, intravenous insulin for hyperglycaemia control, and a protocol for sedation/analgesia) that were introduced in a medical ICU.

There have been a number of case reports published describing use of Xigris within and also outside the current licensed indication. These were part of the annual licence reassessment dossier.

There have also been a number of publications related to potential means of identification of patients who may benefit most from Xigris treatment, including the use of an appropriate biomarker. For instance, Shorr et al. (2008) concluded that based on systematic analyses of 11 variables measured in severe sepsis clinical trials, protein C level at baseline and day 4 was the only variable consistently correlated with both Xigris treatment effect and survival, and John et al. (2007) reported that patients with severe sepsis who have elevated troponin have increased mortality; these may be patients in whom treatment with APC could improve outcome. Chapital et al. (2008) suggested that transcutaneous partial pressure of oxygen as an indicator of microcirculatory perfusion may help to identify which septic patients may benefit from APC.

There have been several review articles regarding the use of Xigris in sepsis patients. Many of these reviews, if not all, highlight the same issues that were discussed during previous annual reassessments of the Xigris EU licence. For instance, Barie (2007) discussed some of the controversies leading to and implications of performing the PROWESS SHOCK study. Kalil and Sun (2008) suggest that, using a Bayesian design, a confirmatory trial with approximately 600 patients with severe sepsis and high risk of death can provide a convincing answer for both the mild and moderate skeptic physicians concerning the efficacy of Xigris in severe sepsis. However, such a Bayesian approach requires acceptance of previously generated data, and in effect an acceptance of a larger p-value indicating statistical significance, so would not provide the "confirmatory" study that has been requested.

Marti-Carvajal et al. (2008) provided an update of the Cochrane Database review which was discussed in last year's report where the following was noted: "in analysing those patients with APACHE ≥25, similar to the meta analysis published by Friedrich (2006) discussed in last year's clinical overview, a relatively high weighting has been given to the ADDRESS study, even though PROWESS provided the vast majority of patients and events (Williams et al 2006). The authors did not include an analysis of ADDRESS and PROWESS using the EU indicated population with multiple organ dysfunction, and thus this publication has limited applicability to the EU". The MAH has previously submitted to the CHMP as well as published (Williams et al. 2006) a combined analysis of multiple organ dysfunction patients from

PROWESS and ADDRESS indicating a significant treatment benefit. No new data analysis was provided in current Cochrane review.

Some review articles suggest new avenues for the use of rhAPC. For instance, Perri and Fumagali (2008) reviewed trials evaluating the use of Xigris in transplant recipients experiencing sepsis. They conclude that "coagulation inhibitors represent major mechanisms to control microvascular dysfunction during ischemia–reperfusion and sepsis, and additional clinical trials are necessary to evaluate the optimal timing and dosing of Xigris and to better assess its efficacy and safety in transplant recipients". Gilbert and Marsden (2008) reviewed the potential role of activated protein C and diabetic nephropathy. Lust et al. (2008) proposed that the protein C pathway has an important role in governing intestinal microvascular inflammation and might provide a novel therapeutic target in the management of inflammatory bowel disease.

Investigator sponsored study

Several investigator sponsored studies are currently ongoing in the EU. The CHMP was made aware of a large non-sponsored, prospective, multicentre, randomised, blinded, 4-arm, placebo-controlled (1 arm) study comparing Xigris (standard posology; 1 arm) with low-dose corticoids (iv hydrocortisone TID + oral fludrocortisone QD; 1 arm) and with the combination of Xigris and corticoids (1 arm) in 1280 patients within 24 h of septic shock. The study will be run in the Assistance Publique Hôpitaux de Paris). The endpoints are 28-day and 90-day mortality; safety will be closely monitored (http://clinicaltrials.gov/ct2/show/NCT00625209). The study start date was March 2008 and its estimated primary completion date is December 2011. It is difficult at the present time to know if the results from that study will constitute a valuable addition to the Xigris outcome database.

1.3.3 Update on spontaneous safety data from the market

PSUR 8, submitted in January 2008, covered the period 22 November 2006 to 21 November 2007.
The MAH has included an updated safety report in their submission (Module 5.3.6). This report reviews the 8-month safety data from 22 November 2007 to 21 July 2008. An estimated 12,249 patients have been treated with Xigris worldwide within this reporting period (~10% of the current total). The rate of exposure to Xigris during this period is slightly less than the last PSUR period taking into account the different lengths of the reporting periods. The review of spontaneous events reported in this reporting period is complicated by the fact that 15 serious bleeding events were received from the Italian regulatory authority that had actually occurred in previous reporting periods, as far back as 2003. These events are described in the current report but not included in the calculation in order to keep reporting trends over time understandable.

The main observation points of PSUR 8 are the following:
There had been a suggestion of lower reporting of CNS bleeding events in the non-EU regions in last year's report, and, in this reporting period, the rate of reporting has fallen lower in the non-EU regions and increased in the EU. Review of these cases does not reveal an apparent cause for this increase in reporting in the EU. Given that the rate of reporting of CNS bleeds in the non-EU regions fell, the global rate of reporting of CNS bleeds for this period has not increased and is similar to PSUR 7. Because of the limitations of spontaneous reporting, particularly where the number of events is low, it cannot be determined at this stage if this represents a fluctuation or a change in the trend of reporting CNS bleeding events between regions.

Regarding use of Xigris in paediatric patients, only 1 current report in a patient less than 18 years old from an EU member state has been received in this reporting period. This report involved a 16-year-old patient with meningococcal sepsis and severe disseminated intravascular coagulation (DIC). In addition, 1 report that was received during this reporting period related to a patient treated in Italy in 2003 and so was not included in the tabulation of reports for this period. Since the cut-off for submission of the responses to the PSUR 8 questions, 1 additional paediatric report (from Brazil) has been received, reporting 2 bleeding events (from the nose and mouth) in a 15-year-old patient. Also, since the submission of the PSUR responses, the severe DIC report above has now been listed as a bleeding event. However, the overall conclusion that there has been only 1 report for an EU member state during this reporting period remains unchanged.

During the 8-month reporting period, 4 case reports were identified that met the criteria for an accidental overdose or involved a medication error. This rate is within the reporting fluctuations seen between previous PSURs.

PSUR 9 submitted in January 2009, covered the period 22 November 2007 to 21 November 2008.
During the period of this report, reviews of serious bleeding/serious central nervous system (CNS) bleeding reactions (especially in paediatric patients 17-years of age and younger), thrombocytopenia, convulsions, ECG ST segment elevation/troponin increased/chest pain and a cumulative overdose analysis were performed.

During the reporting period, a total of 16,575 courses of treatment estimated were administered in all global markets. This corresponds to an estimated patient exposure of 16,575 worldwide. In comparison, it was estimated that 19,523 courses of treatment of drotrecogin alfa (activated) were sold worldwide during the previous 1-year period (decrease of +/- 15%). The estimated cumulative worldwide exposure during the period 21 November 2001 through the cut off date of 21 November 2008 is 133,255 courses of treatment.

A total of 260 health care professional (HCP) reports (containing 379 reactions) received during the reporting period are included in the line listing. Of these 379 reactions reported, 315 were classified as serious (185 unlisted and 130 listed) and 64 were non serious (55 unlisted and 9 listed). The number and types of reports and the demographics from this PSUR are generally consistent with the information presented in previous PSURs except for "vascular disorders". The increase in the number of "vascular disorders" SOC cases reported is partly due to a larger number of retrospective cases added to the database from clinical trials and regulatory authorities during this reporting period.
Thus, the highest proportion of reactions (16.1%) was from the "vascular disorders" SOC and consisted mainly of haemorrhage (50/61 total reactions). The second highest proportion of reactions (13.7%) was from the "investigations" SOC and consisted mainly of activated partial thromboplastin time prolonged (15/52 total reactions) and platelet count decreased (11/52 total reactions). The third highest proportion of reactions (12.9%) was from the "general disorders and administration site conditions" SOC and consisted mainly of death (38/49 total reactions).

A total of 275 HCP reports (containing 309 reactions) received during the reporting period are included in the line listing. The "Investigations" SOC accounts for the highest proportion of reactions (24.9%) of which activated partial thromboplastin time prolonged (21/77 total reactions) and platelet count decreased (20/77 total reactions) are the most reported. The second proportion of reactions (13.3%) was from the Vascular disorders SOC and consisted mainly of haemorrhage (32/41 total reactions) and haematoma (3/41 total reactions). This is consistent with the information provided in the previous PSUR.

During the period of this report, reviews of serious bleeding/serious central nervous system (CNS) bleeding reactions (especially in paediatric patients 17-years of age and younger), thrombocytopenia, convulsions, ECG ST segment elevation/troponin increased/chest pain; and a cumulative overdose analysis were performed.

Finally, during the current reporting period, one issue was identified with the overdose language in the current Reference Safety Information (RSI). A change to the RSI for drotrecogin alfa (activated) is recommended within Section C.9 regarding overdose: a case of drotrecogin alfa (activated) reported an administration rate overdose greater than that currently listed in the RSI.

II. DISCUSSION AND CONCLUSION ON CLINICAL SPECTS

2.1 Discussion on clinical aspects

2.1.1 Specific obligation 051 (PROWESS-SHOCK (F1K-MC-EVDP)

The MAH was asked by the CHMP to provide an update to the CHMP with regard to recruitment in the ongoing PROWESS-SHOCK study.

In July 2009 the MAH estimated that last patient visit will occur approximately 1 year later than initially communicated to the CHMP. Based on this timeline, provisional study results could be made available in Q4 2011, during the then ongoing annual licence reassessment, and the final study report could be submitted as part of the next 5-year renewal dossier in February 2012.

The CHMP is supportive of the PROWESS SHOCK clinical trial as it will help better define the patient population. The CHMP was however concerned by the fact that the results of the study will become available later than initially expected.

In August 2009 the MAH provided updated timelines, and estimated that patients' enrolment can be completed 4 months earlier than communicated previously, and that a study report can be made available to the CHMP 2 months earlier than originally planned. This would lead to the submission of the final study report by Q2 2011.

The Ad Hoc Expert Group was therefore asked to discuss whether the results of the PROWESS-SHOCK study could be obtained faster than currently proposed by the MAH and if additional means can be proposed to accelerate the study.
There was a consensus among experts that the MAH is currently doing the maximum to ensure a good recruitment in the trial. No expert suggested additional means to accelerate the study. Some experts were however of the opinion that the suspension of the marketing authorisation could facilitate the enrolment.
Regarding the impact of a potential suspension of the MA on the recruitment, there was not a full consensus among the experts. The majority view (7/11) was that a suspension of MA would seriously hurt the trial through reduced or halted recruitment and would jeopardise its scientific validity, whereas 3/11 thought it would facilitate recruitment and 1/11 thought there would be no change.

With regard to PROWESS-SHOCK, the MAH clarified the following:

- When the proposed timeline for the study was communicated to the CHMP in February 2007, the protocol had not been finalised and a number of key factors were still uncertain (e.g., the protocol required the creation of a specific definition for septic shock). That took some additional time.

- It was not clear that US recruitment would subsequently prove to be so much lower than it was in PROWESS.
- The timeline communicated to the CHMP in May 2009 included the MAH's efforts to get the study timeline back on track as well as the need to be realistic. The planned number of sites to be initiated was increased from 250 to 300. New countries and non-US sites were added. In the 4 months since then, recruitment has exceeded this plan. The MAH now feels more confident that recruitment targets could be further improved, particularly as recruitment has continued to increase in the early summer period. Based on site performance during the past 6 months, the MAH anticipates that patient enrolment can be completed 4 months earlier than communicated in the response submitted in May 2009. The MAH will also explore a number of options to ensure that the current recruitment rates are maintained and potentially improved.
- The study report of PROWESS-SHOCK will be made available to the CHMP more quickly. The MAH proposes producing a "28-day" final study report based on locked, validated data that includes the primary outcome (28-day mortality) and key secondary outcomes, including safety. This report would then be followed by another study report that includes 6 month follow up data

together with the 28-day analyses not included in the first report. The first report could be completed approximately 2 months earlier than originally planned.

- As defined in the protocol and agreed with the CHMP during the 5-year renewal procedure, in the event that lower than expected mortality or higher than expected use of commercial Xigris is observed during the study, the sample size will be increased by up to 500 patients, which would impact the timeline.
- The MAH is committed to completing PROWESS-SHOCK as part of its EU licensing requirements.

The MAH therefore committed to the timelines mentioned in the below table:

Activity	Feb 2007 Timeline	July 2009 Timeline	New Proposed Timeline (September 2009)
Last patient visit (28-day study period)	**Q3 2010**	**Q3 2011**	**Q1 2011**
Database lock	**Q3 2010**	**Q3 2011**	**Q2 2011**
Study report completed (28-day study period)	**Q1 2011**	**Q1 2012**	**Q2 2011**
Submission of study report to CHMP	**Q1 2011**	**Q1 2012**	**Q2 2011**

The MAH committed to update the CHMP on the progress of recruitment and overall mortality in PROWESS-SHOCK every 6 months.

The CHMP notes the MAH's efforts, and apparent success, to speed up recruitment in PROWESS-SHOCK and to provide the 28-day results to the CHMP in an accelerated fashion, with a probable reduction of the initial delay from 1 year to 6 months.

2.1.2 Pharmacogenomic data

The CHMP has been made aware of a public presentation, entitled "Pivotal Trials in PGx", which included preliminary pharmacogenetic biomarker data about Xigris by a Lilly expert, at a large international DIA- and FDA-supported pharmacogenomics meeting in Mexico in May 2008. During that presentation Xigris data was used to illustrate the challenges of developing a clinical biomarker, highlighting biomarker sensitivity and specificity. The presentation made reference to preliminary, unconfirmed genetic data, where protein C and serpine1 polymorphisms subdivided Xigris treated patients in the PROWESS trial into 3 subgroups with apparent differential efficacy. The MAH has been exploring the role of genetic markers including the rs2069912 SNP of protein C (also implicated in higher sepsis mortality in East Asian patients [Russell et al., Hum Genet 2008]) and the rs7242 SNP of serpine1 in the response to Xigris. A combination of these SNPs is linked to an increased risk of coagulation dysfunction after developing sepsis (Mooder et al., and Sirius Genomics, 2008). The MAH had not informed the CHMP of these important pharmacogenetic data related to Xigris because it was not felt by the MAH to be sufficiently developed for formal regulatory review, and because no study report or published manuscript was available, these data has not been submitted to the CHMP. The MAH's primary interest in regards to development of a potential biomarker to guide therapy with Xigris has focused on the multipurpose biomarker, protein C, which is being prospectively researched in the RESPOND Ph II exploratory study. In addition the new placebo-controlled PROWESS-SHOCK study will investigate as a secondary objective if a differential treatment effect is evident in patients with severe protein C deficiency.

The MAH has also investigated the potential utility of other proteins measured as part of the PROWESS study to act as biomarkers. This data was published earlier this year (Shorr et al. 2008) and was included in the publication review of the current ALR. It concluded that based on systematic analyses of the

11 variables measured, protein C was the only variable consistently associated with both Xigris treatment effect and survival.

The MAH also clarified how genetic information was collected: A company approached the MAH to analyse the remaining genetic samples from PROWESS to investigate single nucleotide polymorphisms (SNPs) in coagulation and inflammation genes for association with response to Xigris. Three (3) independent datasets (Saint Paul's Hospital (SPH), Vasopressin and Septic Shock Trial (VASST study) and PROWESS APACHE II ≥25 score cohort) are available to analyse the association between response to Xigris and these SNPs.

The Protein C SNP (rs2069912) was associated with risk of death from sepsis in the Saint Paul's Hosptial (SPH) cohort. SNPs in SERPINE 1 plasminogen activator inhibitor-1 (PAI-1) were found to be associated with mortality outcome with Xigris Therapy in the PROWESS Cohort. A combination genotype of the C allele of the protein C SNP rs2069912 T/C and the T allele of the PAI-1 (SERPINE1) rs7242 T/G has been defined as Improved Response Polymorphism (IRP)+/+. This combination was strongly associated with a positive effect of Xigris treatment in patients who have severe sepsis and high APACHE II scores, based on retrospective analysis of three different datasets (SPH, PROWESS, VASST). When summary results from all three cohorts were combined (n=1381 patients), IRP+/+ patients made up 37.6% of the population and had a 19.7% absolute risk reduction in 28-day mortality in response to Xigris (23.9% *vs* 43.6% in placebo), which corresponds to an odds ratio of 0.40 (CI=0.26–0.61; p<0.0001). On the other hand, IRP+/- and IRP-/- patients showed no statistically significant benefit from Xigris. Of note, the meta analysis results must be interpreted with caution for several reasons including only summary statistic data is available, the cohorts are comprised of disparate patients groups, are of different sizes, the individual genetic marker results are not consistent between the cohorts, and a robust hypothesis generation followed by confirmation study has not been completed.

In addition, more non-bleeding SAEs occurred in the Xigris-treated patients than in placebo patients in the small (10%) IRP-/- genotype (OR=9.7; CI=1.1–460; p=0.02) and, surprisingly, less SAEs occurred in the Xigris-treated patients than in placebo patients in the large (40%) IRP+/+ genotype.

This pattern of effect by genotype across all of these observations and cohorts suggested that this protein C/PAI-1 combination genotype may be able to identify a population with a clearly positive B/R to Xigris treatment.

These data were discussed at a meeting with the FDA's Interdisplinary Pharmacogenomics Review Group (IPRG) in July 2007. Their recommendation was to "cast a wider net" by employing a genome-wide association study (GWAS) of response to Xigris. The MAH has adopted this advice and a GWAS of the PROWESS DNA samples is underway.

The MAH was asked by the CHMP to perform a meta-analysis of the association data linking the IRP and response to Xigris in terms of 28 days mortality and other available endpoints such as 1-year mortality, serious adverse events, and severe bleeding events, among (i) the whole severe sepsis population; (ii) the multiple organ dysfunction (MOD) severe sepsis population (i.e., the EU approved indication) across the three datasets analysed (SPH, VASST and PROWESS) as well as across all other available datasets in controlled groups of patients treated with Xigris.

Based on available data that have been reviewed and analysed to date, the MAH asserts that interesting genetic markers have been identified in PROWESS, but these markers have not been sufficiently replicated or confirmed to conclude that any genetic marker is ready for clinical use. Any such marker would need to be confirmed in additional cohorts and replicated in a prospective trial. Although the specific IRP marker (combination of PROC rs2069912 and PAI-1 rs7242 SNPs) that is the subject of this question was initially believed to be promising, the MAH does not believe upon further evaluation that this would be the best genetic hypothesis to carry forward into replication studies. To that end, the MAH has developed a comprehensive plan to generate and investigate the clinical utility of the hypothesized genetic markers.

The MAH is now working to develop potential markers (protein or genetic) that would identify patients with severe sepsis most likely to benefit from Xigris treatment. As well as the possibility of using genomic markers, the RESPOND study is rapidly approaching completion of enrolment and analysis of these data should help in understanding the potential role of protein C levels in patient identification and treatment. The MAH does not believe that the currently identified genetic markers are ready for clinical testing or for clinical use.

The CHMP noted that the long-term biomarkers and pharmacogenomic research activities might generate the desired information and enable for a clinical use of Xigris on more solid grounds. However, robust data are expected only to become available within 3 to 4 years.

The CHMP agrees that a multi-marker GWAS will provide a better analysis of the genomic associations underlying the response to Xigris in the PROWESS study and also agrees on the timetable proposed by the MAH.

2.1.3 Risk of bleedings

The CHMP noted that following approval of Xigris in 2002, early surveys, clinical studies and post-marketing investigation suggested that the risk of bleeding during clinical use might be greater than was noted in the original phase-3 trial (PROWESS). Increased bleeding with Xigris has been a consistent finding in all sepsis trials conducted to date. In both studies PROWESS (n = 1,690) and in a second randomized controlled trial in adults ADDRESS (n = 2,640), serious bleeding was greater during Xigris infusion than placebo (2.4 vs. 1.0 and 2.4 vs. 1.2%, respectively, p = 0.02 for both comparisons).

The MAH mentioned that given that activated protein C has anticoagulant activity, it is not unexpected that Xigris use has been associated with increased rates of bleeding. However, the following points should be considered:

- The absolute increase in the rate of bleeding during infusion in PROWESS (1.4%) is small relative to the mortality reduction seen in PROWESS (absolute risk reduction in patients with multiple organ dysfunction [MOD] = 7.4%), such that 5 lives would be saved for each additional serious bleeding event (Figure 1).

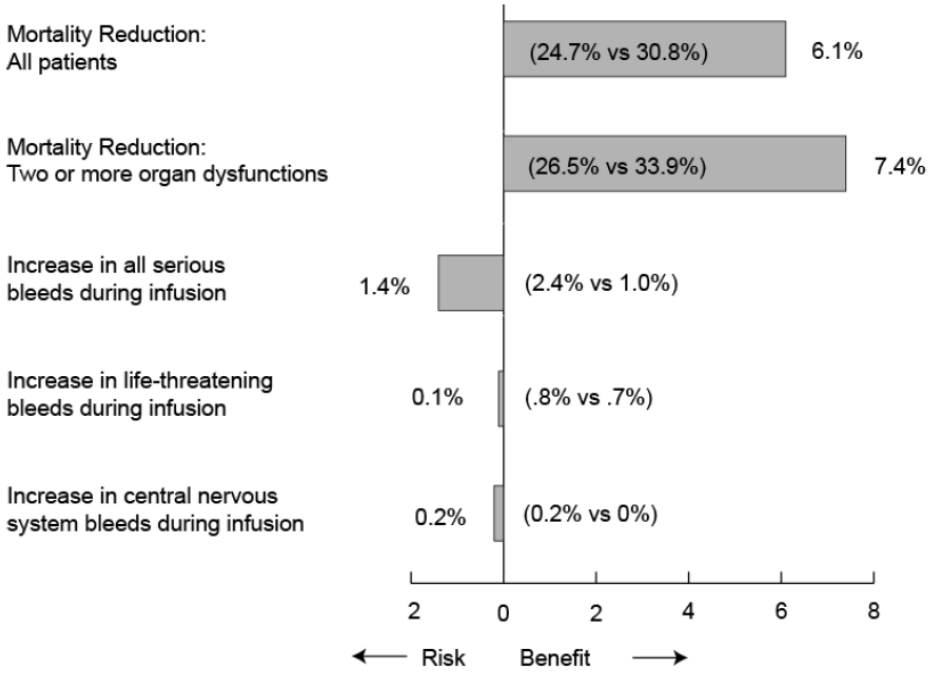
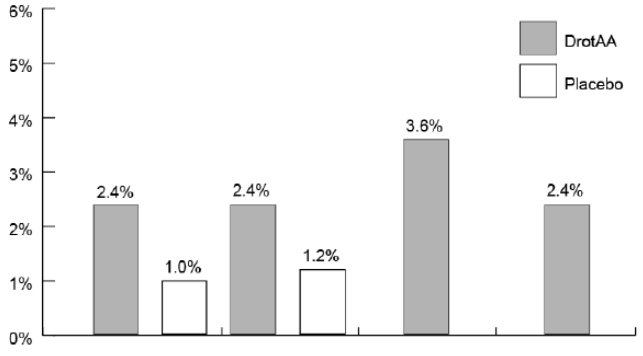


Figure 1. Benefit/risk of drotrecogin alfa (activated) in PROWESS.

- The rate of serious bleeding events has remained relatively consistent across a number of clinical trials. In placebo-controlled studies, the increase in serious bleeding events did not translate into an increase in the overall rate of serious adverse events. The increase in serious bleeding events during the infusion in PROWESS and ADDRESS is primarily driven by events not classified as central nervous system, life-threatening, or fatal bleeds (Figure 2).



	PROWESS		ADDRESS		ENHANCE	XPRESS
	DrotAA	Plac	DrotAA	Plac	DrotAA	DrotAA
	N=850	N=840	N=1317	N=1293	N=2378	N=1935
Serious Adverse Events (%)	6.8	6.5	5.7	6.0	7.0	6.6
CNS, Life Threatening, or Fatal Bleeding (%)	1.3	0.8	1.3	0.9	1.7	1.4
Other Serious Bleeding (%)	1.1	0.1	1.2	0.3	1.9	1.0

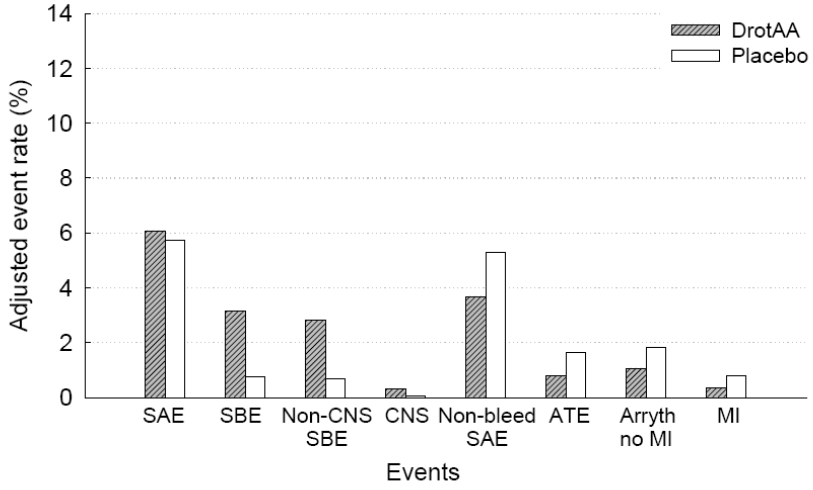
Figure 2. **Serious bleeding events during the infusion period in clinical studies.**

- The incidence of serious bleeding events during the infusion period was higher in ENHANCE patients (all treated with Xigris) compared to Xigris patients in PROWESS (3.6% versus 2.4%; Figure 2 above). That increase may have resulted from the enrolment of patients with a higher risk of bleeding. This was illustrated by a higher rate of serious bleeding events not only during the infusion period, but also during the post infusion period when no direct additional bleeding risk would be anticipated due to the short half life of the drug. In PROWESS, the rates of post-infusion serious bleeding events were similar in Xigris and placebo patients. In ENHANCE, the primary baseline predictors of bleeding during the infusion were hepatic dysfunction, surgery, and haematologic dysfunction, and there were a higher proportion of such patients enrolled in ENHANCE compared with patients enrolled in PROWESS. Of note, the incidence of haemorrhage-related deaths and study-drug related deaths in ENHANCE was the same or lower than that observed in PROWESS.

- There is a background rate of clinically relevant bleeding in the untreated severe sepsis population, or even in the critically ill population from general intensive care units. For instance, the rates of central nervous system bleeding were 0.4 % in the latter group (Oppenheim-Eden et al., 1999) and 0.4% in the placebo arm of the KyberSept study which had similar inclusion and exclusion criteria to PROWESS (Warren et al., 2001).

- In addition to the rate of serious bleeding events, it is also important to consider the overall rate of serious adverse events as well as the types of events. As noted in the literature review of the current annual licence reassessment document, Dhainaut (2008) reported the results of a clinical evaluation committee (CEC) review of the safety of Xigris therapy from the INDEPTH database, which primarily included the PROWESS and ENHANCE patient populations together with placebo patients from 3 other Phase 2 studies in severe sepsis, all with similar entry criteria. They conclude that although serious bleeding events occurred more often, non-bleeding serious adverse events (for

example, arterial thrombotic events and arrhythmias) occurred less frequently with Xigris. This decrease was found to be statistically significant in this large propensity-adjusted database. Overall, the incidence of serious adverse events was not increased with Xigris (Figure 3).



Abbreviations: SBE = serious bleeding event; CNS = central nervous system bleed; ATE = arterial thrombotic event; arryth = arrhythmia; MI = myocardial infarction.

Figure 3. **INDEPTH adjusted serious adverse event rates during infusion.**

- In the post-marketing period, since 2001, the MAH has closely evaluated safety in Lilly-sponsored clinical trials and in safety reports from health care professionals and consumers through routine pharmacovigilance and surveillance activities. The Company Core Safety Information (CCSI) and product labels have been regularly updated. In addition, in a Follow-up-Measure from the third annual license reassessment, the MAH proactively communicated recent significant SPC changes (for example, the paediatric information included from Study EVBP) to the most frequent Xigris users and paediatric intensivists as a measure to prevent potential off-label use of Xigris. This activity was part of an EU Risk Management Plan submitted to CHMP in April 2006.

- Nine PSURS have been submitted since marketing approval, every 6 months for 3 years and annually, thereafter. The safety data from these 9 PSURs do not raise new concerns (e.g., compared to the results of clinical trials). The CHMP has requested special monitoring or review of certain adverse events in each PSUR. Following these reviews, a causal association with Xigris was not established and specific and required monitoring has not been necessary. Five special topics continue to be evaluated: serious bleeding, including central nervous system bleeding, thrombocytopenia, adverse events in paediatric patients (especially bleeding), convulsions, and overdose.

- In clinical trials, 54% of the serious bleeding events reported during the infusion period were classified as central nervous system, fatal, or life-threatening bleeds; in spontaneous health care provider reports, 44% were so classified (Reporting Rate, 31 events/10,000patients). Thus, there do not appear to be more of these more clinically relevant bleeds occurring in clinical practice compared to clinical trials.

- Thrombocytopenia is a known complication of severe sepsis and clinical trial data do not suggest a causal association between Xigris and thrombocytopenia. The rate of thrombocytopenia event reporting has been stable over the last two reporting periods and the overall rate of reporting has decreased over time.

- Spontaneous reporting rates for convulsion do not raise concerns about a causal association to Xigris; these rates are low (1/10000) and have remained consistent over time.

- Although spontaneous adverse event reporting in a population cannot reliably estimate the population's use of a drug, in the last PSUR only 3 paediatric (<18 years of age) cases were reported. Two of these cases were from the EU and 1 of the 2 was a retrospective case from Italy from 2003. This does represent a decrease from earlier PSURs before the introduction of the Warning and Precautions in the SPC that Xigris is not recommended in children and indicates alignment with the SPC.

- Cumulative evaluation of overdose with Xigris has concluded that 70% of cases are not associated with an adverse event. In the remaining cases, the events do not differ from all patients receiving Xigris. Thus, Xigris overdose did not produce unique or increased rates of reporting of adverse events. There did not appear to be a dose relationship to bleeding events.

In summary, the post-marketing data confirm that Xigris is associated with serious bleeding events including CNS bleeds, but that there is no suggestion that reporting rates are increasing over time or that bleeding in clinical practice is more severe than in clinical trials. No new safety concerns/signals associated with Xigris use have been identified through routine pharmacovigilance surveillance and after comprehensive evaluations of special topics.

The MAH also discussed published Xigris registry data. In general, these registries have demonstrated that patients receiving Xigris in clinical practice have greater disease severity and higher mortality compared to patients treated in clinical trials, and also greater disease severity compared to clinical practice patients who do not receive Xigris.
Bleeding events were only reported in some of the registries, and comparisons with clinical trial results are not always easy as some used different definition for serious bleeding events. In the largest UK study (Rowan et al. 2008), the rate of serious bleeding during the infusion was higher than PROWESS, but similar to that seen in ENHANCE. In the other UK study (Ridley at al. 2008), serious bleeding events were similar to PROWESS. In the GiViTI registry, the rate of serious bleeding events was higher than in PROWESS and ENHANCE; however, as acknowledged in the manuscript, this is probably due to differences in the criteria used to define serious bleeding events in terms of blood transfusion between the 2 studies (administration of more than 2 units of packed red cells in GiViTI versus administration of 3 units on two consecutive days in PROWESS and ENHANCE).

The CHMP noted that the rates of serious bleeding events during infusion in PROWESS and ADDRESS were identical to one another (2.4% for patients treated with Xigris in both studies). Serious bleeding events in the non-comparative study ENHANCE were slightly higher at 3.6%.
Post-authorisation observational studies and registers have in some cases reported higher rates of bleeding, but the case definitions for serious bleeding events were not comparable to those used in the placebo-comparative clinical trials, making direct comparisons somewhat unreliable.
Some CHMP members noted that the increased risk of bleeding with the use of Xigris is undoubted. In addition, more or less vulnerable patient groups will suffer more intensely from bleeding than others. Despite the presentation of the MAH with further statistical evaluations it might be noticed that evaluation of bleeding risk outside clinical trials remains conflicting.

2.1.4 Italian GiViTI study (FUM 060)

The Italian Medicines agency has provided the CHMP with the final report of the GiViTI group (Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva) on the use of Xigris in Italian intensive care units between 2003 and 2007.
The final GiViTI report has been prepared by Guido Bertolini & Carlotta Rossi (Laboratorio di Epidemiologia Clinica, Istituto di Ricerche Farmacologiche 'Mario Negri' Ranica) and is dated October 10, 2007. It covers the period from July 2003 to September 2007 and reviews 1083 cases of Xigris treatment (1001 of which could be analyzed) in 161 ICUs in Italy. Previously, in March 2007, Bertolini et al. had published the results of a similar analysis on 709 cases of Xigris treatment (668 analysed) collected between July 2003 and March 2006 in 134 ICUs. This article in the journal

Intensive Care Medicine[1] was accompanied by a harsh editorial by Eichacker & Natanson.[2] The article and the editorial have been taken into account by the CHMP during their assessment of the 5-year renewal of the marketing authorisation of Xigris completed in early 2008.

The CHMP noted that the proportion of patients recruited in this study (50-60% of all patients treated with Xigris in Italy) is quite high and probably higher than in most similar pharmaco-surveillance studies. Even though the selection of patients for Xigris treatment is uncontrolled, the Registry should be considered a precious source of information, especially because a comparison is made with a control group, through a logistic regression analysis (Bertolini et al., 2007).

Overall, 82 patients out of 1083 (7.6%) were excluded from the analysis because still in ICU or under query. The remaining 1001 patients were analysed. Data relative to 344 patients were obtained with the first CRF while those of the remaining 657 were obtained with the modified CRF (>January 2005). Overall mortality in the ICU was 45.4%. Mortality was much higher ($p<0.0001$) in elective surgical patients (66.7%) than in either emergency surgical patients (37.2%) or non-surgical patients (46.6%). The reasons for this large difference cannot be inferred from the current dataset.

In 253 patients (23.4%) the infusion of Xigris was definitely stopped before the 96-h course was over. The main reasons for stopping treatment were death (48%) and bleeding (30%). Thus, about 7% of patients stopped treatment due to bleeding. There was no apparent change over time in the number of patients stopping treatment and in the proportion of patients who did so because of bleeding.

Overall, bleeding occurred in 103/1001 patients (10.3%), of whom 30% bled in the gastrointestinal tract, 20% in the skin and soft tissues, and 16% in the thorax. Intracranial haemorrhage occurred in 7/1001 patients, i.e. 0.7%. Again, these numbers did not appear to change over time from 2003 to 2007. Furthermore, only 44% of all bleedings were assessed as probably associated with Xigris administration, and 50%, as possibly associated.

Mortality was not associated with bleeding, even if the p value was close to the 5% conventional cut-off for significance (53.4% with bleeding vs. 44.4% without bleeding, $p=0.08$). The authors did not analyse the relationship of bleeding with post-surgical status.

Off-label use of the drug was quite frequent in the GiViTI study: it was present in 15.6% of patients before the introduction of timing restriction by the EMEA on January 2005 and in 27.3% after that. After 2005, 39.1% of patients were treated within 24 h of their first sepsis-related organ failure, 39.2% were treated between 24 and 48 h, and 20.8% were treated "off-label" beyond 48 h. On a strict stance, patients who started treatment between 24 and 48 h after the onset of organ failure (39.2%) could be considered "borderline" off-label use according to the EU SPC.

In addition to these data, a further 29 patients recruited with the modified CRF (4.4%) were considered possibly off-label since the drug was started on the same day a surgical procedure was performed, whereas according to the SPC it should not be administered within 12 h from surgery. The overall off-label use in the second part of this observational study may thus be close to 30%.

The authors of the study concluded that this study, along with data from available RCTs, indicates that the risk-to-benefit profile of Xigris is questionable. Particularly, treatment with Xigris can be harmful for some subsets of patients that match the current indications.

The CHMP concluded that data regarding 50-60% of all Italian patients treated with Xigris in real life are a rare example of an efficient post-marketing monitoring and should be considered a precious source of information. Therefore, it is worrying that, using a control group of eligible patients who did not receive Xigris, no significant effect of Xigris could be demonstrated through logistic regression

[1] Bertolini G et al. Use of drotrecogin alfa (activated) in Italian intensive care units: the results of a nationwide survey. *Intensive Care Med*. 2007 Mar; 33(3):426-434.
[2] Eichacker PQ, Natanson C. Increasing evidence that the risks of rhAPC may outweigh its benefits. *Intensive Care Med*. 2007 Mar; 33(3):396-399.

analysis in this group of patients at high risk of death, i.e. higher than in the clinical studies performed so far with Xigris.

The MAH was therefore asked to re-discuss the benefit-risk balance of Xigris in patients at very high risk of death (~40-50%) treated according to the current clinical practice in Europe and to collect all available data, especially from registries in the UK, Canada,, Poland and Belgium., describing the type of patient population currently receiving Xigris and to compare that population with those included in the main clinical trials.

In its analysis, the MAH has used data from their own sponsored studies PROWESS, ENHANCE, and XPRESS, as well as data from the 8 major observational studies published in international journals, and one study submitted for publication (PROGRESS registry), with enrolments ranging from 97 to 1292 patients who received Xigris.

A comparison of the baseline characteristics of patients enrolled in the observational studies and the Lilly clinical studies indicated that patients treated in clinical practice are more severely ill than clinical study patients:

	Lilly clinical studies	Observational studies
Mean number of organ dysfunctions	2.4 to 2.7	2.9 to 3.4
% patients with ≥4 dysfunctions	18 to 25 %	38 to 78 %
% patients with CV dysfunction	71 to 83 %	84 to 96 %
% patients with metabolic acidosis	30 to 35 %	47 to 77 %

These observational studies have all demonstrated that patients treated with Xigris in ICUs across EU and US have more organ dysfunction and higher mortality compared to patients treated in the Lilly clinical studies.

In the GiViTI registry, the only disease severity measure presented in the baseline characteristics table was the presence or absence of shock, which was reported as being less in the Xigris treated group than in controls. The overall mortality was less in the Xigris treated group compared with the non-treated group (46% versus 55%). Although the adjusted effect of Xigris administration on mortality was not significant for the overall population, the MAH was of the opinion that this registry was not statistically powered to detect a significant treatment effect. Furthermore, in the presence of significant interactions involving treatment (Xigris-by-surgical status as identified in the article), the choice of the statistical model can have a large impact on the estimate of overall treatment effect and on the significance of the test of this effect, particularly when there is a wide disparity in sample sizes for the subgroups involved in the interaction term (from 152 elective surgery patients to 1063 nonsurgical patients, for instance). The MAH also concluded that it is difficult to quantify the magnitude of the Xigris effect on mortality from the GiViTI registry. Further analyses from GiViTI focused on the subgroups of scheduled surgical patients, unscheduled surgical patients, and nonsurgical patients. Although they report increased mortality in the smallest of these subgroups with scheduled surgery (11% of the Xigris treated cohort), the other 2 groups (89% of the Xigris cohort) demonstrated results consistent with PROWESS.

In the largest of the published registries (UK-1; Rowan et al. 2008), which enrolled almost 1300 patients treated with Xigris in UK, crude hospital mortality was reported as 45%. Of 8 relative risks estimated from individually matched (0.75 to 0.85) and propensity-matched (0.82 to 0.90) controls, 7 were consistent with the results of PROWESS. Restricting the analysis to patients receiving Xigris during the first 24 hours resulted in larger treatment effects (relative risks 0.62 to 0.81). Further analysis demonstrated statistically significant benefit in the high risk subgroups.

Data related to the use of Xigris in the PROGRESS registry (submitted for publication), which included 882 patients who received Xigris, have been analysed using various different logistic regression models, and, all models showed results consistent with PROWESS.

Similarly, logistic regression analysis of data from an observational study in Poland (Poland; Kubler et al. 2006) has demonstrated a significant mortality reduction with Xigris treatment. In addition, studies in

Belgium (Belgium-1; Vincent et al. 2008) and the United Kingdom (UK-2; Ridley et al. 2008) have demonstrated mortality in patients receiving Xigris lower than predicted for non-treated patients when adjusted for disease severity. Another observational study from Belgium (Belgium-2; Decruyenaere et al. 2009) and also a study from the United States (US-1; Wheeler et al. 2008) have demonstrated similar mortality to comparable treated patients from PROWESS. The US-1 study also highlighted the importance of early treatment. A study from Canada (Kanji et al. 2007) noted a higher disease severity and a hospital mortality of 45% in patients receiving Xigris; however, adjusted analyses were not performed. The authors concluded "In light of more plausible reasons for the high mortality rate (i.e., patients with greater severity of illness) this study provides no reason to believe that the risks associated with Xigris therapy outweigh the benefits although efforts aimed at earlier disease recognition, earlier assessment of treatment eligibility, and greater awareness of relative contraindications may still make the benefit/risk ratio more appealing."

In these observational studies in which the mortality rate of patients receiving Xigris was compared to mortality in a control group (adjusted for covariates) or to an expected mortality, lower mortality was observed in the Xigris treated cohorts. Thus, these observational studies do not undermine the use of Xigris in high risk patients, but reinforce the findings from PROWESS in which significant mortality benefit was demonstrated in patients with 2 or more and 3 or more organ dysfunctions.

The CHMP noted that several observational studies of Xigris treated patients in ICUs across EU and US have been published. In almost all cases, patients treated in clinical practice appear more severely ill than clinical study patients. In clinical practice, patients treated with Xigris and their adjusted controls have a mean of 3 organ dysfunctions and an ICU/hospital mortality rate of 40 to 55%, compared with about 30-35% in the MAH-sponsored clinical trials. There is no clear evidence that this difference in mortality rates between clinical trials and current ICU practice is a real concern. First, the beneficial effect of Xigris in the pivotal study PROWESS was concentrated in the higher risk population with mortality rates approaching those of the current clinical population. Second, the MAH has shown in its comparative analysis that the observational studies do not demonstrate a lack of efficacy of Xigris (although they are not designed to show a proof of efficacy). One may add that the observational studies do not raise serious safety concerns, as reflected in the conclusions of all PSURs so far, except under some special circumstances such as the scheduled surgical patients in the GiViTI study.

The CHMP also concluded that in the GiViTI study, a higher risk of death was observed in patients treated with Xigris after elective (scheduled) surgery compared with patients treated after emergency surgery or in medical patients. The MAH was therefore asked to analyse their whole database to explain the meaning of that observation and possibly propose new contra-indications to the use of Xigris.

According to the MAH, the available clinical trial data are not consistent with the data presented in the GiViTI article. There was a suggestion of lack of benefit in the elective surgery subgroup in the GiViTI article; however, a similar finding was not seen in the available clinical trial data. The individual components of the APACHE II score, which include information on elective and emergency surgery, were only collected in the Phase 2 study (F1K-MCEVAA) and PROWESS.
A statistically significant treatment-by-surgical status interaction was observed (p=0.054). However, the direction was opposite to the observations of the GiViTI study. In the clinical trials, for emergency post-operative patients, higher 28-day all-cause mortality was observed for Xigris patients compared with placebo patients. However, the number of patients was small and the effect seemed to have been driven by a low mortality in the placebo group rather than an increased mortality in the Xigris group. An examination of the baseline characteristics of patients with emergency surgery showed that there were 16 more patients 65 years or older in the Xigris group than in the placebo group [Xigris: 103, placebo: 87]. Age 65 or older was associated with a greater than 2-fold increase in mortality in the placebo group (age <65 years: 20.9%, age ≥65: 42.4%). Thus, this analysis is not consistent with the data presented in the GiViTI manuscript where there was a suggestion of lack of benefit in the elective surgery subgroup, rather than the emergency surgery subgroup.

The MAH has provided 28-day mortality outcomes by surgical status for the 2 largest placebo-controlled studies, PROWESS and ADDRESS.

In PROWESS, the overall mortality results were similar to those discussed for the ISS population (above) as PROWESS made up the vast majority of this population. Subgroups stratified by age generally resulted in subgroups with higher mortality in the older age groups, but did not greatly alter the pattern of results seen in the overall population. Stratification by site of infection resulted in many small subgroups where interpretation of mortality results is not possible. However, in 2 of the largest subgroups, lung and intra-abdominal, again the pattern of results were not greatly different from the pattern of results seen in the overall population.

In ADDRESS, information on elective and emergency surgery status is not available. Overall mortality in surgical patients with single organ dysfunction treated with Xigris has been previously noted to be higher than placebo patients, resulting in the SPC warning above. Thus, the analysis provided only includes patients with multiple organ dysfunction. Although having multiple organ dysfunction, such patients have been assessed as not meeting the indication for Xigris in that country, and mortality was low at just over 20%. Given the relatively small subgroup size and low event rate in this population, it is difficult to draw conclusions from this data in the overall and also stratified subpopulations. However, there do not appear to be any clear safety issues identified by such analyses.

Based on these discussions, the MAH did not believe that a change to the SPC concerning scheduled or emergency surgery is warranted at the present time.

The CHMP concluded that this observational prospective Italian study (GiViTI) showed an association of Xigris with a significant increase in mortality in elective surgical patients, and with no significant effect in unscheduled surgical and in non-surgical patients. These results (obtained under "real life" conditions) question the outcome of the Prowess trial. However regarding patients undergoing elective surgery, the CHMP agreed with the MAH's conclusion that, at the current time, it does not appear justified to change the label based on a small subgroup [70 Xigris and 82 untreated patients] from a single registry, particularly where the other available data do not support this conclusion and when all confounders have not been excluded.

2.1.5 Safe use in the Paediatric population

The CHMP had noted that the paediatric study (RESOLVE-study) was stopped prematurely for futility. In this respect, the overall, 28-day mortality, serious bleeding events, including fatal central nervous system bleeding events, serious adverse events, and major amputations were similar in Xigris compared with placebo. However, study-drug-related serious adverse events and study-drug-related serious bleeding events (as determined by the investigator) were statistically significantly higher in the Xigris group compared with the placebo group. The majority of these events occurred during Study Days 0 through 6, as 10 patients (4.2%) in the Xigris group had a study-drug-related serious adverse event during this time period, compared with 1 patient (0.4%) in the placebo group, resulting in a safety concern for the use of this product in children. Following this evaluation a warning in the SPC was agreed by the CHMP in April 2006 and after the appropriate communication to the paediatric intensive care physicians the use of Xigris has remarkably declined. However, according to the assessment of subsequent PSURs the safety issue "cerebral haemorrhage in children" remains a concern for the paediatric population despite this warning statement in the product labelling.
Considering the possible life threatening ADRs (e.g. cranial haemorrhage) treatment with a medicinal product not proven to be effective in this age-group is not acceptable by the CHMP.

The MAH mentioned that in the RESOLVE study, although there were more central nervous system bleeds in the Xigris group, there were more haemorrhagic deaths in the placebo group, and no overall increase in fatal central nervous system bleeding events or serious bleeding events overall. Thus, the safety signal from RESOLVE is not clear cut. The MAH agreed that Xigris should not be used in children, and, since the introduction of a warning to this effect in 2006, together with proactive communication of this SPC change to paediatric intensivists, data reviewed in the PSUR indicates that paediatric use has declined. The MAH suggested that if CHMP insisted on a contraindication in children Xigris should be contraindicated in patients ≤ 3 years of age, as it was this age group of patients who experienced all the central nervous system bleeds in RESOLVE.

However the data from the Resolve Clinical study report (dated 20 October 2005) concerning bleeding events are as follows:

Serious bleeding events (day 0-28) Table EVBP 12.31 page 333

Age group	N	Bleeding events	
0-1 mo	14	3	(21.4%)
1-12 mo	62	5	(8.1%)
1-5 y	81	4	(4.9%)
5-10 y	39	2	(5.1%)
10-18 y	44	2	(4.5%)

CNS bleeding events (day 0-28) Table EVBP 12.34 page 341

Age group	N	CNS Bleeding events	
0-1 mo	14	2	(14.3 %)
1-12 mo	62	3	(4.8 %)
1-5 y	81	4	(4.9 %)
5-10 y	39	0	(0.0 %)
10-18 y	44	2	(4.5%)

The above recalled data from the Clinical study report do not support the MAH's suggestion for a paediatric subgroup <3 years of age being at specifically higher risk ("as it was this age group of patients who experienced all the central nervous system bleeds in RESOLVE").

The CHMP therefore requested a contra-indication in the concerned age-group which means all paediatric patients below the age of 18 years as defined by the RESOLVE inclusion criteria.

2.1.6 Lack of confirmation of benefit

The CHMP noted that until now, proof of efficacy and confirmation of the early results of the PROWESS trial are in an unchanged open state despite high efforts of detailed investigations. Neither of the controlled trials that followed PROWESS (i.e., ADDRESS and RESOLVE) noted any significant benefit with Xigris, regardless of underlying severity of disease. Across all trials that compared Xigris to placebo (enrolling approximately 5,000 patients), only two subgroups from PROWESS study demonstrated benefit (i.e., the two highest APACHE-II quartiles). Notably, the later ADDRESS trial also enrolled high-risk patients (i.e., APACHE-II score ≥ 25) and those with multifunctional organ failure, receiving either Xigris or placebo, but failed to reproduce the finding of efficacy. In fact, for APACHE-II score ≥ 25, the treatment effect in ADDRESS was on the side of harm, opposite to and significantly different from the effect of Xigris in the PROWESS trial.

In their response, the MAH has briefly reviewed the results from the main clinical trials of Xigris in adults, i.e. PROWESS (F1K-MC-EVAD), ENHANCE (F1K-MC- EVBE/F/G), ADDRESS (F1K-MC-EVCL/CM), and XPRESS (F1K-MC-EVBR), as well as the RESOLVE (F1K-MC-EVBP) study in children. The results of all these studies have already been extensively discussed by the CHMP during the initial marketing authorisation and subsequent annual licence reassessments.

Regarding ADDRESS in particular, which was the subject of renewed CHMP discussions during the current licence reassessment, the MAH agrees that ADDRESS does not confirm efficacy, but would disagree that it can be used to undermine the efficacy in the indicated population. One of the main arguments is that randomisation was not stratified by disease severity subgroup (either MOD or APACHE II) in ADDRESS; thus, randomisation cannot be assumed to have produced populations of equal disease

severity or predicted outcomes. Analysis of the MOD subgroup indicated that they were a low risk group compared to PROWESS (28-day placebo mortality was 21.9 % in ADDRESS versus 33.9% in PROWESS), and the mortality in this subgroup was in fact similar to the single organ dysfunction subgroup from PROWESS (21.2%).

The MAH provided the result of a meta-analysis of the two randomised, placebo-controlled studies, PROWESS and ADDRESS. A first step in a meta-analysis is the test for heterogeneity of treatment effects. The relative risk reduction in 28-day mortality in the MOD subgroup of ADDRESS was not statistically significantly different from the MOD subgroup in PROWESS (Breslow-Day interaction p-value = 0.18). The non-significant Breslow Day p-value indicates that it is statistically valid to combine the studies in the analysis (though the results should be interpreted with caution due to differences in inclusion criteria in the studies). In the combined analysis there was a statistically significant reduction in mortality. Thus, based on this meta-analysis, the combined evidence in MOD patients indicates a benefit of Xigris.

The MAH then discussed a possible explanation for the different results in PROWESS and ADDRESS. In PROWESS, the absolute benefit of Xigris was larger with MOD than single organ dysfunction. In ADDRESS, the majority (76%) of patients in the MOD subgroup had 2 organ dysfunctions, a subgroup in which the results were very similar in both studies. The main driver of lower benefit in the MOD subgroup in ADDRESS compared to PROWESS was the unusually low placebo mortality of 12.5% in patients with 3 organ dysfunctions compared with 34.4% of patients in PROWESS, whereas the mortality for Xigris patients with 3 organ dysfunctions in ADDRESS and PROWESS was similar, 24.4% and 26.2%, respectively. It is interesting to hypothesise how patients with 3 organ dysfunctions could have such a low mortality. One possibility is that they were in a phase of their organ dysfunction where their clinical condition was actually improving. Thus, one possibility for updating the indication statement could be to introduce the concept that treatment with Xigris is for patients with a clinical condition that is not improving.

The MAH also discussed the meta-analyses of the high APACHE II group (≥25) in PROWESS and ADDRESS. These meta-analyses give different results, depending on whether a random effect analysis (Friedrich et al. 2006) or a fixed effect analysis (Williams et al. 2006) is used.

A question that follows from the discussions related to the ADDRESS results, above, is: How well do MOD and APACHE II ≥25 define the indicated population? On the one hand, in ADDRESS, these patients were identified by the investigators as "non-indicated" so one could argue that such patients were identified to be at low risk even within the current indication; however, it could also be argued that other criteria, in addition to MOD, could be beneficial to more clearly define a high risk patient. Thus, a new approach could be to look at dynamic changes in organ dysfunction rather than just baseline characteristics, and to focus more on absolute risk reductions rather than relative risk reductions. Analysis of SOFA data from the placebo population from PROWESS has indicated that patients who fail to improve their organ function during the first day experience high mortality rates.

Thus, a target population could be the population in which organ dysfunction does not improve despite the initiation of best standard care, which would be a group with a much higher risk of death compared to patients with organ function that does improve. In ADDRESS, it was not possible to be certain if patients had low disease severity because they were early in their disease process (the target population) or had low disease severity because their clinical condition was actually improving.

Based on this reasoning, the MAH proposed an addition to the indication statement for further discussion:
"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 **where a patient's clinical condition is not improving with best standard care and** when therapy can be started within 24 hours after the onset of organ failure (for further information see section 5.1)".

During the Ad-Hoc expert group, the experts were asked, given the current knowledge on the safety and efficacy and its limitations as reflected in the product information, if Xigris is a medicinal product

for which physicians can easily identify a patient population where the benefit is considered to outweigh the risks.
There was no consensus from the experts on defining a specific patient population where the benefit is considered to outweigh the risks. The MAH proposal to amend the Xigris indication was also discussed and the experts were not in disfavour of slightly adjusting the indication as this represents clinical practice with the caveat that it should be made very clear that best standard care and clear protocol are very important and evolving all the time. Others experts didn't think that the amendment of the indication was needed.

The CHMP concluded that there is no need at the present time to update section 4.1 "Therapeutic indication" of the SPC.

Also, the CHMP was of the opinion that at present the ADDRESS study is presented in a way downplaying its contradiction of the PROWESS results. The CHMP requested the MAH to amend section 5.1 of the SPC to mention that no benefit of drotrecogin alpha (activated) was observed in the subgroup 872 patients at low risk of death with multiple organ dysfunction, so ADDRESS did not confirm the efficacy results of the PROWESS study.

The CHMP also acknowledged the efforts of the MAH to modify the outcome of the clinical trials following PROWESS with biostatistical approaches. However, it might be recapitulated that these trials focussed on varied target groups which does not allow retrospective comparison of subgroups. Subsequently the CHMP feels that reliable identification of a patient group who benefits from treatment with Xigris remains open. This situation bears the risk of harm in non-target patients. To find an interim solution until additional proof of efficacy has been established the CHMP recommended the inclusion of a general statement into the SPC in line with the wording regarding ADDRESS. Consequently SPC section 4.4 Special warnings should start with the following sentence: "No further clinical study has confirmed the efficacy results of the single pivotal trial".

2.2 Conclusion on clinical aspects

The CHMP remains of the opinion that the most reliable evidence available concerning the risk-benefit of Xigris is to be found in the three placebo-controlled studies PROWESS, ADDRESS and RESOLVE. The 28-day mortality reduction shown in PROWESS – 6.1% overall, and 7.4% in adults with two or more organ system dysfunctions, compensates for the 1.4% increased risk of serious bleeding compared to placebo (2.4% vs. 1.0%). The increase in CNS bleeding events seen in PROWESS compared to placebo was low at 0.2% (0.2% vs. 0%).

The rates of serious bleeding events during infusion in PROWESS and ADDRESS were identical to one another (2.4% for patients treated with Xigris in both studies). Serious bleeding events in the non-comparative study ENHANCE were slightly higher at 3.6%. Post-authorisation observational studies and registers have in some cases reported higher rates of bleeding, but the case definitions for serious bleeding events were not comparable to those used in the placebo-comparative clinical trials, making direct comparisons somewhat unreliable.

At the current time, it does not appear justified to change the label related to elective surgery based on a small subgroup from a single registry, particularly where the other available data do not support this conclusion

The results of ADDRESS and RESOLVE do not confirm the results of PROWESS – the overall 28-day mortality in patients treated with Xigris was not shown to be different from placebo. Therefore the CHMP recommended the amendment of section 4.4 of the SPC as follows:"No further clinical study has confirmed the efficacy results of the single pivotal trial".

ADDRESS was conducted in a population of adults with less severe sepsis than in the adults treated in PROWESS. Most patients treated in ADDRESS had only one organ system failure (1709/2613) and this group weighted the outcome for the whole trial. For the 649 patients in ADDRESS with 2 organ system failures the 28-day mortality favoured the Xigris group and was 5.1%, which is similar to the

reduction in mortality seen in patients with two or more organ system dysfunctions in PROWESS. Although the data in other subgroups was not consistent with PROWESS, these were based on relatively small numbers. Xigris is only indicated for the treatment of patients with sepsis associated with multiple organ failure. The CHMP was however of the opinion that at present the ADDRESS study is presented in a way downplaying its contradiction of the PROWESS results. The CHMP requested the MAH to amend section 5.1 of the SPC to mention that no benefit of drotrecogin alpha (activated) was observed in the subgroup 872 patients at low risk of death with multiple organ dysfunction, so ADDRESS did not confirm the efficacy results of the PROWESS study.

RESOLVE was conducted in children and the primary end-point was complete resolution of organ failure. The natural history of sepsis in children is not necessarily comparable to sepsis in adults. There is no clear evidence that the off-label use of Xigris is high. In particular, the use of Xigris in children has probably become quite rare. However the CHMP has recommended a contra-indication for children below 18 years of age as a precautionary measure.

The MAH committed in 2007 to perform the new-placebo controlled study (PROWESS-SHOCK) to assert the benefit/risk profile of Xigris. The CHMP has reiterated the importance of completing this study within the shortest possible timeframe. The CHMP has acknowledged the efforts of the MAH in attempt to reduce the duration of this study. The final report of the study should now be available in 2Q2011. In the CHMP's opinion, this timetable is acceptable. However, the MAH should commit to update the CHMP on the progress of recruitment and overall mortality in PROWESS-SHOCK every 6 months.

The MAH has provided extensive analyses of the pharmacogenomic markers that were identified in 2007 and discussed with the FDA IPRG group without confrontation with the CHMP Rapporteurs. Although the specific "IRP" marker (combination of PROC rs2069912 and PAI-1 rs7242 SNPs) suggested was initially believed to be promising, the MAH does not believe upon further evaluation that this would be the best genetic hypothesis to carry forward into replication studies. Today, the MAH asserts that interesting genetic markers have been identified in PROWESS, but these markers have not been sufficiently replicated or confirmed to conclude that any genetic marker is ready for clinical use. Any such marker would need to be confirmed in additional cohorts and replicated in a prospective trial. To that end, the MAH has developed a comprehensive plan to generate and investigate the clinical utility of the hypothesized genetic markers. The CHMP is mostly in agreement with this reasoning and plan, which could lead to a clinically useful marker within 3 to 4 years. The MAH has committed to follow that strategy.

2.3 Change of the Product Information

The CHMP and the MAH agreed to amend the Summary of Product Characteristics and package leaflet ass follows:

Section 4.2:
"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)**".

Section 4.3:
"**Drotrecogin alfa (activated) is contraindicated in children below the age of 18 years (see section 5.1)**".

The PIL is updated accordingly.

Section 4.4
"**No further study has confirmed the efficacy results of the single pivotal trial**".

Section 5.1:

"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".

The following paragraph was moved from section 4.4 to section 5.1:
"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".

The MAH has also taken the opportunity to correct the contact detail of the Slovenian local representative.

III. OBLIGATIONS PENDING TO BE FULFILLED OR ONGOING

3.1 Specific Obligations (SOs)

- **SPECIFIC OBLIGATION**

EMEA SOB 051: "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".
The final study report will be provided to the CHMP by Q2 2011

IV. BENEFIT/RISK ASSESSMENT

The CHMP concluded that since the 5th annual re-assessment, no further data has become available that would alter the B/R of Xigris. The CHMP has reiterated the importance of completing the PROWESS-SCHOCK study within the shortest possible timeframe as this study will assert the benefit/risk profile of Xigris.

The CHMP however recommended as a precautionary measure and based on the absence of further data on efficacy and safety of Xigris in children, the contraindication of Xigris in children below 18 years of age.
The results of ADDRESS and RESOLVE do not confirm the results of PROWESS – the overall 28-day mortality in patients treated with Xigris was not shown to be different from placebo. Therefore the CHMP recommended the amendment of section 4.4 of the SPC as follows:" No further clinical study has confirmed the efficacy results of the single pivotal trial". The CHMP also recommended the amendment of section 5.1 of the SPC related to the ADRESS trial to reflect the results in a more factual way.

Finally, further to the assessment of the data provided in the context of this 6th Annual Reassessment, the CHMP considers that the risk/benefit balance of Xigris remains favorable. The product remains licensed under exceptional circumstances while waiting for the update on recruitment status in the ongoing PROWESS-SHOCK study as well as for the results of that study which are now planned for Q2 2011. There is a need for further information on the pharmacogenetic data that were not part of the MAH submission but are considered important for the annual reassessment of the benefit/risk balance of Xigris.

V. OVERALL CONCLUSION AND RECOMMENDATION

The CHMP concluded by majority that, on the basis of the data submitted since the 5th annual re-assessment, the benefit/risk profile for Xigris in 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"* remains positive.

The majority of the CHMP recommended the updating of the Annexes I and IIIB of the Community Marketing Authorisation for Xigris. However the CHMP concluded that there was still a Specific Obligation that remained to be fulfilled. The assessment of the pending commitments will form the basis of the next annual re-assessment. Therefore the Marketing Authorisation for Xigris will remain under exceptional circumstances.

On 24 September 2009 the CHMP adopted an Opinion by a majority of 18 out of 22 votes on the 6th annual re-assessment of the benefit/risk profile of Xigris, subject to the additional commitments undertaken. The Icelandic CHMP member agreed with the above mentioned recommendation of the CHMP.

A revised Letter of Undertaking dated 22 September 2009 including the amended list of Follow-up Measures has been adopted accordingly by the CHMP.

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