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Product name: **XIGRIS**
Procedure No. **EMEA/H/C/396/S/0013**

SCIENTIFIC DISCUSSION

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I SCIENTIFIC DATA PROVIDED BY THE MARKETING AUTHORISATION HOLDER

1. Chemical and Pharmaceutical aspects

No additional data have been provided with this submission.
See section II OBLIGATIONS PENDING TO BE FULFILLED for Follow-up Measures related to pharmaceutical aspects.

2. Preclinical aspects

No additional data have been provided with this submission.

3. Clinical aspects

3.1 Efficacy aspects

An update on clinical trials (ENHANCE and ADDRESS studies) during the past 12 months was presented by the MAH.
As of 21 May 2004, a total of up to 5814 adult patients have been exposed to drotrecogin alfa (activated) in completed and ongoing clinical trials, 3695 of which were included in the ENHANCE and ADDRESS studies.

ENHANCE study
(Studies F1K-MC-EVBE, F1K-MC-EVBF, and F1K-MC-EVBG)

ENHANCE was a multi-country, single-arm, open-label study of drotrecogin alfa in adult and paediatric patients with severe sepsis. A total of 2378 adult patients received part or all of the 96-hour drotrecogin alfa infusion. Follow-up at study day 28 was available for 2375 adult patients.
The primary purpose of the study was to gather additional safety and 28-day all-cause mortality data using PROWESS as a historical control. The study completed enrolment in early 2003, and datalock occurred in April 2003. At the time of the first annual licence reassessment, the final clinical study report had not been completed; however, provisional data was included in the risk/benefit assessment of the last expert report. The final clinical study report was completed and submitted in December 2003. Responses to CPMP questions (including labeling proposals) were submitted on 25 May 2004, and responses to outstanding issues were submitted on October 1st 2004. All the questions raised by the CHMP have been adequately answered. Following the evaluation of the final report of ENHANCE, the MAH submitted a Type II variation (EMEA/H/C/396/II/0014) for which the CHMP adopted a positive opinion on 15 December 2004.

Efficacy in ENHANCE study
According to the MAH, the study supported the efficacy associated with drotrecogin alfa that was observed in PROWESS. The Kaplan-Meier survival curves were nearly identical and showed similar pattern of survival throughout the 28-day study period. In clinically relevant subgroups, including multiple organ dysfunction, the observed mortality rates in ENHANCE were similar to those observed in PROWESS. There appeared to be an association between mortality and duration of organ dysfunction that might have important implications on the use of drotrecogin alfa in clinical practice. This finding suggested that earlier treatment with drotrecogin alfa (within 24h of the onset of organ dysfunction) may be associated with more favourable outcome (23.0% mortality vs 27.4%, p=0.014). New wording to reflect this information has been proposed in the SPC with the Type II variation EMEA/H/C/396/II/0014 for which the CHMP gave a positive opinion on 15 December 2004. Namely, section 4.2 "Posology and method of administration" in the SPC was amended to specify that "*treatment should be started within 48 hours, and preferably within 24 hours, of onset of the first documented sepsis-induced organ dysfunction"*.

In the assessment report on efficacy, the CHMP agreed that results on mortality in adults (25.3%) supported those of PROWESS (24.7%), but this was not surprising as the inclusion and exclusion criteria were similar in the two studies. It was also stated that the ENHANCE study provided additional information regarding the association between mortality, protein C activity levels at the end of the infusion and the change in protein C activity levels between baseline and end of infusion.

CHMP's conclusions

The final study report for ENHANCE has been submitted and examined by the CHMP. The MAH has answered all outstanding questions and the Type II variation EMEA/H/C/396/II/0014 has been submitted to amend the SPC especially with regard to the need for early onset of treatment: "*Treatment should be started within 48 hours, and preferably within 24 hours, of onset of the first documented sepsis-induced organ dysfunction"*. On 15 December 2004 the CHMP adopted a positive opinion for Type II variation EMEA/H/C/396/II/0014. The choice of the baseline population appears an extremely important factor in determining the benefit/risk balance of Xigris.

ADDRESS study

(Studies F1K-MC-EVCL and F1K-MC-EVCM)

ADDRESS was an international multicentre, randomised, double-blind, parallel, placebo-controlled study that was conducted as two separate sub-studies and investigated the efficacy and safety of drotrecogin alfa (activated) in adult patients with early stage severe sepsis (i.e. a lower risk of death). The primary objective was to investigate the differences in all-cause mortality. Additional safety objectives were to determine the rate for formation of anti-activated protein C (anti-APC) antibodies and to demonstrate that drotrecogin alfa (activated) has an acceptable safety profile in this patient population. One-third of the patients had multiple organ dysfunction (MOD), as compared with three quarters in PROWESS.

Enrolment of new patients was suspended based on a recommendation from the independent Data Monitoring Committee (DMC) on 9 February 2004. Upon review of an interim analysis report of 1500 patients enrolled in the trial, the DMC recommended discontinuation of enrolment based on a low likelihood of detecting statistically significant reduction in the 28-day mortality in patients at low risk of death from severe sepsis (i.e., stopping for futility). At the time of the second annual licence reassessment, the final clinical study report had not been completed; however, provisional data was included in the risk/benefit assessment of the expert report. On 15 December 2004 the MAH submitted the clinical study report for ADDRESS as part of the responses to the request for supplementary information that was adopted at the CHMP plenary meeting in November 2004. At the time the study was stopped, 2640 patients had been enrolled (1333 drotrecogin alfa, 1307 placebo).

Efficacy in ADDRESS study

Following the assessment of the preliminary data provided by the MAH, during its plenary meeting in November 2004, the CHMP concluded that further supplementary information on the ADDRESS study should be submitted by the MAH together with the final study report for ADDRESS before an agreement on the annual re-assessment could be reached. The request of supplementary information included also a list of questions on heparin-Xigris interaction to be addressed by the MAH (section "Scientific discussion on specific obligation 1").

On15 December 2004 the MAH submitted the clinical study report for ADDRESS study as part of the responses to request for supplementary information.

Xigris is indicated for the treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care. Since the results of the ADDRESS study indicated that the benefit/risk balance of Xigris may not be positive the MAH was requested to justify the current indication or propose a more restricted indication. In the ADDRESS study, there was no statistically significant beneficial effect of Xigris in a placebo-controlled subgroup of 455 evaluable patients (vs 407 placebo) meeting the inclusion criteria of severe sepsis with multiple organ failure. On the other hand safety was not improved over similar PROWESS patients.

Although, the CHMP acknowledged that the power to detect a significant difference in mortality within the subgroup of patients with MOD (multiple organ dysfunction) was insufficient, the CHMP

noted that the gain in outcome of sepsis patients with MOD receiving Xigris was minor: mortality was 20.7% versus 21.9%, i.e. an improvement of 1.2%, or a relative improvement of 5.5%. In PROWESS, the subgroup of patients with at least 2 acute organ dysfunctions at baseline benefited more clearly from Xigris: the mortality was 26.5% in the Xigris group (168 out of 634) and 33.9% in the placebo group (216 out of 637), i.e. an absolute improvement of 7.4% and a relative improvement of 22%.

The CHMP acknowledged that the absence of an obvious effect of Xigris in ADDRESS-MOD may be due to a selected population with a less severe status, and certainly with a lesser risk of death compared to PROWESS-MOD. Therefore the CHMP highlighted that it is crucial that intensive care unit physicians are able to discern, at baseline, which patients will benefit from Xigris based on clinical parameters. The presence of a suspected or known infection and two failing organs may be an insufficient combination of parameters.

In summary, it has to be admitted that there was an apparent lack of effect of Xigris in the ADDRESS-MOD subgroup, (the EU-indicated population), compared to the PROWESS-MOD group, which formed the very basis for this indication. This apparent lack of effect in ADDRESS-MOD is probably multifactorial:

- The major factor is a "**sequence effect**" phenomenon that was much more apparent in ADDRESS than in PROWESS due to the large number of centers with low recruitment (due to more heterogeneous trial and premature stopping). The statistical guidelines for futility provided to the Data Monitoring Committee of ADDRESS may have been inadequate as they did not account for a potential learning curve that might be observed in a clinical trial.

- For every level of OD (from 1 to 5 failing organs), **patients were less sick in ADDRESS**, as revealed by several parameters, in particular APACHE II or acute physiology scores, metabolic acidosis/shock, or the mere placebo mortality rates. Therefore the question to be addressed by the MAH was: among patients with severe sepsis and MOD, should the indication be restricted to "*those with a higher risk of death as assessed by either high APACHE II scores or acute physiology scores, or by the presence of shock* "?

- **Recent surgery** was a predictor of poor effect for Xigris in the ADDRESS study. However, the effect of Xigris has been demonstrated unambiguously in the more severely affected PROWESS pivotal patients, so in the CHMP's opinion recent surgery should not be put forward as a contraindication, provided patients with sufficiently severe sepsis are selected. The combination of recent surgery and a single organ failure is already excluded from the indicated population.

- The comparison between ADDRESS-MOD and PROWESS-MOD reinforces the importance of treating patients as early as possible after the development of sepsis. In the trials, the **time-to-onset of treatment** was calculated starting with the first organ failure. Treating within 24 h or even less was clearly more beneficial than waiting until the second day. However, due to the EU-based restriction to treat only MOD patients (i.e., at least a second organ must fail before Xigris is started), physicians must keep on the alert for optimal timing of Xigris.

Therefore the CHMP concluded that the involvement of an Ad Hoc Expert Group was necessary to address some issues, including: 1) the definition of a better target population for the indication of Xigris; 2) the question of patients with recent surgery and single organ failure; 3) the sequence effect and 4) the time to treatment.

1) Target population

The analyses of the successful pivotal PROWESS study demonstrated that the benefit/risk balance of Xigris was best ensured by restricting its use to severe sepsis patients with higher risk of death. The MAH continued to believe that the current indication of multiple organ dysfunction (MOD) does define a high-risk target population with a positive benefit/risk balance. In the PROWESS MOD subgroup, Xigris was associated with a relative risk of death of 0.78 compared to placebo (p=0.004, 95% confidence interval = 0.66–0.93, N=1271). These results from ADDRESS are consistent with those of PROWESS in that the 95% confidence interval for the ADDRESS results encompass the point estimate from PROWESS. In a combined analysis of all MOD patients from both PROWESS and ADDRESS, the relative risk was 0.82 (p=0.007, 95% confidence interval = 0.71–0.95, N=2133).

Comparison of MOD subgroup data from PROWESS and ADDRESS indicates that further clarification of the indicated MOD population would not result in the selection of clinically relevant populations with a greater or more consistent treatment benefit than the currently indicated group. For instance, the subgroups common to each study that had qualitatively similar findings (numerically lower mortality in the Xigris group compared to the placebo group) included: two organ dysfunctions at baseline, no vasopressors at baseline, mechanical ventilation at baseline, age ≥65 years, surgical patients, and medical patients. None of these characteristics is likely to be clinically useful as a means of further refining the indication. For instance, even though older age is associated with higher mortality, probably reflecting lower physiological reserve, an arbitrary age cut-off would not appear to be an appropriate way to clarify the indication.

In order to fully establish the benefit/risk balance, the MAH also evaluated the expected risks (serious adverse events, serious bleeding events, nonbleeding serious adverse events, CNS bleeding, and the combination of death or any serious bleeding event) in the chosen patient population in PROWESS, ADDRESS, and in the two studies combined. These analyses demonstrate that for both studies the relative risk of having a serious adverse event was similar for both Xigris and placebo patients.

The MAH concluded that the MOD population is a well-defined and easily identified patient population and therefore represents a suitable definition in clinical practice. As a matter of fact, post-marketing experience shows that as of November 2004, approximately 2000 patients have been treated across the EU, supporting the idea that Xigris is not being used broadly outside the indication. Additionally, data from the Belgium Xigris Reimbursement Registry shows that Xigris is only being used within the indicated population, and that 73% of patients even had three or more organ dysfunctions, indicating that Xigris use is largely confined to the more severely ill subset of the MOD population. Data from a similar registry in Italy supports these conclusions. Such observations do not suggest that further clarification of the indication would benefit the severe sepsis patients in the EU.

The Ad Hoc Expert Group and the MAH agreed that none of the characteristics identified by subgroup analyses in the PROWESS and ADDRESS studies is likely to be clinically useful as a means of further refining the indication. When asked whether a positive benefit/risk balance of Xigris had been demonstrated beyond reasonable doubt in all patients suffering from multiple organ dysfunction (MOD), the Expert Group was split. The lack of confirmatory or replication study in this very population was highlighted.

After assessing the Expert Group's conclusions, the majority of the CHMP acknowledged that there is a strong need to ensure that Xigris is used exclusively in high-risk patients, as an add-on to best standard care.

The majority of the CHMP concluded that the combined needs to target high-risk patients and to treat early can be met by amending the therapeutic indications in order to include "*The use of Xigris should be considered mainly in situations when therapy can be started within 24 hours after the onset of organ failure"* (see paragraph 4 "Change of the product information" of this report). Therefore the revised indication is: "Xigris is indicated for the treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care. *The use of Xigris should be considered mainly in situations when therapy can be started within 24 hours after the onset of organ failure* (for further information see Section 5.1)*"*.

2) Recent surgery and single organ failure

Xigris may increase mortality in the subgroup of patients with recent surgery and a single organ failure, both in ADDRESS and PROWESS. This effect was statistically significant in the ADDRESS study, but not in PROWESS, probably because the number of patients was much lower: only 98 patients met these criteria in PROWESS (5.8% of the whole population) vs 636 in ADDRESS study (24.1% of the whole population).

Among the explanations, it is possible that surgery in itself mimics many of the signs of sepsis and also results in the need for cardiovascular and respiratory organ support. The CHMP agreed with the MAH that surgical patients with single organ dysfunction may be a population where the risks associated with bleeding are not outweighed by survival benefit, and thus may represent a group of patients with an unfavourable risk/benefit profile for treatment with Xigris. The MAH proposed to translate this piece of information into a new warning in section 4.4 "Special warnings and special precautions for use" in the SPC (see paragraph 4 "Change of the product information" of this report).

3) "Sequence effect"

The CHMP agreed that the sequence effect is present in all sites (or most sites), irrespective of the final number of patients enrolled in that particular site. The role of protocol violations is possible although not formally proved in ADDRESS as such data were not available in that study.
The analyses of baseline imbalances in early- and later-enrolled patients revealed a few significant factors that could have played a role in the sequence effect, although this role should have been minor due to the small differences observed. In particular, later (3rd and onward)-enrolled patients tended to originate a little bit more frequently from centres in Europe (33.7% vs 28.9% for the first 2 patients; $p<0.001$) or in non-USA/Canada sites (60.5% vs 47.6% for the first 2 patients), and to be slightly more often on baseline heparin (60.7% vs 55% for the first 2 patients; $p<0.005$), with a trend towards unfractionated heparin. The mean time from first OD to treatment was 21.8 h for 3rd patients onward vs 24.1 h for the first >2 patients ($p<0.001$), again a small but understandable difference.
The CHMP was of the opinion that none of these factors is worth highlighting as a *major* explanation for the sequence/learning curve effect. Similarly, according to the MAH's analysis, no obvious bias seemed to have been introduced between patients excluded from the placebo and the Xigris arms during sequence effect analysis.
Although the sequence effect was clear in both ADDRESS-MOD and in ADDRESS patients with APACHE II score >24, it was absent from the same subgroups in PROWESS. This disparity may be related to the fact that patients were sicker in PROWESS, but there may also be other reasons that could not be quantified based on the ADDRESS data.

The involvement of an Ad Hoc Expert Group was necessary to address the issue of the "sequence effect" and its clinical relevance.
Overall, the expert group was inclined to conclude that the so-called learning curve could merely reflect a marginal efficacy of Xigris in the lower risk patients in the ADDRESS study.

The majority of the CHMP agreed with the MAH's suggestion to adapt Section 4.2 of the SPC to include "Xigris should be *used by experienced* ~~prescribed by~~ doctors ~~experienced~~ *in institutions skilled* in the care of patients with *severe* sepsis".

The majority of the CHMP concluded that the information on the "sequence effect" should be reflected in section 5.1 of the SPC as well.

4) Time to treatment

The MAH was requested to discuss the effect of time-to-treat on the mortality rates. The MAH agrees that, once patients are diagnosed with severe sepsis with MOD, treatment with Xigris should be started as soon as possible. In the open label ENHANCE study, where the median time to treatment was 25 hours, lower mortality was observed in those patients treated with Xirgis ≤ 24 hours from the first sepsis-induced organ dysfunction compared to those treated >24 hours, and this obsevation is

mentioned in the SmPC. It should be noted that although the benefit might be increased in patients treated early, this does not mean that patients treated later have no benefit.

The involvement of an Ad Hoc Expert Group was necessary to assess the importance on the time to treatment.

The experts and the MAH were in general agreement on the need for early treatment of any patient with newly-diagnosed sepsis-induced multiple organ dysfunction. Data from the ENHANCE study, with a patient population very similar to that in PROWESS, reinforce this impression.

However, the CHMP noted that what has not been considered is the importance of the time-frame between the first and the second organ failures. Yet, it should be reminded that the PROWESS trial was globally positive, and in that trial 89% of the patients were treated within 24 hours of the first sepsis-induced organ dysfunction (median time to treatment = 18h). In ADDRESS-MOD, that time was appreciably longer: 26.6h. A short interval between the first and second organ failures may reflect either the severity of the disease or a lower physiological reserve, meaning a higher risk of death and therefore a better response to Xigris.

It means that instead of using an illness severity score, with its many shortcomings, requiring the use of Xigris mainly in situations when therapy can be started within 24 hours after the onset of organ failure may be a better way to restrict the indication to the sickest patients and thereby to increase the benefit/risk balance of Xigris.

Therefore, the majority of the CHMP concluded to change the current indication to include "*The use of Xigris should be considered mainly in situations when therapy can be started within 24 hours after the onset of organ failure"*. Therefore the revised indication is: "Xigris is indicated for the treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care. *The use of Xigris should be considered mainly in situations when therapy can be started within 24 hours after the onset of organ failure* (for further information see Section 5.1)*"*. (See paragraph 4 "Change of the product information" of this report).

CHMP's conclusions

"Sequence effect" in PROWESS and ADDRESS

Although the MAH stated that the sequence effect is a sign of a learning curve for the investigators, similar to what happens in the management of many complex disease states, it may rather reflect a marginal efficacy of Xigris in the lower risk patients in the ADDRESS study.

The majority of the CHMP agreed with the MAH's suggestion to adapt Section 4.2 of the SPC to include "Xigris should be *used by experienced* ~~prescribed by~~ doctors ~~experienced~~ *in institutions skilled* in the care of patients with *severe* sepsis".

Further the CHMP agreed that the observed sequence effect should be mentioned in section 5.1 in the SPC.

Target population and early treatment

None of the characteristics identified by subgroup analyses in the PROWESS and ADDRESS studies is likely to be clinically useful as a means of further refining the indication. However, the majority of the CHMP concluded that the combined needs to target high-risk patients and to treat early may be met by adapting the indication as follows:

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

The arguments in support of this proposal are:

- In the globally positive pivotal trial PROWESS, 89% of the patients were treated within 24 hours of the first sepsis-induced organ dysfunction (median time to treatment = 18h). In ADDRESS-MOD, that time was appreciably longer: 26.6h. In the open label ENHANCE study, where the median time to treatment was 25h, lower mortality was observed in those patients treated with Xigris ≤ 24 hours from the first sepsis-induced organ dysfunction compared to those treated >24 hours.

- A short interval between the first and second organ failures may reflect either the severity of the disease or a lower physiological reserve, meaning a higher risk of death and therefore a better response to Xigris.

Instead of using an illness severity score, with its many shortcomings, requiring the use of Xigris mainly in situations when therapy can be started within 24 hours after the onset of organ failure may be a better way to restrict the indication to the sickest patients and thereby to increase the benefit/risk balance of Xigris.

3.2 Safety and Pharmacovigilance aspects

3.2.1 Safety Reviews since the first annual risk/benefit assessment

The following safety review documents have been submitted to the CHMP since the last benefit/risk assessment:

Periodic Safety Update Reports:	PSUR n. 3 (22 May 2003 – 21 November 2003)
	PSUR n. 4 (22 November 2003 – 21 May 2004)
	PSUR n. 5 (22 May 2004 – 21 November 2004)

3.2.2 SPC changes since the last risk/benefit assessment

Following the review of the first two PSURs, the Type II variation EMEA/H/C/000396/II/0008 was submitted on 23 December 2003 to update the SPC with new information on overdose cases from spontaneous reports. On 24 March 2004 the CPMP adopted an opinion on this variation. The variation included changes in section 4.9 (Overdose) and section 6.6 (Instruction for use and handling) in the SPC. The MAH also committed to make a proposal to reduce the number of overdose cases.

On 15 December 2004, the CHMP adopted an opinion on Type II variation EMEA/H/C/396/II/0014, for an update of the sections 4.2 (Posology and method of administration), 4.4 (Special warnings and special precautions of use), 4.8 (Undesirable effects), and 5.1 (Pharmacodynamic properties) in the SPC with relevant data from the ENHANCE study. Further, in line with the post-opinion commitment from variation EMEA/H/C/396/II/008, the MAH proposed a further change to section 4.2 (Posology and method of administration) and 6.6 (Instructions for use and handling) of the SPC and the instructions for use and handling in the Package Leaflet.

3.2.3 Safety in clinical trials

Safety in ENHANCE study

The incidence of serious bleeding events during the infusion period was higher in ENHANCE patients compared to drotrecogin alfa (activated) patients in PROWESS (3.6% vs 2.4%). This was attributed to the enrolment of patients with a higher risk of bleeding. Primary baseline predictors of bleeding during the infusion were hepatic SOFA score, any surgery, haematology SOFA score and site of infection class. The incidence of haemorrhage-related deaths and study-drug related deaths in ENHANCE was the same or lower than that observed in PROWESS.

According to the CHMP who assessed the results of the ENHANCE study, the most important conclusions from the safety part of the study were:

- there was a higher rate of serious bleeding event in this observational study than in the PROWESS trial (3.6% vs 2.4% during the infusion period and 6.5% vs 3.5% in the 28-day study period); a difference between the two studies was found for all indicators except for study-drug related deaths (0.4%) and hemorrhage-related deaths (0.7%), despite the fact that efficacy was similar in ENHANCE and PROWESS;
- a higher percentage of patients presented risk factors for bleeding in the ENHANCE study, e.g., low platelet count, surgical procedure, organ dysfunction or age class; this might at least partly explain the differences between the two studies;
- the most frequent serious bleeding events during the infusion period were gastrointestinal and intra-abdominal, both occurring at a rate of 0.8%, intracranial haemorrhage occurred at a rate of 0.6%; independent adjudication of the intracranial haemorrhage cases showed most of them had an underlying cause;
- in adults, 9 deaths were considered possibly related to the drug by the investigator; however, these cases had sepsis, organ dysfunction and multiple concomitant drugs; the cause of death was haemorrhage in all cases;
- co-administration of heparin did not increase the risk of bleeding;

- an original aspect of this study was the inclusion of children aged <18 years; the serious bleeding rate (5.9% during infusion and 8.5% during the 28-day study period) was higher than in adults, but the two groups may probably not be compared; only one child died for a reason thought to be drug-related and one death (due to haemorrhage) was considered possibly related to the drug;

Safety in ADDRESS study

On the safety side, the ADDRESS study confirmed a small but statistically significant increased risk of serious bleeding during the infusion period (2.3% of Xigris patients vs 1.1% of controls). The expert states that this rate was similar to that in PROWESS (2.4%), but it should be reminded that the patient population in PROWESS had more severe sepsis. The numbers of hemorrhagic deaths during the 28-day period was 7 in the Xigris group (4 of which occurred in patients with recent surgery and single organ failure) and 2 in the placebo group. The rate of CNS bleeding appeared similar between drotrecogin alfa and placebo (0.3% and 0.2%, respectively). Although the DMC stated that there was a safety concern related to the higher incidence of serious bleeding events for patients receiving Xigris, this trend was expected in patients receiving active treatment.

Bleedings

Some factors that may predict a higher risk of bleeding have been highlighted in ADDRESS. Apart from those already mentioned in the SPC as contraindications or special warnings, one may note that recent surgery (within 30 days prior to study entry) was associated with a numerically, if not statistically significantly, higher risk of serious bleed during the infusion period in ADDRESS: 18/496 (3.63%) patients with recent surgery had a serious bleeding event versus 13/818 (1.59%) without recent surgery. For the placebo group, the corresponding values were 1.61% and 0.88%, respectively. However, the interaction p-value was not significant.

The majority of the CHMP agreed on the proposal from the MAH to include information on bleeding events regarding the ADDRESS study in section 4.8 "Undesirable effects" in the SPC (see paragraph 4 "Change of the product information" of this report).

3.2.4 Update on Post-marketing safety data

As of April 2004, it is estimated that 38,656 patients have been exposed to marketed drotrecogin alfa. Direct comparison of spontaneous reports to clinical trial reports is difficult given the inherent reporting bias prevalent in spontaneous reporting.

The reporting rate of bleedings is presented in the following tables, for CNS and non-CNS bleedings.

Rates of **non-CNS bleedings** from the spontaneous reporting system and studies

	Spontaneous reporting	**PROWESS**	**ENHANCE**	**ADDRESS**
Non-CNS serious bleeding during infusion	0.51%	2.1%	3.1%	2.1%
Non-CNS serious bleeding, incl. unknown timing	0.56%			

Rates of **CNS bleedings** from the spontaneous reporting system and studies

	Spontaneous reporting	**PROWESS**	**ENHANCE**	**ADDRESS**
CNS serious bleeding during infusion	0.18%	0.2%	0.6%	0.3%
CNS serious bleeding, incl. unknown timing	0.22%			

The MAH suggests that the severity of CNS bleedings is associated with a higher reporting rate than for non-CNS bleeds, explaining that the rate of CNS bleeding is similar for the spontaneous reporting system and for clinical trials.

In PSUR #4, the analysis of spontaneous events showed that reporting rates for serious bleeds were higher in Europe and rest of the world than in the U.S. A similar trend was noted for CNS bleeds in the ENHANCE study. There is no apparent explanation for the difference.

In PSURs numbers 3 and 4, cumulative review of cases of thrombosis, disseminated intracoagulation and thrombocytopenia were performed. In PSUR#4, the CHMP concluded that "regular" monitoring through line listings (there is no need to include a specific review of all cases) was considered sufficient for the following events: disseminated intracoagulation disorders, thrombotic disorders, coagulation disorders, cardiac disorders and allergic disorders. However, the following issues had to be continuously monitored: bleeding disorders, thrombocytopenia, and ADRs in children, including an estimation of their frequency in ongoing paediatric clinical trials.

The MAH proposes to discontinue the special monitoring of thrombocytopenia events that have been undertaken since PSUR#2, because the rate of thrombocytopenia or platelet count decreased has remained constant in the last three reports and there is no evidence to suggest a link between drotrecogin treatment and thrombocytopenia. The CHMP's conclusions regarding thrombocytopenia platelet count decreased in PSURs#2, #3 and #4 are reported in the table below:

PSUR	Conclusion
#1	A few cases of thrombocytopenia were believed to have been related to the administration of drotrecogin alfa (activated), but their assessment is difficult due to the underlying clinical condition and the lack of details in the ADR report. The company is asked to concentrate on such cases in the future.
#2	The MAH concludes that the information reviewed from the data does not support a causal association between drotrecogin alfa and thrombocytopenia and platelet count decrease. However clinical trial data show that more patients experience a decrease in the platelet count during treatment with drotrecogin alfa than with placebo, even if the difference is small. Regarding the death rate and organ dysfunction, it is difficult to distinguish the effect on sepsis from the possible thrombocytopenic effect.
#3	Assessment of data of PSUR#3 does not lead to change the conclusion of PSUR#2. The reporting rate is 0.63%, to be compared to 0,56% in PSUR#2 and 1.27% in PSUR#1. Thrombocytopenia and decreased platelet count still require a specific monitoring in the following PSURs.
#4	The CHMP agrees with the MAH's evaluation that at this stage there does not appear to be a causal relationship of drotrecogin alfa (activated) to thrombocytopenia

In PSUR#4, the CHMP considered that the monitoring of cases of thrombocytopenia should be continued. This conclusion is unchanged at the present time, and monitoring of cases of thrombocytopenia should be continued for PSUR#5.

The MAH has provided a line listing of spontaneous reports from 22 May 2004 to 21 August 2004. A total of 80 reports (73 spontaneous and 7 post-marketing study cases) containing 152 events (109 serious and 43 non serious) have been received. They included 20 CNS bleeding events, 29 non-CNS serious bleeding events and 11 non-serious bleeding events reported. There were also 9 serious thrombotic events and 20 thrombocytopenia/platelet count decreased events. All these rates are within reporting rate fluctuations seen on a monthly basis. There were no significant increases in reporting rates compared to previous reporting periods for any group of events. The MAH concludes that no new significant safety issue has been identified during this reporting period.

CHMP's conclusions

The majority of the CHMP agreed that no new safety issue has emerged from these data.

In PSUR#4, the CHMP considered that the monitoring of cases of thrombocytopenia should be continued. This conclusion is unchanged at the present time, and monitoring of cases of thrombocytopenia should be continued for PSUR#5.

4. Change of the product information

The MAH and the majority of the CHMP agreed that the following changes were necessary at this time in light of the data coming from the ADDRESS study.

SUMMARY OF PRODUCT CHARACTERITICS

Section 4.1 "Therapeutic indications"

Following the scientific discussion on the target population and the early treatment with Xigris, the majority of the CHMP and the MAH agreed to change the indication as follows:

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

Section 4.2 "Posology and method of administration"

Following the scientific discussion on the "sequence effect" with Xigris, the majority of the CHMP and the MAH agreed to add the following text:

> *"*Xigris should be *used by experienced* ~~prescribed by~~ doctors ~~experienced~~ *in institutions skilled* in the care of patients with *severe* sepsis*"*.

Section 4.4 "Special warnings and special precautions for use"

The majority of the CHMP agreed on the following text based on the proposal from the MAH:

> *"Patients with single organ dysfunction and recent surgery*
> *Xigris is not approved for the treatment of patients with single organ dysfunction and should not be used in this particular subgroup of patients, especially if they had recent surgery (within 30 days). In each of two randomized, placebo-controlled trials, PROWESS and ADDRESS (see 5.1), ~~post-hoc analyses showed that~~ 28-day and in-hospital mortality were higher in patients treated with drotrecogin alfa (activated) compared to placebo for the sub-population of patients with single organ dysfunction and recent surgery (n=98 in PROWESS and n=636 in ADDRESS).~~The observation in this particular group may have resulted from difficulty in determining whether the organ dysfunction was sepsis-induced~~*".

Section 4.8 "Undesirable effects"

The majority of the CHMP agreed on the changes proposed by the MAH.

Section 5.1 (Pharmacodynamic properties):

The majority of the CHMP agreed on the changes proposed by the MAH.

II OBLIGATIONS PENDING TO BE FULFILLED

The MAH shall complete the following programme of studies within the specified time frame, the results of which form the basis of the second annual re-assessment of the benefit/risk profile.

1. Specific Obligations (SO)

CLINICAL DATA

SPECIFIC OBBLIGATION 1

> *"A further clinical study will be conducted to investigate the possible interaction between Xigris and heparin. The study will start within 3 months of receiving the Scientific Advice final letter. Update on patient enrolment will be provided quarterly. The final study report will be provided by the end of June 2005."*

The MAH was asked to further discuss a potential "heparin phenomenon" based on observations from the pivotal PROWESS study (F1K-MC-EVAD). As part of the Specific Obligations for drotrecogin alfa (activated), the MAH agreed to undertake a clinical study to investigate the possible interaction between drotrecogin alfa (activated) and heparin. After obtaining scientific advice from the CHMP, two studies have been initiated :

- **Study F1K-MC-EVCL/F1K-MC-EVCM (ADDRESS)**: multicentre, randomised, double-blind, parallel, placebo-controlled study design to evaluate the efficacy and safety of drotrecogin alfa (activated) in patients with early stage severe sepsis who are at low risk of death. This study was discontinued.
- **Study F1K-MC-EVBR**; this study will enrol approximately 2,000 patients who will be blindly randomised to receive unfractionated heparin, low molecular weight heparin or placebo in a 1:1:2 ratio. All patients will receive Xigris.

After the early stop of ADDRESS, it is obvious that the data will not provide all of the anticipated information on the heparin-drotrecogin alfa (activated) relationship, and this is unfortunate.

The expert discusses this issue in great detail. What is not easily explainable is the difference between PROWESS, ENHANCE and ADDRESS when it comes to the relative risk of death in the group of patients treated with heparin.

Indeed, if one considers only the Xigris-treated patients:

- a slightly higher mortality with heparin use was observed in PROWESS (RR=1.15 for all baseline heparin exposure, but only 1.03 after adjustment; RR=1.31 for any heparin exposure, reduced to 1.13 after adjustment; although these differences are not statistically significant);
- whereas in ENHANCE, the trend was opposite (RR=0.88 for all baseline heparin exposure, with or without adjustment; R=0.85-0.82 for any heparin exposure; the latter RR reveals a significant interaction as mesured in a Cox regression model);
- and in ADDRESS, heparin treatment was also associated with a lower risk of death (RR=0.95-0.91 for all baseline heparin exposure; RR=0.81-0.77 for any heparin exposure; p=0.05 in a Cox model after adjustment). In the ADDRESS MOD subgroup, "any exposure" to heparin was clearly associated with a better outcome (RR=0.57, Chi-square p=0.01).

If one considers the placebo patients in PROWESS and ADDRESS, all RR's for heparin use vs no use were slightly below 1 but non-significant. In the ADDRESS MOD subgroup, they were slightly above 1.

The expert reiterates the biases induced by analyzing a variable (heparin exposure) that is time-dependent. These biases are well acknowledged.

According to the expert, any further understanding of a potential "heparin-drotrecogin alfa (activated) phenomenon" could only come from the data of a randomised study such as the ongoing EVBR study (Xigris therapy with or without randomised heparin). Quoting a large literature, the expert explains that the efficacy of high- or low-molecular weight heparin for preventing death in human sepsis has never been demonstrated (even in patients with DIC), that heparin and LMWH are heterogeneous mixtures and may very well have different effects, and that preclinical trials of heparins in animal models of sepsis have shown inconsistent results. The expert concludes that few data would support the conduct of a Phase III study of heparin vs placebo, or heparin vs Xigris, in severe sepsis.

Consequently, the MAH states it has made every effort to fulfil the Specific Obligation about the heparin phenomenon.

Scientific discussion on specific obligation 1

The only consistent conclusion from the "heparin" data of the PROWESS, ENHANCE and ADDRESS studies presented in the expert report is that concomitant heparin use in Xigris-treated patients tends to signal a favourable outcome in ENHANCE and ADDRESS but not in PROWESS, whereas concomitant heparin use in placebo-treated patients was associated with a rather favourable outcome in both ADDRESS and PROWESS (there was no placebo group in ENHANCE).

During the November 2004 CHMP plenary meeting the CHMP concluded that further supplementary information on clinical aspects, including also the heparin-Xigris interaction, should be submitted by the MAH before an agreement on the annual re-assessment could be reached. Therefore, during the November 2004 CHMP plenary meeting, the CHMP adopted the request for supplementary information to be addressed by the Marketing Authorisation Holder.

Further analyses of the potential heparin-Xigris interaction across the three studies PROWESS, ENHANCE and ADDRESS confirmed the prediction that prophylactic heparin tends to be used in patients with a lower risk of death. The possible reduced efficacy of Xigris when combined with heparin in the overall PROWESS study is not confirmed when the analysis is restricted to the MOD subgroup, or when the same analysis is performed on the ADDRESS study data. Prophylactic heparin does not raise any particular safety issue and it should not be contraindicated in patients receiving Xigris. The results of the specific heparin-Xigris interaction study F1K-MC-EVBR will be available in 1Q2006.

CHMP's conclusions on specific obligation 1

More data on the effect of heparin, or at least on the safety of concomitant use of heparin and drotrecogin alfa (activated), will come from the randomised study EVBR. Until then, the exceptional circumstances for granting Xigris a MA should not be lifted.

Trials comparing Xigris with heparins would be interesting in MOD sepsis patients. Maybe one will have to wait until a particular type of heparin, or heparin mimetic, or a combination of anticoagulant and antiinflammatory medications, has demonstrated some benefit in early Phase II studies before such a comparison can be run. For instance, several published reports of heparins in "classical" animal models of sepsis (continuous endotoxin infusion or cecal ligation-puncture) have demonstrated a reduction in mortality when therapeutic, but not prophylactic, doses of unfractionated heparin were used (see Schiffer et al., 2002; Yang et al., 1994; and even Sun et al., 1997, where improvements in early survival rates and survival times were demonstrated).
Finally, it should be realized that the concern of the CHMP, when looking at the heparin data in the PROWESS study, was that some subgroup of patients may clearly not benefit, or may even suffer, from drotrecogin alfa (activated) treatment. The hint that heparin-treated patients may represent such a group was not confirmed by the subsequent studies ENHANCE and ADDRESS, and that is well acknowledged. However, the ADDRESS study has now identified a subgroup of patients who may suffer from Xigris treatment (patients with recent surgery and single organ failure).

The majority of the CHMP was favourable to maintain the specific obligation 1. According to the letter of Undertaking submitted by the MAH, the final study report will be provided by end of February 2006 instead of end of June 2005.
Therefore the revised specific obligation 1 will be:

> *"A further clinical study (F1K-MC-EVBR) is being conducted to investigate the possible interaction between Xigris and heparin. Update on patient enrolment will be provided at the time of the annual license reassessment. The final study report will be provided by the end of February 2006".*

SPECIFIC OBBLIGATION 2

> *"All bleeding events will be addressed every 6 months by providing a detailed section on bleedings in the PSURs."*

Cumulative bleeding reports (risk of bleeding) have been provided in each of the two PSURs (January 2004 and July 2004).
According to the MAH, no new signals have arisen and the data confirms the safety of drotrecogin alfa as established at the time of initial approval. Given that the reporting of serious bleeding events (both CNS and non-CNS) has remained relatively constant, together with the difficulty in identifying specific risk factors from spontaneous reports in the population of severe sepsis which has a high rate of associated morbidity, the MAH proposes that it would be appropriate to discontinue the specific obligation of producing a six monthly bleed report. The monitoring of bleeding events could now be adequately covered by the general obligation of submitting a PSUR on a regular basis.

The CHMP's conclusions from special reports on bleeding events in PSURs #1, #2, #3 and #4 are presented in the following table :

PSUR	Conclusion
#1	• No new signal has arisen thus far. The apparently increased risk of bleeding in open trials versus controlled trials has already been stressed in the SPC. It does not seem to worsen, provided one follows the company's advice not to include the "anaemia without bleeding site" in the "bleeding events". • The same holds for intracranial haemorrhage. Therefore, no changes to the SPC concerning this issue seem suitable at this time. • This bleeding safety issue needs further close monitoring. A special report on bleeding events should be prepared for the next PSUR. • The anticoagulant effect of Xigris, which relates to inactivation of factors Va and VIIIa, is probably increased in patients with low platelet counts. The relationship between adverse bleeding and thrombocytopenia should therefore be examined more carefully. • The company states that there seems to be no significant difference in the incidence of bleeding events in children versus adults, but since the number of paediatric patients who have been treated is unknown, this cannot be demonstrated.
#2	The report provided with PSUR# 2 does not alter the evaluation made in PSUR#1. The apparently increased risk of bleeding in open trials versus controlled trials is already mentioned in the SPC. The overall bleeding rates provided by spontaneous reporting were small and in general consistent with the clinical data, although a direct comparison between both sources of information is impossible due to several reasons such as underreporting of spontaneous reports. Moreover, there is an association of an increased risk of bleeding and intracranial haemorrhage with severe thrombocytopenia and severe coagulopathy. Other risk factors, such as prophylactic heparin administration, should be further studied. Bleeding events should be continuously monitored. However, only new information should be assessed in the next PSUR.
#3	Data from the spontaneous reporting system are consistent with clinical trial data regarding the high risk of haemorrhage associated with Xigris. They also show that haemorrhage can occur in a large number of different sites. Although the fatality rate is much lower for Xigris-related non-ICH events than for Xigris-related ICH events (15.9% vs. 51.6%), both contributed to a large percentage of the total number of deaths in these patients (respectively 36.4% and 84.2%). In the analysis of the results of the ENHANCE study, the MAH has assessed risk factors associated with fatality. It would also be useful to examine risk factors associated with lethality due to ICH and non-ICH haemorrhage and evaluate if they differ according to the

	location of bleeding. For intracranial haemorrhage, it would be useful to have information on the long-term follow-up in terms of disabilities and neurological consequences. As there have been 83 spontaneous reports of serious bleeding events, 32 intracerebral haemorrhage and 51 non-intracerebral haemorrhage in this reporting period, information on bleeding events from post-marketing data should be reflected in section 4.8 of the SPC.
#4	Bleeding rates from clinical trials are comparable to those reported in the previous PSUR. Data for the period of interest do not raise new concerns. Spontaneous pharmacovigilance data presented in the PSUR do not add new information with respect to the risk of bleeding. In the context of the evaluation of the results of the ENHANCE study, the assessor has recommended a revision of sections 4.4 and 4.8 of the SPC, especially regarding bleeding events and intracranial haemorrhage. The amendment of the SPC is ongoing.

It can be concluded from the evaluation of special reports provided in PSURs #1 to #4 that bleeding rates from open post-marketing studies are apparently higher than in controlled trials. Additional clinical trials carried out post-authorisation have confirmed data from previous trials. Data from the spontaneous reporting system examined in the four PSURs have not added new information in comparison to what was already known from clinical trials. Results of the ENHANCE study suggest that this difference is probably associated with differences in the study population, particularly in patients' risk set. The SPC has been revised insections 4.4 and 4.8 in order to reflect information gathered in the ENHANCE study regarding bleeding events and intracranial haemorrhage.

CHMP's conclusions on specific obligation 2
Therefore, the majority of the CHMP was favourable to the MAH's request to discontinue the specific obligation of producing a six monthly bleed report.

2. Follow-up Measure (FUM)

CLINICAL

Follow-up Measure 1 (FUM 017)
Progress report on the paediatric study (F1K-MC-EVBP)
(From letter of undertaking dated 20th April 2005)

"FOM 1: Paediatric study: A further clinical study has been conducted in children with severe sepsis, including patients with purpura fulminans. The final study report will be provided by the end of October 2005."

The MAH is conducting a study, F1K-MC-EVBP, in children with severe sepsis, including patients with purpura fulminans. As of 31st August 2004, 360 patients have been enrolled, with 130 centers in 18 countries currently active.

Enrolment in the paediatric study F1K-MC-EVBP was suspended based on the feedback from the Data Monitoring Committee (DMC). On 8 March 2005 the DMC met to review the interim analysis report of 400 patients enrolled in the trial and it recommended that Lilly should suspend enrolment based on futility in paediatric patients with severe sepsis.
On 9 March 2005 the MAH decided to accept the DMC's recommendation: the enrolment was suspended and study drug administration was discontinued. The trial is still ongoing until all patients complete Day 28. The final study report will be provided by the end of October 2005.

Further commitment from variation EMEA/H/C/396/II/007:
(From letter of undertaking dated 20th April 2005)
Lilly agrees to provide data from a study on two full-scale lots to further support three freeze/thaw cycles in conjunction with 36 months storage.
Data will be submitted by September 2005.

PHARMACEUTICAL

Already submitted as of November 2004, but evaluation still ongoing

FOM 4: From question 17
Data on the validation of the lyophilizer.

FOM 5: From question 38
Lilly agrees to submit data on the Tandem Chromatography column lifetime.

FOM 12: From questions 50, 52 and 58
Data on the clearance of SV40 by the Xigris nanofiltration process step. Data on the evaluation of SV40 clearance by gamma irradiation of Fetal Bovine Serum and the ExCyte process steps will also be submitted.
Testing for Bovine Polyoma Virus in Fetal Bovine Serum, Thrombin and Excyte and in 5 Xigris process bioreactors will be conducted when a validated method is available. It is estimated that data will be available by the end of July 2004.

FOM 13: From the Inspection of DSM-Pharmaceuticals
Additional information regarding environmental controls (also from question 19 on the marketing authorisation application).

FOM 18: From question 20
Lilly agrees to re-evaluate the acceptable Comparative Ratio ranges for the oligosaccharide profile method to mean +/- 4SD based on analysis of all full-scale Drug Substance batches using the current reference standard and the first 20 analyses of full-scale batches using the new rhAPC Reference Standard. It is estimated that these data will be available for submission in July 2004.

FURTHER COMMITMENTS ON PSURs

The MAH commits to further monitor the following issues in the third PSUR:
Thrombocytopenia, coagulation disorders (increased and prolonged prothrombin time), bleeding disorders, incl. Intracranial haemorrhage, with discussion of risk factors such heparin administration; thrombotic events, including stroke and acute myocardial infarction; cardiac conduction disorders and allergic reactions.

Concerning specific post-marketing measures, the CHMP recommends:
- to discontinue the specific obligation of producing a six monthly bleed report;
- to discontinue the specific monitoring of disseminated intracoagulation disorders, thrombotic disorders, coagulation disorders, cardiac disorders and allergic disorders, such as recommended in PSUR#4;
- to continue the monitoring of cases of bleeding disorders, thrombocytopenia and ADRs occurring in children, including an estimation of their frequency in ongoing paediatric clinical trials.

III BENEFIT/RISK ASSESSMENT

The majority of the CHMP concluded that there is a strong need to ensure that Xigris is used exclusively in high-risk patients, as an add-on to best standard care. This goal could be reached by: (i) requesting an amendment in section 4.2 in the SPC ("*Xigris should be used by experienced doctors in institutions skilled in the care of patients with severe sepsis*"), and by: (ii) defining the target population as those patients that can be treated early, i.e. *"The use of Xigris should be considered mainly in situations when therapy can be started within 24 hours after the onset of organ failure"* (section 4.1 in the SPC).

"Sequence effect" in PROWESS and ADDRESS

Although the MAH stated that the sequence effect is a sign of a learning curve for the investigators, similar to what happens in the management of many complex disease states, it may rather reflect a marginal efficacy of Xigris in the lower risk patients in the ADDRESS study.

The majority of the CHMP agreed with the MAH's suggestion to adapt Section 4.2 of the SPC to include "Xigris should be *used by experienced* ~~prescribed by~~ doctors ~~experienced~~ *in institutions skilled* in the care of patients with *severe* sepsis".

The majority of the CHMP concluded that the sequence effect should be mentioned in section 5.1 in the SPC.

Target population and early treatment

None of the characteristics identified by subgroup analyses in the PROWESS and ADDRESS studies is likely to be clinically useful as a means of further refining the indication. However, the majority of the CHMP concluded that the combined needs to target high-risk patients and to treat early may be met by adapting the indication as follows:

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

The arguments in support of this proposal are:

- In the globally positive pivotal trial PROWESS, 89% of the patients were treated within 24 hours of the first sepsis-induced organ dysfunction (median time to treatment = 18h). In ADDRESS-MOD, that time was appreciably longer: 26.6h. In the open label ENHANCE study, where the median time to treatment was 25h, lower mortality was observed in those patients treated with Xigris ≤ 24 hours from the first sepsis-induced organ dysfunction compared to those treated >24 hours.
- A short interval between the first and second organ failures may reflect either the severity of the disease or a lower physiological reserve, meaning a higher risk of death and therefore a better response to Xigris.

Instead of using an illness severity score, with its many shortcomings, requiring the use of Xigris mainly in situations when therapy can be started within 24 hours after the onset of organ failure may be a better way to restrict the indication to the sickest patients and thereby to increase the benefit/risk balance of Xigris.

However, two CHMP members had a divergent opinion. They were of the view that the results of the ADDRESS study did not show a difference between Xigris and placebo either in the total, included population or in the subgroup with multiple organ failure and this raised concerns with regard to the efficacy of Xigris in the indication approved in the EU. They considered the benefit/risk profile of Xigris unfavourable in the current indication and therefore these two CHMP members recommended the suspension of the Community Marketing Authorisation for Xigris.

Nevertheless the majority of the CHMP considered that the benefit/risk profile of Xigris was favourable and concluded that the combined needs to target high-risk patients and to treat early could be met by amending the therapeutic indications of Xigris.

IV OVERALL CONCLUSION AND RECOMMENDATION

On the basis of the data submitted since the first annual re-assessment, the benefit/risk profile for Xigris in the indication: *"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 II of the Community Marketing Authorisation for Xigris.
On 21 April 2005 the CHMP adopted a positive Opinion by a majority of 24 out of 26 votes on the second annual re-assessment of the benefit/risk profile of Xigris.
A revised Letter of Undertaking dated 20 April 2005 to revise Specific Obligations and Follow-up Measures has been adopted accordingly by the CHMP.