London, 22 February 2007
Product name: **XIGRIS**
Procedure No**: EMEA/H/C/000396/S/0021**

SCIENTIFIC DISCUSSION

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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.
See section III OBLIGATIONS PENDING TO BE FULFILLED related to pharmaceutical follow-up measures.

1.2 Preclinical aspects

No additional data have been provided with this submission.

1.3 Clinical aspects

The Marketing Authorisation Holder (MAH) has submitted the following documents to support the 4th annual re-assessment of Xigris:

- update on clinical trials during the past 12 months;
- update on planned Phase II Protein C Study F1K-MC-EVDK (RESPOND);
- update on the PROGRESS registry (observational study);
- publications;
- update on Spontaneous Safety Data from the market during the past 12 months.

1.3.1 Update on clinical trials during the past 12 months

As of 21 August 2006, a total of up to 6,894 adult patients have been exposed to Xigris in completed and ongoing clinical trials.

The preliminary final report on the RESOLVE (paediatric) study was assessed by the CHMP in the framework of the Type II variation EMEA/H/C/000396/II/0016 (opinion adopted at the October 2005 CHMP plenary meeting). The interim analysis of the RESOLVE study did not show a significant difference in the primary endpoint of "Composite Time to Complete Organ Failure Resolution" in the Xigris and placebo groups (CTCOFR score of 9.8 versus 9.7 mean days, respectively). There was also no difference in 28-day mortality in the Xigris and placebo groups (17.1% versus 17.3%, respectively). The CHMP concluded that the data from the RESOLVE study did not establish the efficacy of Xigris in paediatric patients suffering from severe sepsis, acute infection, systemic inflammation and respiratory and cardiovascular organ dysfunction. Thus, the CHMP concluded that no dosage recommendation could be made and the use of Xigris was not recommended in children below the age of 18.

The final report on the XPRESS (heparin interaction) study was under assessment within the parallel Type II variation EMEA/H/C/000396/II/0020 (opinion adopted at the February 2007 CHMP plenary meeting). For the CHMP's discussion and conclusion on the XPRESS study, refer to section II of this assessment report.

1.3.2 Update on planned Phase II Protein C Study F1K-MC-EVDK (RESPOND)

Study F1K-MC-EVDK (RESPOND) is a Phase II exploratory study. The results of this Phase 2 study are intended to give information on the design of a potential randomised, controlled Phase 3 study. CHMP scientific advice would be sought prior to initiating such a Phase 3 study. The ultimate goal of this clinical development program is to establish serial plasma protein C measurements as a biomarker that will aid in the identification of severe sepsis patients most likely to benefit from Xigris, and enable the adjustment of Xigris therapy for individual patients to further improve the benefit/risk balance (specifically the possibility to use a higher dose and to provide a shorter or longer infusion duration until protein C levels are normalised).
Previous studies have indicated a positive association between normalisation of protein C levels and survival. Analysis of data from PROWESS also indicated that Xigris increased the proportion of patients who normalise their protein C levels. Thus, it is hypothesised that by giving higher doses and/or a longer infusion of Xigris more patients will eventually normalise their protein C. If improvements in protein C levels are demonstrated in this study then a subsequent larger study would be required to investigate if

this improvement in protein C is also associated with a further statistically significant improvement in survival.

1.3.3 Update on the PROGRESS registry

As concluded by the CHMP after the 3rd annual re-assessment, the MAH was requested to provide a robust analysis of results of the PROGRESS Severe Sepsis Registry in the 4th annual re-assessment. PROGRESS was an observational study designed to document the following:

- demographic and disease severity characteristics of severe sepsis patients treated in the intensive care unit (ICU);
- patient management;
- ICU and hospital outcomes.

Data collection was web-based and was designed to also enable participating institutions to conduct exploratory analyses of their severe sepsis patient population and compare this to national and global data.

The PROGRESS study provides descriptive data on a large number of severe sepsis patients from around the world. These data reflect everyday clinical practice and show the variation in treatment and outcome across various countries with different health care systems. The website was available for patient entry between December 2002 and December 2005, during which time 12,570 adult patients with severe sepsis were included, but only 2734 from EU member states, mostly from Germany and Belgium (1855 and 370 patients, respectively). Only 7 EU member states participated in the PROGRESS study: Austria, Belgium, Germany, Hungary, Poland, Slovakia, and The Netherlands.

Patient entry was terminated earlier than expected because of low recruitment rates during 2005, and the decision was taken not to initiate a planned second study (PROGRESS II) which would have focused more closely on collection of data related to the timing of the development of organ dysfunction and the delivery of specific therapies. The MAH explained that it did not progress with the second study partly in response to a request from members of the Surviving Sepsis Campaign, who were concerned that PROGRESS II may have competed for patients in an initiative that they have now started in collaboration with the Institute for Healthcare Improvement (IHI), which collects similar types of data.

Patients entered in the PROGRESS study were severely ill and at high risk of death: nearly 90% had multiple organ dysfunction (based on the 7 organ dysfunctions recorded in PROGRESS) and 68% had 3 or more organ dysfunctions. Intensive care unit mortality was 39% and hospital mortality was nearly 50%. There was considerable variation in mortality between countries from 31% in Columbia to 81% in Puerto Rico. Within EU countries mortality varied less, from 36% in The Netherlands to 62% in Slovakia. Because PROGRESS was an observational study, it was not possible to determine to what extent the observed variations in mortality resulted from differences in the baseline characteristics of the patients entered versus differences in the therapies they received. In addition, other specific characteristics that were not collected in the study, such as the timing of organ dysfunction and the timing of the various treatments received, were also likely to affect patient outcome. All of these factors may also be influenced in a systemic fashion by organisational differences in the general provision of health care between countries. Of the supportive and severe sepsis therapies that patients received, nearly all patients received systemic antibiotics (99.3%) and a large majority of patients received enteral nutrition (72.5%), fluid resuscitation (86.7%), or sedation (76.0%); were on mechanical ventilation (85.4%) or received vasopressors (78.7%). The most commonly administered severe sepsis therapies were low-dose steroids (36%), albumin (21%), high-dose steroids (13%), and Xigris (7%).

The analyses of hospital mortality by supportive care and severe sepsis therapies received were also included in the 4th annual re-assessment dossier. It is of note that most “standard” therapies provided in the ICU are associated with statistically higher mortalities compared to those who did not receive the therapy, with the exception of antithrombin infusion, intravenous gamma globulin, nitric oxide, and Xigris. The most likely explanation for this is that more “acute” therapies are provided to the sickest patients who also have high mortalities even with these interventions.

The patients entered into the study who received Xigris represented 27% of patients entered in the United States and only 5% of patients entered in Germany. Patients who received Xigris were somewhat younger (median age of 59 versus 64 years) and were less likely to have comorbid conditions. However, patients who received Xigris had a greater degree of organ dysfunction (84% versus 67% had 3 or more organ dysfunctions) and higher median APACHE II scores (25 versus 23). Although there was similar mortality between patients who received Xigris and those who did not (49.6% versus 49.7%), when adjusted for age and number of organ dysfunctions, there was a 25% reduction in the odds of death associated with Xigris treatment. Age and number of organ dysfunctions have been shown in previous analyses to be important factors in determining mortality, and in this study number of organ dysfunctions had the greatest predictive ability (69.3%) followed by APACHE II score (68.8%). In addition, number of organ dysfunctions had the least amount of missing data compared to the other severity scores. Although such simple adjusted analyses were useful in helping to better understand the likely effect of known imbalances, they do not adjust for all known imbalances, and cannot adjust for any unknown imbalances that may also be present.

An examination of Xigris use in the patients entered in the 7 EU countries showed little off-label use in patients with single organ dysfunction or paediatric patients. Of the 212 EU adult patients who received Xigris, only 2 had single organ dysfunction; of the 24 EU paediatric patients entered into the study, only 1 received Xigris.

Analyses of patients entered in Germany and Belgium reflect the variability observed across countries. The majority of patients entered in Germany were surgical patients and most had cardiovascular and respiratory dysfunction; 71% had 3 or more organ dysfunctions, and the mean APACHE II score was 27. The majority of patients entered in Belgium were medical patients, 49% had 3 or more organ dysfunctions, and the mean APACHE II score was 24. Hospital mortality was 43% in Germany and 53% in Belgium.

Forty-three patients (11.9%) entered in Belgium received Xigris, compared to 5.4% in Germany. Similar to the overall population, patients who received Xigris in these EU member states seemed more severely ill than patients who did not. Odds ratios adjusted for age and number and type of organ dysfunction favoured treatment with Xigris in Belgium, but were in disfavour of treatment in Germany. However the 95% confidence intervals for patients entered in Germany and Belgium are wide and reflect the uncertainty about the estimate in these subgroups based on these small sample sizes.

1.3.4 Publications

As requested by the CHMP at the conclusion of the 3rd annual re-assessment, the MAH discussed publications related to Xigris within the 4th annual re-assessment, which have been published between October 2005 and August 2006.

It emerged that a number of nonclinical publications have investigated potential mechanisms of action of APC, as well as its use in various animal models of disease.

In terms of clinical pharmacology, a case-controlled study at a single site in France concluded that "*rhAPC (recombinant human activated protein C) rapidly improved the vascular tone in septic shock patients as assessed by a decrease in the norepinephrine dose required to maintain arterial pressure*" (Monnet et al, 2005). Also using a case-controlled design including patients with severe sepsis, De Backer et al (2006) concluded that "*rhAPC administration rapidly improves sepsis-induced microvascular alterations, whereas its cessation is associated with a transient deterioration*".

A number of authors have published their experience with Xigris in the form of case reports or case series, detailing their experience in specific sepsis conditions, for example, purpura fulminans, malaria, or their general experience with the drug within their hospital, region, or country. The data from 2 formal, country registries have also been published. In Poland, Kübler et al (2006) reported 3233 cases of severe sepsis (almost all had multiple organ dysfunction (MOD)) in the National Severe Sepsis Register, between April 2003 and November 2005. 9.3% of the patients (301) were treated with Xigris. In the

patients treated with Xigris, the relative risk of death was lower by 31% than in those who were not treated; however, the Xigris group was younger (46.0 *v*s 53.5 years). In a multivariate logistic regression model, the use of Xigris was, independent of the patient's age, severity of the clinical condition, and type of organ dysfunction, the most significant mortality-reducing factor in severe sepsis. Low-molecular-weight heparin was also a mortality-reducing factor. The results of the GIVTI Italian Xigris registry have been published (Bollettino d'informazione sui farmaci, 2006). Although the publication covers 351 Xigris cases (324 with complete data) received between June 2005 and March 2006, 40% were backdated, referring to treatments carried out during 2003, 2004, and the early part of 2005. The reported ICU mortality was 47.2%. The rate of all bleeding events appeared to be less than that seen in clinical trials and the rate of serious bleeds similar or slightly higher. Off-label use was reported in 117 (33%) of users: 44 patients with single or no organ dysfunction, 70 patients with use after 48 hours of organ dysfunction, and 3 children. However, 40% of patients were included before the therapeutic indication was updated in the EU to include that treatment "*should be considered mainly in situations where therapy can be started within 24 hr after the onset of organ failure*", or the addition of the warning regarding single organ dysfunction surgery patients. Also it was not clear if they used a similar definition for the onset of organ dysfunction as was used in PROWESS, that is, the time of onset of the first documented sepsis induced organ dysfunction.

Two manuscripts related to cost effectiveness have been published. Green et al (2006) concluded that in the UK "*whereas the therapeutic cost for Xigris appears high (at around £5,000 per patient) and the potential impact on the provider budget is considerable, Xigris is clinically effective, represents a cost-effective use of resources, and is a significant advance in the treatment of severe sepsis in patients requiring intensive care*." Riou Franca et al (2006) concluded that in France "*Xigris is cost-effective in the treatment of severe sepsis with multiple organ failure when added to best standard care. The cost-effectiveness of the drug increases with baseline disease severity, but it remains cost-effective for all patients when used in compliance with the European approved indication*".

During this reporting period a number of editorials and commentaries were published that questioned the efficacy of Xigris. Many of these pursued common themes and were most easily summarised by considering the issues raised in the commentaries by Mackenzie (2005) and Friedrich (2006):

- There were methodological flaws in the PROWESS study.
- The results of the ADDRESS and RESOLVE studies bring into question the efficacy of Xigris as established by the PROWESS study.

The MAH noted that data and concerns from the above studies have been extensively discussed by both the CHMP and the FDA before and after the initial approval of Xigris and that the timing of these recent publications reflected that the regulatory authorities were provided with new information sooner than the general scientific community, thus academic debate laged behind discussions with regulatory authorities. For example, the ADDRESS data was published in the New England Journal of Medicine in September 2005, but was first shared with the CHMP a year earlier, when the data was still provisional as part of the 3rd annual re-assessment, and the preliminary RESOLVE study results had been shared with the CHMP as part of the 3rd annual re-assessment, whereas the peer reviewed manuscript is currently awaiting publication. Letters in response to such publications, in support of Xigris have also been published (Agarwal and Nath 2006; Macias 2006; Vincent 2006) or submitted (Williams et al, 2006) as well as other commentaries and reviews supporting the use of the drug (Dellinger 2006).

The MAH concluded that on review of the above publications, there did not appear to be any new information that would warrant additional changes to the SPC, or significantly affect the risk/benefit assessment of Xigris in the indicated patient population.

1.3.5 Update on post-marketing Spontaneous Safety Data

The PSUR submitted in January 2006 (PSUR n. 6) covered the period from 22 November 2004 to 31 October 2005. Thus, a safety report was included in this application, which reviews the 10 months safety data from 1 November 2005 to 21 August 2006 ("this reporting period"). This safety report has incorporated feedback received from the CHMP after the review of the PSUR n. 6. On 19 January 2007

the MAH submitted PSUR n. 7 covering the period between 1 November 2005 and 31 October 2006 which is under assessment by the CHMP.

As of 21 August 2006, it was estimated that 92,023 patients have been exposed to marketed Xigris worldwide, 16,793 within this reporting period (compared to 20,438 in the previous 9-month period).

An increased risk of bleeding is the only adverse event known to be associated with treatment with Xigris. The reporting rate of spontaneous CNS and non-CNS bleeding events has been fairly stable across the previous PSUR reporting periods, and has remained so in the current reporting period, with bleeding event rates being within the reporting rate fluctuations seen before. Rates were also comparable between EU, North America (NA) and the Non-EU Non-NA region. At the request of the CHMP following the last annual re-assessment, the MAH conducted a cumulative review of all of the spontaneously reported cases of CNS bleeding searching for possible cases of purpura fulminans, meningitis, or meningococcal disease. Seven (7) such cases out of 325 reports of CNS bleeding were identified, which was less than the 7/39 identified in adult patients in the clinical trial publication referenced by the CHMP (Vincent J.L. et al 2005). This probably reflected more comprehensive data collection in the clinical trial database. More information may become available in the future (PSUR n. 7) since detailed information on bleeding events is now being collected as part of the Modified Serious Bleeding Follow-up Form agreed during the last annual re-assessment.

A cumulative review of the MAH's safety database (from 21 November 2001 to 21 August 2006) was conducted to assess the number of convulsions or seizures reported spontaneously and in clinical trials with Xigris in compliance to a CHMP request following review of PSUR n. 6. The overall reporting rate of spontaneously reported convulsion reactions was 2/10,000 based on the total exposure from 21 November 2001 to 21 August 2006. The adverse event rate reported in clinical trials was higher (13/6894 = 19/10,000); however, this probably reflected that convulsions were a recognised complication of severe sepsis, and the rate of "possibly related" clinical trial events was more similar: 3/10,000 (2/6894). The review of convulsion in critically ill patients with severe sepsis was confounded by the multiple metabolic (e.g., hypoxia, glucose abnormalities, acidosis, alkalosis), electrolyte (e.g., sodium, magnesium) and organic derangements (e.g., CNS bleeding, CNS infections) present in these patients, together with the multiple other medications that may be administered to this critically ill population in the ICU, which may increase the risk of seizures.

During the last annual re-assessment the CHMP raised a concern regarding a possible high rate of off-label use of Xigris and the MAH noted that off-label use was difficult to assess based on these spontaneous reports. As a result of this discussion, at the conclusion of the 3rd annual re-assessment a number of action and follow-up measures were agreed between the MAH and the CHMP. Therefore, by the end of March 2006 the MAH circulated a Dear Health Care Professional Letter to intensivists and paediatric intensivists highlighting that in adults Xigris should be used mainly if treatment can start within 24 hours of organ failure onset and that Xigris was not indicated for children. Additionally, in May 2006 the MAH reported on follow-up with the most frequent Xigris users verifying their hospital protocols were in compliance with the SPC, specifically regarding the points outlined in the communication strategy (Follow-up Measure 047). Although the communication plan was completed successfully, it was noted that only just over 1/3 of sites provided treatment protocols, with many refusing to share or discuss their protocols with a pharmaceutical company. However, review of the protocols received demonstrated a high level of concordance with the SPC in the areas of the indicated population, presence of a time window for treatment, and advise not to administer within 12 hours of major surgery. Because most of the ICUs contacted were exclusively treating adults, it was understandable that not every hospital protocol contained a statement about the non-treatment of children.

To better identify potential off-label use in spontaneously reported events, the MAH proposed the development of a bleeding event form to help collect such information: therefore a Modified Serious Bleeding Follow-up Form was implemented in February 2006. Analysis of the return rate of this form has demonstrated both a difficulty in the ability to make contact with the reporting health care professionals and, where contact was possible, a low completion rate despite repeated attempts to collect this information. The data currently obtained did not provide much additional insight to the potential for off-label use; however, it was premature to fully assess the value of this process. The MAH will explore

options to see if this response rate can be improved, and include an updated assessment in PSUR n. 7, which is currently under assessment by the CHMP. The activities were also included as components of a Risk Management Plan (Follow-up Measure 045) that was submitted in April 2006 as requested by the CHMP at the conclusion of the 3rd annual re-assessment. This FUM is still ongoing.

II DISCUSSION AND CONCLUSION ON CLINICAL SPECTS

2.1 Discussion on clinical aspects

With regard to the update on clinical trials, the CHMP assessed the results of the RESOLVE study (Type II variationEMEA/H/C/000396/II/0016) and concluded that they did not establish efficacy of Xigris in paediatric patients suffering from severe sepsis, acute infection, systemic inflammation and respiratory and cardiovascular organ dysfunction. Nevertheless, considering that severe sepsis was significantly different in adults and children, the CHMP concluded that the results of the RESOLVE study in children did not directly influence the benefit/risk balance of Xigris in adults. Additionally, in the framework of the 3rd annual re-assessment the CHMP requested the MAH to update the SPC to include that Xigris should not be recommended in children and to inform accordingly the Health Care Professionals through an appropriate communication campaign. Thus, by the end of March 2006 the MAH distributed a Dear Health Care Professional Letter to paediatric intensivists highlighting that Xigris was not indicated for children.

On 17 May 2006 the MAH submitted the XPRESS study within the framework of Type II variation EMEA/H/C/000396/II/0020 which was reviewed in parallel with the 4th annual re-assessment by the CHMP (opinion adopted at the February 2007 CHMP plenary meeting). Having assessed the results of the XPRESS study, the CHMP noted that the numerically lower mortality rate observed in the overall heparin group (heparin 28.3% *vs* placebo 31.9%, respectively) must be tempered by the opposite results in sub analyses of patients in European centres (heparin 27.8% *vs* placebo 24.4%) and the post hoc analysis of patients in the EU indicated population (patients with multiple organ dysfunction treated within 24 hours of their first sepsis-induced organ dysfunction: heparin 30.3% *vs* placebo 26.9%). Thus, these results of the XPRESS study cannot be translated into useful recommendations for the use of Xigris in the EU indicated population.
The CHMP noted that the clinical results of XPRESS, taken in conjunction with results from other recent studies, raised concerns on the overall benefit/risk balance of Xigris.
The CHMP concluded that the XPRESS study had not brought a response to the question whether there is a pharmacodynamic interaction between heparin and Xigris; on the contrary uncertainties related to the interactions between heparin and Xigris remain. Thus, as the XPRESS results did not further clarify the benefit/risk balance of Xigris, the CHMP concluded that a revised Specific Obligation was necessary to clarify the benefit/risk balance of Xigris.

The MAH informed the CHMP about the status of the Phase 2 RESPOND study, which had just started and could extend into a Phase 3 study. The RESPOND study is aimed to refine dose and duration of therapy in the current indicated population, based on protein C monitoring. The CHMP requested that at the time of the 5-year renewal the MAH should confirm that the planned Phase 2 study RESPOND will include a sufficient number of patients with MOD who will start treatment within 24 h of the first sepsis-induced organ failure. Additionally, considering that if a Phase 3 study follows Phase 2, its results will likely not be available before 2012, the CHMP noted that the RESPOND study is unlikely to influence the benefit/risk balance of Xigris in a significant way in the near future.

The MAH informed the CHMP about the status of the Phase 4 EXTEND study which was designed to examine a potential extension of the duration of therapy if patients remain in shock at the end of the 96-h Xigris infusion. The CHMP noted that this study is unlikely to influence the benefit/risk balance of Xigris in a significant way in the near future.

The MAH informed the CHMP about the status of the PROGRESS Registry. The CHMP noted that only few significant conclusions can be drawn from the completed collection of data on 12,570 adult patients with severe sepsis, which include only 2734 patients from EU member states. Most EU data originate from Germany (where 5% of potentially indicated patients received Xigris) and Belgium (where 12% of patients

received Xigris) and may not be representative of the overall EU trend in Xigris usage. Although the comparative efficacy of Xigris cannot be deduced from the provided data, the CHMP noted that odds ratios adjusted for age and number and type of organ dysfunction were in disfavour of Xigris in Germany, the country with the highest number of patients (1,855) entered into the PROGRESS registry in the EU. From the PROGRESS registry it emerged that the proportion of severe sepsis patients meeting the EU criteria for Xigris indication and effectively treated with Xigris was low, probably between 10% and 20%, leading to the assumption that Xigris was not considered standard care for severe sepsis patients with multiple organ dysfunction in the EU as it also appeared from the recent publications. Importantly, due to low recruitment in 2005 during the first phase of the PROGRESS study, the MAH had decided not to initiate the planned second phase of the study (PROGRESS II) which would have focused more closely on collection of data related to the timing of the development of organ dysfunction and the delivery of specific therapies. The CHMP considered that these data would have been more helpful in supporting the benefit/risk of Xigris in its current indication than the completed PROGRESS data.

The CHMP was informed that a third of patients included in the Italian GIVTI Registry between 2003 and 2005 were treated off-label (mostly for single organ dysfunction), versus almost none in registries from Germany, Belgium and Poland. Nevertheless, based on spontaneous reports, overall the off-label use of Xigris in the EU seemed rather limited. Further information on the use of Xigris in the hospitals will be provided by the MAH by June 2007 in the framework of the on-going Follow-up Measures 045 and 047.

A review of 2005-2006 scientific publications on Xigris showed that no new comparative study has been performed. Several independent editorials have highlighted not only the limited evidence for the efficacy of Xigris in its current indication, which was well known at the time of approval under exceptional circumstances, but especially the lack of confirmation from further comparative studies. The Eli Lilly-supported Surviving Sepsis Campaign, which strongly defends Xigris use, has been severely criticised by Eichacker et al. in a recent New England Journal of Medicine perspective report (October 2006) for having "*usurped guideline development for commercial purposes, possibly compromising highly regarded, third-party arbiters of medical quality in the process.*" For instance, the Surviving Sepsis Campaign has awarded Xigris a highly favourable rating (grade B), whereas established therapies for sepsis (such as antibiotics, fluids, and vasopressors) received lower ratings (grade D or E) because most had not undergone randomised, controlled trials.

A recent Eli Lilly-funded retrospective analysis of ~4500 clinical trial patients by J.L. Vincent et al. (2006) has confirmed that earlier treatment with Xigris, within 24 hours of organ dysfunction (OD), was associated with lower risk-adjusted mortality than later treatment (more than 24 hours after OD). The CHMP noted that this information was already included in the SPC during the 2nd annual re-assessment.

From the update on post-marketing Spontaneous Safety Data it emerged that the worldwide use of Xigris seemed to "plateau" (an estimated 17,000 patients have been exposed during this 10-month reporting period compared to 20,500 during the previous 9-month period), which was a further sign that Xigris was not considered a universal standard of care in severe sepsis. There was no new signal from the spontaneous reporting system and bleeding rates were stable. However, the CHMP highlighted that these events were only acceptable if Xigris has a sufficient benefit. Therefore, every effort should be made to restrict its use to patients that are most likely to benefit. As requested by the CHMP at the conclusion of the 3rd annual re-assessment, the MAH introduced a focused Risk Management Plan to proactively communicate the recent SPC changes to the most frequent Xigris users and paediatric intensivists, and in the context of off-label use, to introduce a Modified Serious Bleeding Follow-up Form to be completed for every bleeding event in the spontaneous reporting system. Nevertheless, the real impact of this measure was still difficult to assess since only about a third of the hospital protocols for Xigris use could be examined, the change in physicians' behaviour has not been evaluated yet, the outcome of the Modified Bleeding Event Follow-up Form remains unknown, and data confirming that Xigris is not used in children remained scarce. Therefore, the real impact of the communication strategy and the use of Modified Bleeding Event Follow-up Form on the benefit/risk will be re-evaluated in the framework of the on-going Follow-up Measures 045 and 047 for which additional data will be provided by the MAH by June 2007.

At the conclusion of the 3rd annual re-assessment, the MAH was requested to provide summary data of 5 bleeding categories in surgical *vs* non-surgical (=medical) patients (Follow-up Measure 048) from 5

major studies (PROWESS, ENHANCE, ADDRESS, RESOLVE, XPRESS). At the November 2006 CHMP plenary meeting the CHMP concluded that these data revealed a consistent overall increased risk of serious bleeding events in surgical patients (within 30 days) receiving Xigris as compared to medical patients (i.e. non-surgical patients) receiving Xigris (4.3% *vs* 2.5% during the infusion period, and 6.7% *vs* 4.3 % during Days 0 through 28, respectively, in a total population of 4534 patients). Therefore, on 18 January 2007 the MAH submitted Type II Variation EMEA/H/C/000396/II/0022 to update sections 4.4 "Special warnings and special precautions for use" and 4.8 "Undesirable effects" of the SPC with information on increased risk of serious bleeding events in surgical patients compared with medical patients. The CHMP adopted a positive opinion for this Type II variation at the February 2007 CHMP plenary meeting.

2.2 Conclusion on clinical aspects

The results of the XPRESS study (type II variation EMEA/H/C/000396/II/0020) did not clarify whether there was a pharmacodynamic interaction between heparin and Xigris and did not contribute to clarify the benefit/risk balance for Xigris. The CHMP noted that no further study of the effectiveness of Xigris is ongoing or planned, besides a specific Phase IV study (EXTEND) designed to examine a potential extension of the duration of therapy and a planned Phase II study (RESPOND) on the role of protein C as a biomarker, which could lead to a further Phase III study. The CHMP concluded that more targeted studies were needed to strengthen the positive benefit/risk balance of Xigris.

The CHMP had noted that the initial efficacy results of the PROWESS study could not be reproduced in further studies. Furthermore, the CHMP noted that there was an increasing list of warnings and restrictions to the use of Xigris. In particular, at the time of its 3rd annual re-assessment the CHMP concluded that a warning should be included in section 4.4 of the SPC to emphasise that Xigris should not be used in children below the age of 18. Especially, the CHMP recommended that the MAH should reinforce the message that Xigris should not be used off-label and especially should not be used in children, through a communication strategy to be addressed to intensive care units.

Additionally, the CHMP had concerns related to the delay in obtaining meaningful biomarker data regarding protein C levels, the need for further caution in post-surgical patients and the need to treat within 24 h to obtain potential benefit of Xigris. Furthermore, Xigris has not become a universal standard of care in patients with severe sepsis and MOD and post-marketing data confirmed that the use of Xigris has reached a "plateau". The CHMP concluded that the results of the XPRESS study did not further clarify the interaction between heparin and Xigris; on the contrary uncertainties related to this interaction remain.

Thus, as the XPRESS results did not further clarify the benefit/risk balance of Xigris, the CHMP concluded that the concerns which motivated the current Specific Obligation have not been satisfactorily addressed and the Marketing Authorisation for Xigris should remain under exceptional circumstances. Taking all the available data together, the CHMP considered that the benefit/risk balance of Xigris required additional clarification and that there was a need for another clinical trial to further prove the efficacy of Xigris in the target population.

Therefore, the MAH committed to perform an additional 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. The study will be a placebo-controlled study with a primary endpoint of 28-day all cause mortality and a 20% relative risk reduction in all cause mortality at 28-days would be the basis for the sample size calculation. The draft study protocol along with a time schedule was submitted by the MAH on 9th of February 2007 and is under evaluation by the CHMP. This placebo-controlled clinical trial is required to fulfil the revised Specific Obligation to be reviewed annually by the CHMP.

2.3 Changes to the Product Information

The Annex II of the Product Information has been amended to reflect the revised Specific Obligation.

The Product Information includes the changes adopted in the framework of type II variations EMEA/H/C/000396/II/0020 and EMEA/H/C/000396/II/0022 at the February 2007 CHMP plenary meeting. These changes contribute to the assessment of the overall benefit/risk balance of Xigris, and are necessary for the safe and the effective use of Xigris.

III OBLIGATIONS PENDING TO BE FULFILLED

3.1 Specific Obligations (SOs)

- **SPECIFIC OBLIGATION**

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 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, should be performed to assert the benefit/risk profile of Xigris.

3.2 Follow-up Measures (FUMs)

PHARMACEUTICAL

FUM 043 (from Type II variation EMEA/H/C/396/II/11)
The MAH committed to notify the CHMP if any of the stability indicating analytical properties at any of the time points is outside the specifications. In addition the CHMP would be notified if a trend would become obvious in any of the analytical properties and upon finishing the 36 month period the stability data for the 3rd lot will be provided (by Q2 2008).

FUM 049 (from Type II EMEA/H/C/396/II/19)
The MAH committed to put two additional lots of each strength in the new container/closure system into stability program and to report any out of specification results to the EMEA when applicable.

CLINICAL

EMEA FUM 017 (Final study report on RESOLVE study)
A further clinical study has been conducted in children with severe sepsis, including patients with purpura fulminans (RESOLVE study). The MAH submitted the final study report on 8 November 2005. The assessment of this FUM is on-going. Nevertheless, based on the preliminary analysis of this study, on 2 August 2005 the MAH submitted Type II variation EMEA/H/C/396/II/0016 to update the SPC with relevant data from the the study F1K-MC-EVBP in paediatric patients with severe sepsis, indicating that efficacy has not been established in the paediatric population. On 13 October 2005 the CHMP adopted a positive opinion on this Type II variation.

FUM 045 (from 3rd annual re-assessment)
On 20 April 2006 the MAH submit the Risk Management Plan. Following the assessment of the Risk Management Plan, at its November 2006 CHMP plenary meeting, the CHMP concluded that further information should be provided by the MAH (namely an analysis of all adverse events and all serious bleeding events in children over time and an update on publications of studies with Xigris and its impact on the use of Xigris). Thus, this FUM is still on-going.

EMEA FUM 047 (from 3rd annual re-assessment)
On 25 May 2006 the MAH submitted the information on follow-up with the most frequent Xigris users verifying their hospital protocols were in compliance with the SPC, specifically regarding the points outlined in the communication. Following the assessment of this information, at its November 2006 CHMP plenary meeting, the CHMP concluded that the MAH should re-contact 300 hospitals to check

regarding appropriate changes in their protocol treatment (non-recommendation in children, 24-h optimal time window for starting Xigris) and re-contact EU paediatric intensivists to check for compliance with the SPC as related to the special warnings and precautions for paediatric patients (by April 2007). Thus, this FUM is still on-going.

EMEA FUM 048 (from 3rd annual re-assessment)

On 20 April 2006 the MAH submitted summary data of 5 bleeding categories in surgical *vs* non-surgical (=medical) patients from 5 major studies (PROWESS, ENHANCE, ADDRESS, RESOLVE, XPRESS). Following the conclusions of this FUM, on 15 January 2007 the MAH submitted Type II variation EMEA/H/396/II/0022 to update sections 4.4 "Special warnings and special precautions for use" and 4.8 "Undesirable effects" of the SPC with information on increased risk of serious bleeding events in surgical patients. On 22 February 2007, the CHMP adopted a positive opinion on this Type II variation.

IV BENEFIT/RISK ASSESSMENT

The CHMP concluded that the initial efficacy results of the PROWESS study could not be reproduced in further studies.

Additionally, the CHMP noted that there was an increasing list of warnings and restrictions to the use of Xigris. These include the contra-indication in children, the concerns about off-label use recommendation in hospital protocols, the delay in obtaining meaningful biomarker data regarding protein C levels, the need for further caution in post-surgical patients and the need to treat within 24 h to obtain potential benefit of Xigris.

Furthermore, with regard to the results of the XPRESS study, the CHMP noted that the numerically lower mortality rate observed in the overall heparin group (heparin 28.3% *vs* placebo 31.9%, respectively) must be tempered by the opposite results in sub analyses of patients in European centres (heparin 27.8% *vs* placebo 24.4%) and the post hoc analysis of patients in the EU indicated population (patients with multiple organ dysfunction treated within 24 hours of their first sepsis-induced organ dysfunction: heparin 30.3% *vs* placebo 26.9%). The results of the XPRESS study cannot be translated into useful recommendations for the use of Xigris in the EU indicated population. The CHMP concluded that the XPRESS study had not brought a response to the question whether there is a pharmacodynamic interaction between heparin and Xigris; on the contrary uncertainties related to the interactions between heparin and Xigris remain.

The clinical results of the XPRESS study, taken in conjunction with the results from other recent studies, raised concerns on the overall benefit/risk balance of Xigris.

Thus, as the XPRESS results did not further clarify the benefit/risk balance of Xigris, the CHMP concluded that the concerns which motivated the current Specific Obligation have not been satisfactorily addressed and the Marketing Authorisation for Xigris should remain under exceptional circumstances. Taking all the available data together, the CHMP considered that the benefit/risk balance of Xigris required additional clarification and that there was a need for another clinical trial to further prove the efficacy of Xigris in the target population.

V OVERALL CONCLUSION AND RECOMMENDATION

On the basis of the data submitted since the 3rd annual re-assessment, the benefit/risk balance 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. However, the CHMP concluded that a revised Specific Obligation remained to be fulfilled. The assessment of the pending commitment will form the basis of the next annual re-assessment. Therefore, the Marketing Authorisation for Xigris will remain under exceptional circumstances.

The CHMP recommended the updating of the Annexes II of the Community Marketing Authorisation for Xigris.

On 22 February 2007 the CHMP adopted an Opinion on the 4th annual re-assessment of the benefit/risk balance of Xigris.

A revised Letter of Undertaking dated 21 February 2007 including the amended list of Specific Obligation and Follow-up Measures has been adopted accordingly by the CHMP.

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