HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 June 2007

XIGRIS 5 mg, powder for solution for infusion
Box of 1(CIP: 564 254-2)

XIGRIS 20 mg, powder for solution for infusion
Box of 1 (CIP: 564 255-9)

Applicant: LILLY

Drotrecogin alfa (activated)
(recombinant version of Human Activated Protein C)

ATC code: B01AD10

List I
Medicinal product reserved for use in hospital, with its prescription reserved for departments specialized in resuscitation. Medicinal product requiring special monitoring during treatment.

Date of the Marketing Authorisation (MA,centralised European procedure): 24 April 2002
Latest revision of MA: 15 November 2005.

Reason for request: in keeping with the Transparency Committee's request, LILLY Laboratories are presenting the clinical data available since the opinion issued by the Committee on 18 December 2002. In specific terms:
- major amendments to the SPC of XIGRIS, following in particular the analysis of the results of four clinical studies envisaged by the European assessment procedure (post-MA evaluation data): ENHANCE study, ADDRESS study in particular.
- pharmacovigilance data.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Drotrecogin alfa (activated)[1]
(recombinant human Activated Protein C)

1.2. Indications

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

Reminder of previous indication's wording: "XIGRIS is indicated for the treatment of adult patients with severe sepsis with multiple organ failure as a complement to the optimum conventional treatment."

1.3. Dosage

Treatment should be started within the 48 hours and preferably within the 24 hours of onset of the first documented sepsis-induced organ dysfunction (see Section 5.1 SPC).
The recommended dose is 24 µg/kg/h, given as a continuous intravenous infusion, for a total duration of 96 hours. If the infusion is interrupted for any reason, XIGRIS should be restarted at the 24 µg/kg/hr infusion rate and continued to complete the full recommended 96 hours of dosing administration. Dose escalation or bolus doses of XIGRIS are not necessary to account for the interruption in the infusion.

No dose adjustments are required in adult patients with severe sepsis with regard to age, gender, hepatic function (as measured by transaminase levels), renal function or co-administration of prophylactic heparin. The pharmacokinetics of drotrecogin alfa (activated) have not been studied in patients with severe sepsis and pre-existing end stage renal disease and chronic hepatic disease.

Paediatrics: no dosage recommendation can be made and the use of XIGRIS is not recommended in children below the age of 18 (see Section 4.4 of the SPC).

[1] XIGRIS is a recombinant version of the natural human plasma-derived activated Protein C. Excessive coagulation activation in the microcirculatory bed plays a significant part in the pathophysiology of severe sepsis. Furthermore, activated Protein C is an important modulator of the systemic response to infection and has antithrombotic and profibrinolytic properties.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

B : Blood and blood-forming organs
01 : Antithrombotic agents
AD : Enzymes
10 : Drotrecogin alfa (activated)

2.2. Medicines in the same therapeutic category

None.

XIGRIS is the only representative of its class.

2.3. Medicines with a similar therapeutic aim

None.

NB: Apart from conventional early management, low doses of corticosteroids (hydrocortisone hemisuccinate 200 to 300 mg/day for at least 5 days followed by a progressive reduction) are used as a supplement by certain medical teams in the case of septic shock[2],[3].

[2] Bochut P-Y. Calandra T. Pathogenesis of sepsis: new concepts and implications for future treatment. Clinical review. BMJ 2003; 326: 262-266.
[3] Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating severe sepsis and septic shock. The Cochrane Database of Systematic Reviews 2006 Issue 2.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

A- Reminder of the data reviewed by the Committee in 2002 (PROWESS study)

In the PROWESS study drotrecogin alfa was compared in a double-blind, placebo-controlled trial of 1,690 patients with severe sepsis.

The patients meeting the clinical diagnosis of severe sepsis had:

a) a known or suspected infection
b) clinical evidence of a systemic response to infection, including fever or hypothermia, leucopenia or leucocytosis, tachycardia and tachypnoea, and
c) acute organ failure[4], evolving for less than 24 hours.

NB: Exclusion criteria encompassed patients at high risk of bleeding, patients who were not expected to survive for 28 days due to a pre-existing, non-sepsis related medical condition, HIV positive patients whose most recent CD4 count was ≤ 50/mm^3, patients on chronic dialysis, patients who had undergone bone marrow, lung, liver, pancreas or small bowel transplantation, and patients with acute clinical pancreatitis without a proven source of infection.

In the PROWESS trial, treatment was initiated within 48 hours of onset of the first sepsis-induced organ dysfunction. The median duration of organ dysfunction prior to treatment was 18 hours. Patients were given a 96-hour constant rate infusion of Xigris at 24 µg/kg/hr (n=850) or placebo (n=840). Xigris was added to best standard care[5].

The primary endpoint was all-cause mortality assessed during the 28 days following the start of the treatment. Subgroup analyses (based on the APACHE II[6] score and the presence of one or more organ dysfunctions) envisaged by the protocol were carried out.

Results

More than 70% of the patients included were in septic shock and 75% of the patients had at least two organ dysfunctions. Almost 75% of patients were treated with a prophylactic dose of heparin.

The overall 28-day mortality was lower in the group receiving XIGRIS (25%) than in the one receiving the placebo (31%), p = 0.005, i.e. a 6% reduction in mortality (measured by the absolute risk reduction) (NNT = 16) in favour of the group of patients treated with XIGRIS.

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[4] The typical features of organ failure were shock, arterial hypotension or the need for vasoactive treatment in spite of adequate filling, relative hypoxaemia (ratio of partial oxygen pressure in the arterial blood in mm Hg to the percentage of the oxygen fraction absorbed in the air, expressed as a decimal number [PaO_2/FiO_2] < 250), oliguria in spite of adequate filling, a noticeable drop in the number of platelets and/or high levels of lactic acid.

[5] The standard care comprised a prescription of antibiotics, the control of the infection incoming, end the symptomatic treatments if necessary.

[6] The APACHE II score is designed to assess the risk of mortality based on acute physiology and chronic state health evaluation.

But as part of a subgroup analysis, it was noted that this reduction in mortality was limited[7] to the subgroups with the most severe patients, i.e. those with an APACHE II score ≥ 25 (13% reduction in mortality assessed in 817 patients) or with at least two organ dysfunctions (7.4% reduction in mortality, NNT = 13, evaluated in 1,271 patients) at the time of inclusion. However, no reduction in mortality was observed among the subgroups of patients with an APACHE II score < 25 or a single organ dysfunction before starting the infusion.

This benefit was accompanied by an increased risk of serious bleeding (NNH = 66) after 28 days. This excessive risk of bleeding was observed too with patients with at least two organ dysfunctions (NNH = 71) (NB: bleeding risk only during product infusion).

The interpretation of these results is nevertheless very difficult due to the existence of several methodological biases.
The study comprised two parts, with the protocol having been modified during the study:
- the patient eligibility criteria were amended so that patients with a single organ dysfunction for more than 24 hours or at major risk of death not linked to sepsis were excluded
- some study centres were removed
- the method for manufacturing drotrecogin alfa (XIGRIS) was amended
- the composition of the placebo was also modified, which therefore makes compliance with the double-blind principle debatable.
These modifications had an impact on the results: no difference was observed between the two arms of the study in the 28-day mortality in patients meeting the criteria initially defined[8], whereas a difference was observed afterwards.

The results of the subgroup analyses may have been biased due to the initial non-comparability of the patients in both arms of the study.

The question of extrapolating the results observed in a subgroup to the population likely to receive this treatment in hospital is also raised by the experts.

Overall, it is difficult to estimate the contribution that these different methodological biases could have had to the clinical result. It cannot be reasonably excluded that the size of the effect has been overestimated, but to what extent. The risk of bleeding, on the other hand, has been minimized (non-significant trend in PROWESS).

Furthermore, the identification and follow-up of the patients likely to benefit from the treatment were discussed. In spite of the study's positive results in the included population, the registration authorities decided to restrict XIGRIS indication to the subgroups of patients who had a poor medium-term prognosis.

The FDA (USA) has defined patients with a poor prognosis based on the APACHE II score (treatment reserved for patients with a score above 25). The definition from the EMEA (Europe) is based on the number of organ dysfunctions linked to sepsis (treatment reserved for patients with more than one organ dysfunction). The registration authorities based their decision on the results of a single comparative study for this new specific treatment of sepsis.

For all these reasons, carrying out new clinical studies conditionned the granting of MA. The Transparency Committee asked to be kept informed of these studies' results.

B- New clinical data presented by the company

[7] Waren HS, Suffredini AF, Eichaker PQ et al. Risks and benefits of activated protein C treatment for severe sepsis. N Engl J Med 2002; 347: 1030-1034.
[8] Siegel Jay P. Assessing the use of activated protein in the treatment of severe sepsis. N Engl J Med 2002; 13: 1030-1034

The results of four post-MA clinical studies were presented by the company: follow-up data from PROWESS, results from the ENHANCE, ADDRESS and RESOLVE studies.

Among the population of "severe" patients

B.1. Follow-up data from the PROWESS study

A follow-up observational study evaluated the status of "surviving" patients of the PROWESS study on day 28 (1,243 patients); 654 were given XIGRIS and 589 a placebo. In-hospital and 3 month survival status were reported respectively for 98% and 94% of the 1,690 PROWESS subjects respectively.

For patients receiving treatment with XIGRIS:
- the in-hospital mortality in the overall population was lower in patients receiving XIGRIS (29.4%) than in patients receiving placebo (34.6%), p = 0.023.
- "the survival after 3 months was better than the one observed in the placebo (log rank p = 0.048)."

This data tends to confirm that the effect of XIGRIS is limited to the patients who are most severely affected by sepsis, such as patients with multiple organ dysfunctions and who go into shock at the time the infusion is administered (see MA revision of August 11, 2003). The reservations mentioned previously remain valid with regard to interpreting these results obtained in two subgroups defined as "non-protocol".

B.2. Results of the **ENHANCE (F1K-MC-EVBE, F1K-MC-EVBF, F1K-MC-EVBG)** study

The ENHANCE study is a non-controlled study which restricts its relevance as a "confirmation study".

It includes the data[9] for 2,378 adult patients and 188 children under the age of 18, who received XIGRIS as a treatment for severe sepsis, with at least one organ dysfunction.
The patients received XIGRIS within the 48 hours following the first sepsis-induced organ dysfunction. The median duration for organ failure prior to treatment was 25 hours.
The purpose of this study was to measure the all-cause 28-day mortality and to evaluate the treatment's safety (in particular, the incidence of serious bleeding events).
The inclusion criteria were the same as those in the PROWESS study. Historical comparisons (efficacy and safety criteria) were realised in relation to the PROWESS study.

The 2,562 patients analysed (including 187 children) had an average of 2.7 organ dysfunctions, versus 2.4 in the PROWESS study. Among the adult population, the 28-day mortality (25.3%, 95% CI: [23.5, 27]) was comparable to that observed in the PROWESS study (24.7%). This rate was lower in patients treated within the 24 hours of the first organ dysfunction compared to those treated after 24 hours.
The risk of serious bleeding was higher than in the PROWESS study (incidence of 3.6 % *versus* 2.4 % during infusion and 6.5 % *versus* 3.5 % during the 28-day follow-up period). The mortality rate linked to haemorrhagic accidents was comparable to that observed in the PROWESS study.

Among the population of children, the 28-day mortality was 13.4% (95% CI: 8.5-18.2). During the infusion phase, almost 6% of the children had serious bleeding.

In a population of patients with severe sepsis and a more or less poor prognosis

[9] Data from 3 open phase IIIB studies carried out in different areas of the world (F1K-MC-EVBE, -EVBF, -EVBG).

B.3. Results of the **F1K-MC-EVBC** study

This is a multi-centre, non-comparative study involving 319 patients (including 49 children), carried out as part of a compassionate use of XIGRIS before it was marketed.

The efficacy data (28-day mortality) are not available for all the patients (amendment to the protocol). Consequently, the results of this observational study are not commented in this opinion.

B.4. Results of the **ADDRESS** study
The objective was to assess the impact on the 28-day mortality and the safety of XIGRIS compared to that of the placebo in adult patients with severe sepsis and at a low risk of mortality (for example, patients with an APACHE II score < 25 or with a single organ dysfunction caused by sepsis). Among the 2,640 patients included, 872 had multiple organ dysfunctions.

This trial was stopped after an interim analysis due to the low likelihood of demonstrating a significant difference in the 28-day mortality at the end of the trial (not powerful enough).

Compared to the patients in the PROWESS study who had multiple organ dysfunctions, the patients in the ADDRESS study had one organ dysfunction for a longer duration prior to receiving study drug (median of 25 hours versus 18 hours), a lower APACHE II score (median of 20 versus 25) and were more likely to have two organ dysfunctions (76% versus 43%).

At 28 days the mortality rate for patients in the ADDRESS study with multiple organ dysfunctions was 20.7% among those treated with XIGRIS and 21.9% among those receiving a placebo. In-hospital mortality rates were 23.1% for XIGRIS and 25.3% for the placebo.

A warning was issued to prescribers as the results went against XIGRIS compared to the placebo in patients with single organ failure (increased mortality with XIGRIS at 28 days).

B.5. Data for children: results of the **RESOLVE (F1K-MC-EVBP)** study
The data from this placebo-controlled clinical trial did not demonstrate efficacy of XIGRIS in paediatric patients suffering from severe sepsis, acute infection, systemic inflammation and respiratory or cardiovascular organ failure.
The primary endpoint was the Composite Time to Complete Organ Failure Resolution. This study was discontinued prematurely (477 patients included at the time) after the intermediate analysis (planned after the inclusion of 400 patients), as it showed a low probability of demonstrating a significant difference in the primary endpoint.

NB: There was no significant difference in the 28-day mortality between both arms of the study and a higher rate of bleeding in the central nervous system was found in the XIGRIS group.

C- Other data

Results of the PREMISS study

The before/after-type observational study PREMISS[10] was carried out in France in 103 resuscitation centres which volunteered to take part in the study. The main purpose of this study was to estimate the cost for the hospital of managing patients treated with XIGRIS compared to the cost for comparable patients treated before XIGRIS was made available. It also provided data (secondary objectives) on the 28-day mortality, safety and differential cost-effectiveness ratio for XIGRIS (compared to the phase "before" XIGRIS was made available), as well as on its methods of use.

Compared with the “before” phase, the use of XIGRIS led to:

- a significant increase in the medical resources used, particularly in terms of procedures (apart from tracheal intubation), as well as drugs (other than XIGRIS) and blood products
- a significantly longer period of hospitalisation in the resuscitation department (24.4 days for the “after” phase compared with 21.3 days for the “before” phase)
- an increase in the total hospital costs[11] of EUR 11,150, which includes the cost of purchasing XIGRIS (estimated at an average of just over EUR 6,700), along with the additional costs observed during the “after” phase linked to drugs (apart from XIGRIS), transfusions, and the stay in the resuscitation department.

In terms of efficacy and safety, even if these results should be treated with caution, particularly because of the lack of power:

- the 28-day mortality was (afterwards apparently) 37.4% for patients in the “before” phase and 34.1% for patients in the “after” phase. The absolute difference in the mortality rate (3.3%) is not, however, significant.
- the patients treated with XIGRIS had on average significantly more bleeding (13.57% of patients in the "before" phase versus 21.67% of patients in the "after" phase, p = 0.0021).

Finally, the PREMISS study also provided data on the use of XIGRIS in clinical healthcare practice in France. In this study 84.6% of patients received XIGRIS within the 48 hours following the onset of severe sepsis and 91.2% of injections were administered at the dosage of 24 µg/kg/h. The recommendation to administer XIGRIS over a total duration of 96 hours was followed in a third of cases.

3.2. Adverse effects

XIGRIS increased the risk of bleeding in patients who received it.

- In the PROWESS study (1,690 patients) the proportion of patients who had at least one bleeding event was 24.9% with XIGRIS and 17.7% with the placebo.
- In the ADDRESS study which was carried out on adult patients with severe sepsis and at a low risk of mortality (1,317 patients treated with drotrecogin alfa (activated) and 1,293 patients treated with placebo), the proportion of patients who presented with at least one bleeding event[12] was 10.9% with XIGRIS and 6.4% with placebo ($p < 0.001$).

[10] A total of 1,096 patients were included: 509 patients in the phase “before” XIGRIS was made available and 587 in the phase “after” it was made available. The average age of patients was 60.8 years and they had 3.8 organ dysfunctions.
Recruitment biases were highlighted between the groups compared. Compared to the patients in the “before” phase, the patients treated with XIGRIS (“after” phase) were younger, less likely to die within a year, admitted sooner to the resuscitation department after being admitted to hospital and had fewer infections at the time of inclusion. In order to reduce these biases, a subsample of 840 comparable patients was created from the two phases (propensity score method).

[11] In terms of the total cost of hospitalisation.

[12] The bleeding events included serious bleeding events, bleeding events considered by the investigator as being potentially linked to the study product, bleeding events requiring a transfusion of red blood cells and bleeding events which led to the definitive discontinuation of the study product.

- During infusion: in the ADDRESS study the proportion of patients treated who had at least one serious bleeding event per haemorrhage site was similar to that observed in the PROWESS study. Their incidence during infusion (defined as the period from Day 0 to Day 6 of the study) was 31 (2.4 %) with XIGRIS and 15 (1.2 %) with the placebo (p = 0.02).

Recent surgery (within 30 days prior to inclusion in the study) was associated with a numerically higher risk of serious bleeding during infusion, in both the groups treated with drotrecogin alfa (activated) and placebo (in the XIGRIS group: 3.6% in patients who had recent surgery *versus* 1.6% in patients who had no recent surgery; in the placebo group: 1.6% and 0.9% respectively).

- During the 28-day period
- the incidence of serious bleeding events was 3.5% with XIGRIS and 2.0% with the placebo in the PROWESS study
- the incidence of serious bleeding events during the 28-day period was 6.5% in the open-label ENHANCE study
- it was 51 (3.9%) for XIGRIS and 28 (2.2%) for the placebo (p = 0.01) in the ADDRESS study.

In patients treated with XIGRIS the incidence of bleeding in the central nervous system during the 28-day period was 1.5% in the ENHANCE study, 0.2% in the PROWESS study and 0.5% in the ADDRESS study.

NB: in the PROWESS and ENHANCE studies the serious bleeding events included any intracranial bleed, any life-threatening or fatal bleed, any bleeding event requiring the administration of at least 3 units of packed red blood cells for 2 consecutive days or any bleeding event assessed as serious by the investigator. In the ADDRESS trial the serious bleeding events included any fatal bleed, any life-threatening bleed, any bleeding event in the central nervous system (CNS) or any bleeding event assessed as serious by the investigator.

In children, the data published in the paediatric study F1K-MC-EVBP, after 477 patients aged 0 to 17 were treated, indicated a higher rate of bleeding in the CNS in the XIGRIS group than in the placebo group (see SPC).

Results of the XPRESS study
"In XPRESS, a randomised study of prophylactic heparin *versus* placebo in adult severe sepsis patients, all treated with drotrecogin alfa (activated), serious bleeding rates were consistent with those observed in previous studies over the treatment period of 0-6 days, and prophylactic heparin did not increase the risk of serious bleeding compared to placebo (2.3% *versus* 2.5%, respectively), including CNS bleeding (0.3% on both arms). However, prophylactic heparin increased the risk of non-serious bleeding compared with placebo (8.7% *versus* 5.7%, respectively; p = 0.0116)."
"In XPRESS, serious bleeding rates were consistent with those observed in previous studies during the 28-day study period (days 0-28). Prophylactic heparin did not increase the risk of serious bleeding compared to placebo (3.9% versus 5.2% respectively), including CNS bleeding (1.0% *versus* 0.7% respectively)." (Refer to SPC)

However, the EMEA believes that "the XPRESS study had not brought a response to the questions whether there is a pharmacodynamic interaction between heparin and XIGRIS; on the contrary, uncertainties related to the interaction between heparin and XIGRIS remain". The EMEA considers that "the XPRESS results did not further clarify the benefit/risk balance of XIGRIS." (See Scientific Discussion - EPAR February 22, 2007).

3.3. Conclusion

When compared with the placebo and when combined with the best standard care, XIGRIS reduced the 28-day mortality only in a subgroup of patients with severe sepsis characterised by multiple organ dysfunctions (at least two) and/or by an APACHE II score > 25 (results of the PROWESS study).

In its opinion issued in 2002, the Transparency Committee had considered that the benefit gained from XIGRIS had to be evaluated with regard to the associated risk of bleeding and based on each patient, and that this benefit had been noticed in the most severe patients (with an APACHE score above 25), the majority of whom had at least two organ dysfunctions. Furthermore, the Committee had noted that the patients most likely to benefit from XIGRIS were difficult to identify "in practice" and that the population for whom this treatment is justified (target population) had not been quantified.

According to the results of the non-comparative ENHANCE study, the efficacy of XIGRIS seemed to be greater in patients who were administered XIGRIS in the 24 hours following the first occurrence of organ dysfunction.

The post-MA studies (ADDRESS study) indicated that the 28-day mortality and the mortality rate in hospital had been higher in patients treated with XIGRIS than in those who received the placebo in two sub-populations of patients (subgroup analysis): those with just one failed organ and those who had undergone recent surgery during the last 30 days (98 patients in the PROWESS study and 636 in the ADDRESS study).
The data from the comparative ADDRESS study did not highlight any benefit in patients with an APACHE score > 25 (increased mortality at 28 days in the XIGRIS group of 5%) or in those with multiple organ failure (no difference in the 28-day mortality between the two XIGRIS and placebo groups) (see experts' reports).

"In placebo-controlled clinical trials, the treatment effect was most evident at sites enrolling large numbers of patients." (See SPC)

The prescription of XIGRIS in children does not seem to be justified, in view of the unfavourable bleeding safety/risk ratio[13] (RESOLVE study discontinued prematurely).

XIGRIS increases the risk of bleeding (see SPC). In the following conditions, the risks of the administration of XIGRIS should be weighed against the anticipated benefits:

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

Taking into account the numerous, significant methodological limitations of the PROWESS study, it is difficult to interpret its results, as well as the adverse effect of drotrecogin alfa (in terms of mortality) observed in certain patients and the existence of a possible risk of serious bleeding, the question of the real benefit gained from XIGRIS as part of the management of adult patients with severe sepsis is highly controversial[14 15 16].

[13] Kylat RI, Ohlsson A. Recombinant human activated protein C for severe sepsis in neonates. The Cochrane Database of Systematic Reviews 2006 Issue 2.
[14] Antithrombotics therapies for sepsis: a need for more studies. Crit Care Med 2006; 34 (2): 538-541.
[15] Mackenzie A.F. Activated protein C: do more survive? Intensive Care Med 2005 31: 1624-1626.
[16] Carlet J. Prescribing indications based on successful clinical trials in sepsis: a difficult exercise. Crit Care Med 2006; 34 (2): 525-531.

If, in spite of these justified reservations, the assumption is made that XIGRIS is effective in some patients, two major difficulties remain:

1- it is possible and probable that the size of the clinical benefit indicated in patients from the PROWESS study was overestimated (refer to the results of the comparative ADDRESS study) and that the occurrence of serious bleeding events in PROWESS was played down by design (which is confirmed by the results of the post-MA studies and the PREMISS observational study carried out in France).
2- in particular, a large number of specialists believe that, at the moment, it is difficult to define validated, relevant criteria (which excludes the use of the APACHE II severity score as a decision-making tool with regard to providing this treatment) for identifying these patients. Is it sufficient to use the number of organ dysfunctions as a criterion for deciding on treatment, in accordance with the European MA? Implementing this is made even more difficult by the fact that there is no consensual definition for organ failure (experts' opinion) and that the treatment should be prescribed mainly in situations where treatment can be initiated in the 24 hours following the onset of organ dysfunction (see updated SPC).

Nevertheless, based on the clinical data evaluated in 2007 and expert opinion, XIGRIS seems to have some benefit for the most severe patients.

Two comparative randomised studies will be carried out among a population of patients in septic shock: one academic, national study will be carried out as part of the 2007 Hospital Clinical Research Programme, while the other will be an international study promoted by the ELI LILLY laboratory at the request of the EMEA (new specific obligation of the European MA which remains under exceptional circumstances).

The analysis of the results of all the clinical data requested/expected by the EMEA, along with those of the academic study carried out by France should make it easier to define among patients with severe sepsis those who are likely to gain some clinical benefit from treatment with XIGRIS.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The incidence of severe sepsis syndromes (SSS) is increasing all the time: 15% of patients admitted to resuscitation units have had a SSS, most often from the time of admission, according to a recent survey (2001, Episepsis) and around 75,000 cases of SSS (or shock) are apparently admitted to hospital every year[17]. In spite of the progress that has been made in resuscitation, it is one of the major causes of mortality in hospital: around 30% at 28 days and 40% overall. The risk of death is influenced particularly by age and the number of organ dysfunctions.
The mortality rate in ICU among patients with sepsis varies from one European country to another[18].

In light of current clinical data, the use of XIGRIS can only be considered in adult patients with severe sepsis and at least two organ dysfunctions and in the absence of any contraindications (see SPC).
XIGRIS is used to complement conventional management measures and is preferably administered within the 24 hours following the first documented occurrence of organ dysfunction caused by sepsis.

Public health benefit

Given the difficulty in specifying the extent of XIGRIS effect, the benefit derived from this medicine in patients with severe sepsis remains debatable. As a result, its population impact on morbi-mortality cannot be evaluated.

It is difficult in practice to identify the patients who could possibly benefit from XIGRIS and there are probably only a few of them. Given the narrow therapeutic margin XIGRIS has, the fact cannot be excluded that a section of the population being treated will be exposed to an unjustified risk of bleeding.

Taking into account these factors, XIGRIS does not provide a public health benefit, but may well raise the question of having a negative impact on public health.

It has been difficult to establish the efficacy/adverse effects ratio for drotrecogin alfa (activated). It is not advised for use in children, patients at a low risk of death, those who have undergone recent surgery or even in patients at risk of bleeding.

There is no data making it possible to confirm that a subgroup of patients falling under the scope of indication gains any benefit from this treatment.

Conclusion: the actual benefit from XIGRIS is therefore considered to be low, pending results from additional clinical studies (refer to the conclusions from the analysis of the clinical data in Section 3.3). Although certain doubts remain, it cannot be excluded that XIGRIS improves the survival rate in certain adult patients with severe sepsis.

[17] Brun-Buisson C., Meshaka P., Pinton P. and Valet B. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care med 2004; 30: 580-588.
[18] J-L Vincent et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 2006; 34 (2): 344-353.

4.2. Improvement in actual benefit

The Transparency Committee considers that XIGRIS, considering the current data, does not provide an improvement in actual benefit (IAB level V) in the treatment of adult patients with severe sepsis and multiple organ failure, when added to best standard care.

4.3. Therapeutic use

Standard care of severe sepsis combines the control of the infection process with haemodynamic management and restoring tissue infusion.
XIGRIS is used as a supplement to the standard care for patients with severe sepsis. Management must be active and early[19]. It has been shown[20] that it is possible to obtain a major reduction in the mortality rate by using an early haemodynamic management strategy (which does not include activated protein C, low-dose corticosteroid therapy or strict monitoring of blood glucose levels).

The role of corticosteroids in patient management is debatable. When administered at high doses over a short period of a few days, they do not provide these patients with any benefit. On the other hand, recent data[21] [22] [23] suggests they are beneficial in terms of survival and contributing to the regression of septic shock when they are prescribed at low doses over a period of 5 to 7 days.

In current practice, the use of XIGRIS has not obtained any consensus among the community of resuscitation specialists (refer to experts' opinion). Patients benefiting from the prescription of XIGRIS have not been accurately identified. In light of the data available, XIGRIS seems to provide a clinical benefit only in the most severe patients by reducing 28-day mortality, when it is administered early in the 24 to 48 hours after the first organ dysfunction in patients with a low risk of bleeding. Its prescription is currently discussed on a case by case basis in each institution concerned, taking into account the service protocol identifying the most severe patients[24]. The benefit from XIGRIS, depending on the infectious cause of the septic syndrome, has not obtained any consensus at the moment (refer to experts' opinion).

4.4. Target population

The Committee is unable to define the target population for XIGRIS.

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4.5. Transparency Committee recommendations

The Transparency Committee recommends maintaining the product on the list of medicines approved for use by hospitals and various public services in the indications and at the posology of the Marketing Authorisation.
The Committee wishes to reassess the actual benefit from XIGRIS in 18 months.

Study request by the Transparency Committee

The Transparency Committee wishes to be provided with data on the follow-up of the patients being treated with XIGRIS in France. The purpose of this request is to document the methods of treatment in a real-life situation:

- The characteristics of patients being treated: sex, age, clinical profile (background and severity of sepsis, number and type of infections, state of shock, number and type of organ failure, occurrence of DIC, level of bleeding risk etc.)

- The conditions of using this medicinal product, especially the conditions of initiating the treatment: previous treatments with XIGRIS, duration of treatment with XIGRIS, the dosage regimen (dose and duration of infusion(s)) and associated treatments.

- Patients' clinical progress in a real situation where the drug is used (particularly mortality at one month and the causes of death).

If scheduled or ongoing studies, in particular within the scope of European Risk Management plan, are not be able to answer all the questions raised by the Transparency Committee, a specific study must be carried out.

The duration of the study must be justified by an independent scientific committee.