NAME OF THE MEDICINE

Xigris® [drotrecogin alfa (activated) rhu]
Xigris [drotrecogin alfa (activated) rhu] is human Activated Protein C produced by recombinant DNA technology.

DESCRIPTION

Xigris is a recombinant version of the endogenous human activated protein C and is produced by genetic engineering from an established human cell line (HEK-293). The HEK-293 cell line was derived from primary, human embryonic kidney cells. The HEK-293 cells used for the production of Xigris were originally obtained from the American Type Culture Collection (ATCC).

Xigris is supplied as a sterile, lyophilised, white to practically white powder for intravenous infusion. Each vial of Xigris contains 5 mg of drotrecogin alfa (activated). Other ingredients include sucrose, sodium chloride, citrate (buffer system composed of citric acid, sodium citrate, hydrochloric acid and sodium hydroxide), hydrochloric acid, if necessary, and sodium hydroxide, if necessary. Each vial contains an excess of Xigris to facilitate withdrawal of the labelled amount of drug product.

PHARMACOLOGY

Pharmacodynamic effects
Activated Protein C has antithrombotic, profibrinolytic and anti-inflammatory properties. Xigris has similar properties to those of endogenous human Activated Protein C.

In placebo-controlled clinical trials in patients with severe sepsis, Xigris exerted an antithrombotic effect by limiting thrombin generation and improved sepsis-associated coagulopathy, as shown by a more rapid improvement in markers of coagulation and fibrinolysis. Xigris caused a more rapid decline in thrombotic markers such as D-dimer, prothrombin F1.2 and thrombin-antithrombin levels and a more rapid increase in Protein C and antithrombin levels. Xigris also restored endogenous fibrinolytic potential, as evidenced by a more rapid trend toward normalisation in plasminogen levels and a more rapid decline in plasminogen activator inhibitor-1 levels. Additionally, patients with severe sepsis treated with Xigris had a more rapid decline in interleukin-6 levels consistent with a reduction in the inflammatory response.

Pharmacokinetic properties
Xigris and endogenous human Activated Protein C are inactivated in plasma by endogenous protease inhibitors but the mechanism by which they are cleared from plasma is unknown. Plasma concentrations of endogenous Activated Protein C in healthy subjects and patients with severe sepsis are usually below detection limits and do not significantly influence the pharmacokinetic properties of Xigris.

In healthy subjects, greater than 90% of the steady state condition is attained within 2 hours following the start of a constant-rate intravenous infusion of Xigris. Following the completion of an infusion, the decline in plasma Activated Protein C
concentrations is biphasic and is comprised of a rapid initial phase ($t_{1/2\alpha}=13$ minutes) and a slower second phase ($t_{1/2\beta}=1.6$ hours). The short half-life of 13 minutes accounts for approximately 80% of the area under the plasma concentration curve and governs the initial rapid accrual of plasma Activated Protein C concentrations towards the steady-state. Plasma Activated Protein C steady-state concentrations are proportional to the infusion rate over a range of infusion rates from 12 microgram/kg/hr to 48 microgram/kg/hr.

In patients with severe sepsis, infusion of Xigris from 12 microgram/kg/hr to 30 microgram/kg/hr rapidly produced steady-state plasma concentrations that were proportional to infusion rates. In the Phase 3 trial, the pharmacokinetics of Xigris were evaluated in 342 patients with severe sepsis administered a 96-hour continuous infusion at 24 microgram/kg/hr. The pharmacokinetics of Xigris were characterised by attainment of steady-state plasma concentration within 2 hours following the start of the infusion. In the majority of patients, measurements of Activated Protein C beyond 2 hours after termination of the infusion were below the quantifiable limit (<10 ng/ml), suggesting rapid elimination of Xigris from the systemic circulation.

**End stage renal disease** – Patients with end stage renal disease requiring chronic renal replacement therapy were excluded from the Phase 3 study. In patients without sepsis undergoing haemodialysis (n=6), plasma clearance (mean±SD) of Xigris administered on non-dialysis days was 30±8 L/hr. Plasma clearance of Xigris was 23±4 L/hr in patients without sepsis undergoing peritoneal dialysis (n=5). These clearance rates did not meaningfully differ from those in normal healthy subjects (28±9 L/hr) (n=190).

**Additional Information on Immunogenicity**

In adult patients in severe sepsis clinical studies, the frequency of anti-human Activated Protein C IgA/IgG/IgM antibodies or neutralising antibodies is low and is similar between Xigris and placebo-treated patients tested. No apparent correlation of antibody development to adverse reactions was observed. There was no evidence that the antibodies detected represented a specific immune response to Xigris therapy. Samples available from six adult severe sepsis patients who had received a prior course of Xigris were subsequently tested and all were negative for anti-human Activated Protein C antibody (see PRECAUTIONS).

**CLINICAL TRIALS**

The studies described in this section support the use of Xigris in the indicated patient population. In a placebo controlled study in adult sepsis patients at low risk of death (ADDRESS study) the risk/benefit balance of use of Xigris was not favourable (see PRECAUTIONS, “Patients with Single Organ Dysfunction and Recent Surgery”). In a placebo controlled study of Xigris in paediatric patients (RESOLVE paediatric study) the risk/benefit balance for use of Xigris was not favourable (see PRECAUTIONS, “Use in Paediatrics”).

**PROWESS study**

Xigris was studied in a Phase 3 international, multi-centre, randomised, double-blind, placebo-controlled trial (PROWESS) in which 1690 patients with severe sepsis received Xigris (n=850) or placebo (n=840). Entry criteria included 3 or more criteria of the Systemic Inflammatory Response Syndrome (defined abnormalities of temperature, heart rate, respiratory rate, WBC count) and the presence of known or
suspected sepsis associated with acute dysfunction in one or more organs. Organ dysfunction was defined as shock, hypotension or the need for vasopressor support despite adequate fluid resuscitation, relative hypoxemia (ratio of partial pressure of oxygen in arterial blood in mmHg to the percentage of oxygen in the inspired air expressed as a decimal (PaO₂/FiO₂ ratio) < 250), oliguria despite adequate fluid resuscitation, marked reduction in blood platelet counts and/or elevated lactic acid concentrations.

Patients received Xigris or placebo 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 microgram/kg/hr or placebo. Patients treated with Xigris experienced improved 28-day survival compared to those treated with placebo. At 28 days, the overall mortality rates were 24.7% for the Xigris-treated group and 30.8% for the placebo-treated group (absolute mortality reduction 6.1%, p=0.005, see Table 1). Xigris reduced the risk of death by 19.4%. These results indicate that 1 additional life would be saved for every 16 patients treated with Xigris.

An association between high risk of death as determined by APACHE II score and reduction in mortality with Xigris was shown (see Table 1). Treatment effects were most evident in patients in the 3rd and 4th APACHE II quartiles. Other important indicators also supported an association between risk of death and likelihood of benefit with Xigris. Absolute reductions in mortality of 2%, 5%, 8% and 11% with Xigris were observed for patients with 1, 2, 3 and 4 or more organ dysfunctions, respectively. Mortality in the placebo groups with 1, 2, 3 and 4 or more organ dysfunctions was 21%, 26%, 34% and 48%, respectively.

A consistent treatment effect on mortality with Xigris administration was observed in patients with normal Protein C levels and those with low Protein C levels at study entry. No substantial differences in Xigris treatment effects were observed across patient subgroups defined by geographic region, gender and infection type.

Table 1: 28-Day All-Cause Mortality for All Patients and for Subgroups Defined by APACHE II Score

<table>
<thead>
<tr>
<th></th>
<th>Xigris Total N⁰ Nᵦ(%)</th>
<th>Placebo Total N⁰ Nᵦ(%)</th>
<th>Absolute Mortality Difference (%)</th>
<th>Relative Risk (RR)</th>
<th>95% CI for RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>850 210(25)</td>
<td>840 259(31)</td>
<td>-6</td>
<td>0.81</td>
<td>0.70,0.93</td>
</tr>
<tr>
<td>APACHE II quartile (score)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (3-19)</td>
<td>218 33(15)</td>
<td>215 26(12)</td>
<td>0.005</td>
<td>1.25</td>
<td>0.78,2.02</td>
</tr>
<tr>
<td>2nd (20-24)</td>
<td>218 49(23)</td>
<td>222 57(26)</td>
<td>0.88</td>
<td>0.88</td>
<td>0.63,1.22</td>
</tr>
<tr>
<td>3rd (25-29)</td>
<td>204 48(24)</td>
<td>162 58(36)</td>
<td>0.66</td>
<td>0.66</td>
<td>0.48,0.91</td>
</tr>
<tr>
<td>4th (30-53)</td>
<td>210 80(38)</td>
<td>241 118(49)</td>
<td>0.78</td>
<td>0.78</td>
<td>0.63,0.97</td>
</tr>
</tbody>
</table>

⁰Total N = Total number of patients in group

ⁱN = Number of deaths in group

In PROWESS, Xigris-treated patients experienced significantly more days alive without the need for vasopressor support or mechanical ventilation as compared to placebo-treated patients. There were no significant differences between the two treatment groups with regard to duration of SIRS or length of ICU or hospital stay.
PROWESS Follow-up Study

Long-term survival was assessed in a follow-up study of PROWESS patients. In-hospital and 3 month survival was reported for 98% and 94% of the 1690 PROWESS subjects respectively. In-hospital mortality was significantly lower in patients that received Xigris compared with patients receiving placebo (29.4% vs. 34.6%; p=0.023). Survival after 3 months was also significantly higher in the Xigris group compared to placebo (p=0.048). After three months, independent risk factors for mortality were higher age and multiple pre-existing health conditions.

ENHANCE open-label study

In a phase 3b multi-country, single-arm open-label trial (ENHANCE), 2378 adult patients with severe sepsis received Xigris. The entry criteria were similar to those employed in PROWESS. Patients received Xigris within 48 hours of onset of the first sepsis-induced organ dysfunction. The median duration of organ dysfunction prior to treatment was 25 hours. As shown in Figure 1, the pattern of survival throughout the 28 day study period was similar to that observed in the PROWESS study. At 28 days, the mortality rate was 25.3%. The mortality rate was lower for patients treated within 24 hours of organ dysfunction compared to those treated after 24 hours, even after adjustment for differences in disease severity.

Figure 1: Kaplan-Meier survival curves for ITT adult population ENHANCE and PROWESS studies.

INDICATIONS

Xigris is indicated for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have high risk of death (see CLINICAL TRIALS).
CONTRAINDICATIONS

Because Xigris increases the risk of bleeding, it is contraindicated in the following situations:

- Active internal bleeding
- Recent (within 3 months) haemorrhagic stroke
- Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma requiring hospitalisation
- Trauma patients with increased risk of life-threatening bleeding
- Patients with epidural catheter
- Patients with intracranial neoplasm or mass lesion or evidence of cerebral herniation.

Xigris is contraindicated in patients with known hypersensitivity to drotrecogin alfa (activated) or to any of the excipients.

PRECAUTIONS

Bleeding

Xigris increases the risk of bleeding. In the following conditions, the risks of the administration of Xigris should be weighed against the anticipated benefits:

- Concurrent heparin therapy ≥15 International Units/kg/hr
- Platelet count < 30,000 x 10⁶/ L, even if the platelet count is increased after transfusions
- Recent (within 6 weeks) gastrointestinal bleeding
- Recent administration (within 3 days) of thrombolytic therapy
- Recent administration (within 7 days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors
- Recent administration (within 7 days) of aspirin > 650 mg per day or other platelet inhibitors
- Recent (within 3 months) ischaemic stroke
- Patients with intracranial arteriovenous malformation or aneurysm
- Known bleeding diathesis except for acute coagulopathy related to sepsis
- Chronic severe hepatic disease
- Any other condition in which the physician considers significant bleeding is likely.

Should clinically important bleeding occur, stop the infusion of Xigris. Once adequate haemostasis has been achieved, continued use of Xigris may be reconsidered.

For procedures with an inherent bleeding risk, discontinue Xigris for 2 hours prior to the start of the procedure. Xigris may be restarted 12 hours after major invasive procedures or surgery if adequate haemostasis has been achieved. Xigris may be restarted immediately after uncomplicated less invasive procedures.

As a component of routine care, measures of haemostasis (e.g., activated partial thromboplastin time (APTT), prothrombin time (PT) or platelet count) may be obtained during the infusion of Xigris. If sequential tests of haemostasis indicate an uncontrolled or worsening coagulopathy that significantly increases the risk of
bleeding, the benefits of continuing the infusion must be weighed against the potential increased risk of bleeding for that patient.

Prophylactic heparin should not be discontinued unless considered medically necessary.

In a randomised study of prophylactic heparin versus placebo in 1935 adult severe sepsis patients treated with Xigris, discontinuation of baseline heparin was associated with increased mortality and risk of serious adverse events, including cardiac, gastrointestinal, and venous thrombotic events. Therefore, prior to initiating or during treatment with Xigris, prophylactic heparin should not be discontinued unless considered medically necessary (see Interactions with Other Medicines).

**Immunogenicity**
In patients with severe sepsis, the formation of anti-Activated Protein C antibodies was uncommon (<1%) after a single course of therapy. These antibodies were not capable of neutralising the effect of Activated Protein C on the APTT assay. A small number of patients in severe sepsis controlled clinical trials received a prior course of Xigris. No hypersensitivity reactions were reported in these patients. No anti-Activated Protein C antibody formation was detected in healthy subjects, even after repeat administration up to 6 times (see PHARMACOLOGY - Additional Information on Immunogenicity).

**Patients with Single Organ Dysfunction and Recent Surgery**
In each of two randomised, placebo-controlled trials, PROWESS and ADDRESS (a randomised, double blind placebo-controlled trial of adult severe sepsis patients at low risk of death; e.g. patients with APACHE II<25 or with only one sepsis-induced organ failure), post-hoc analyses showed that 28-day and in-hospital mortality were higher in patients treated with Xigris compared to placebo for the sub-population of patients who had both single organ dysfunction and recent surgery.

In PROWESS, 28-day all-cause mortality for patients with single organ dysfunction and recent surgery was 10/49 (20.4%) and 8/49 (16.3%) for Xigris and placebo patients, respectively (p=0.60*). In-hospital mortality was 14/48 (29.2%) and 8/47 (17.0%) for Xigris and placebo patients, respectively (p=0.16*). In ADDRESS, 28-day all-cause mortality for patients with single organ dysfunction and recent surgery was 67/323 (20.7%) and 44/313 (14.1%) for Xigris and placebo patients, respectively (p=0.03*).

In-hospital mortality was 76/325 (23.4%) and 62/314 (19.8%) for Xigris and placebo patients, respectively (p=0.26*). For all enrolled patients in ADDRESS (N=2640), overall 28-day mortality rate was 18.5% for Xigris patients and 17.0% for placebo patients (p=0.34). In-hospital mortality was 20.6% for the Xigris patients and 20.5% for placebo patients (p=0.98).

*Chi-square test without adjustment for multiple comparisons.

**Effects on Fertility**
The potential of Xigris to impair fertility has not been evaluated in male or female animals.

**Use in Pregnancy** - Pregnancy Category C
Animal studies to determine whether Xigris and/or its metabolites are transferred to the fetus during pregnancy have not been conducted. Animal reproductive toxicity studies have not been performed with Xigris, however, thrombolytic agents may
cause placental haemorrhage and subsequent prematurity and fetal loss. It is also not known whether Xigris can cause fetal harm when administered to a pregnant woman. Xigris is not recommended for use during pregnancy.

**Use in Lactation**

It is not known whether Xigris is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Xigris is administered to a nursing woman.

**Use in Paediatrics**

Differences in pharmacokinetics have been observed between age groups (0-<1 yrs, 1-<8 yrs, 8-<18 yrs) in a study of Xigris in children with severe sepsis. This Phase 1B study was not powered to detect differences between age groups in rates of adverse events associated with Xigris. Efficacy was not assessed. The clinical relevance of differences in pharmacokinetic results between age groups is unknown.

Data from a placebo-controlled trial in 477 patients did not establish efficacy of Xigris in paediatric patients, which is a non-indicated patient group. Overall 28-day mortality was similar between the Xigris and placebo groups. There was a higher rate of CNS bleeding in the Xigris group versus the placebo group (see ADVERSE EFFECTS).

**Carcinogenicity**

Long-term studies in animals to evaluate potential carcinogenicity of Xigris have not been performed.

**Genotoxicity**

Xigris was not mutagenic in an *in vivo* micronucleus study in mice or in an *in vitro* chromosomal aberration study in human peripheral blood lymphocytes with or without rat liver metabolic activation.

**Interactions with other Medicines**

Caution should be employed when Xigris is used with other drugs that affect haemostasis (see PRECAUTIONS - Bleeding).

**Co-administration of low-dose heparin for prophylaxis of venous thrombotic events (VTE)**

Low-dose heparin for VTE prophylaxis may be co-administered with Xigris.

In a randomised study comparing heparin and placebo in 1935 adult severe sepsis patients treated with Xigris, prophylactic heparin did not adversely affect the efficacy of Xigris or increase the risk of serious haemorrhagic events, including central nervous system bleeding. The incidence of nonserious bleeding events was increased by low-dose heparin (see Adverse Effects).

**Laboratory Tests**

Xigris has minimal effect on the PT. Prolongation of the APTT in patients with severe sepsis receiving Xigris may be due to the underlying coagulopathy, the pharmacodynamic effect of Xigris and/or the effect of other concurrent medications. The pharmacodynamic effect of Xigris on the APTT assay is dependent on the reagent and instrument used to perform the assay and the time that elapses between
sample acquisition and assay performance. Xigris present in a plasma sample will be gradually neutralised by endogenous inhibitors. Due to these biological and analytical variables, the APTT should not be used to assess the pharmacodynamic effect of Xigris. The interpretation of sequential determination of the PT and/or APTT should take these variables into consideration.

Because Xigris may affect the APTT assays, Xigris present in plasma samples may interfere with one-stage coagulation assays based on the APTT (such as factor VIII, IX and XI assays). Xigris present in plasma samples does not interfere with one-stage factor assays based on the PT (such as Factors II, V, VII and X assays).

**ADVERSE EFFECTS**

Bleeding is the most common serious adverse event associated with Xigris.

**Phase 2, PROWESS and ENHANCE studies**

A total of 1821 adult patients with severe sepsis were evaluated in two placebo-controlled trials (Phase 2 and PROWESS). Patients ranged in age from 18 to 96 years (mean age of 60.5 years). Women and Caucasians comprised 42% and 82% of the patient population, respectively. A total of 940 patients were randomised to and received Xigris. Most patients (80%) received a dose of 24 microgram/kg/hr administered as a constant rate infusion for 96 hours.

A total of 2378 adult patients with severe sepsis received drotrecogin alpha (activated) in a Phase 3b multi-centre, single-arm, open-label trial (ENHANCE).

In the placebo-controlled Phase 2 and PROWESS trials, the percentage of patients experiencing at least one bleeding event during the 28 day study period in Xigris-treated and placebo-treated patients was 23.9% and 17.3%, respectively. In both treatment groups, the majority of bleeding events were ecchymosis or gastrointestinal tract bleeding.

In the Phase 2, PROWESS and ENHANCE studies, serious bleeding events were defined as any intracranial haemorrhage, any life threatening or fatal bleed, any bleeding event requiring administration of ≥ 3 units of packed red blood cells per day for 2 consecutive days, or any bleeding event assessed as serious by the investigator. Table 2 lists the proportion of patients experiencing serious bleeding event by site of haemorrhage during the study drug infusion period (defined as the duration of infusion plus the next full calendar day following the end of infusion).

<table>
<thead>
<tr>
<th>Site of haemorrhage</th>
<th>Phase 2 and PROWESS</th>
<th>ENHANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Xigris (n=940)</td>
<td>Placebo (n=881)</td>
</tr>
<tr>
<td></td>
<td>7 (0.7%)</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>2 (0.2%)</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>Intra-thoracic</td>
<td>4 (0.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>3 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>CNS²</td>
<td>2 (0.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>2 (0.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>
In the placebo-controlled Phase 2 and PROWESS trials, serious bleeding event rates during the 28 day study period were 3.6% and 2.0% in Xigris-treated and placebo-treated patients, respectively. The incidence of CNS bleeding during the 28 day study period was 0.2% and 0.1% for Xigris-treated and placebo-treated patients, respectively.

In the single-arm trial (ENHANCE), the incidence of serious bleeding events during the 28-day study period was 6.5%. The incidence of CNS bleeding during the 28-day study period was 1.5%.

In the Phase 2 and PROWESS clinical trials, 5 patients experienced serious adverse events leading to death and considered to be possibly related to Xigris. Four of the deaths were associated with bleeding events; the fifth patient experienced cerebral oedema and severe hypoxia.

**ADDRESS study**

In a non-indicated patient population in the randomised, placebo-controlled trial in adult severe sepsis patients at low risk of death (ADDRESS), the percentage of patients experiencing at least one bleeding event during days 0-28 in Xigris-treated and placebo-treated patients was 10.9% and 6.4%, respectively (p<0.001). Bleeding events included serious bleeding events, bleeding events assessed as possibly study-drug related by the investigator, bleeding events associated with the need for a red blood cell transfusion, and bleeding events that led to permanent discontinuation of the study drug.

In the ADDRESS study, serious bleeding events were defined as any fatal bleed, any life threatening bleed, any CNS bleed or any bleeding event assessed as serious by the investigator. Table 3 lists the percentage of treated patients experiencing serious bleeding events and serious CNS bleeding events in ADDRESS. The proportion of patients experiencing a serious bleeding event by site of haemorrhage was similar to that observed in the PROWESS trial.
Table 3: Serious bleeding event rates in ADDRESS

<table>
<thead>
<tr>
<th></th>
<th>Xigris (n=1317)</th>
<th>Placebo (n=1293)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total serious bleeding events</strong>(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study drug infusion period(^2)</td>
<td>31 (2.4%)*</td>
<td>15 (1.2%)</td>
</tr>
<tr>
<td>28-day study period</td>
<td>51 (3.9%)*</td>
<td>28 (2.2%)</td>
</tr>
<tr>
<td><strong>CNS bleeding events</strong>(^3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study drug infusion period(^2)</td>
<td>4 (0.3%)</td>
<td>3 (0.2%)</td>
</tr>
<tr>
<td>28-day study period</td>
<td>6 (0.5%)</td>
<td>5 (0.4%)</td>
</tr>
</tbody>
</table>

\(^1\) Serious bleeding events include any fatal bleed, any life threatening bleed, any CNS bleed, or any bleeding event assessed as serious by the investigator.

\(^2\) Study drug infusion period is defined as study Day 0 through Study Day 6.

\(^3\) CNS bleeding includes any bleed in the central nervous system, including the following types of haemorrhage – petechial, parenchymal, subarachnoid, subdural, and stroke with haemorrhagic transformation.

\(*\) Statistically significantly different from placebo

Xigris and Heparin

Table 4 lists bleeding rates from a randomised study (XPRESS) of low-dose heparin versus placebo in 1935 adult severe sepsis patients treated with Xigris. Serious bleeding rates were consistent with those observed in previous studies of Xigris. Low-dose heparin did not increase the risk of serious bleeding, including central nervous system bleeding. Low-dose heparin increased the risk of nonserious bleeding compared with placebo over the study drug infusion period.

Table 4: Bleeding Event Rates in XPRESS

<table>
<thead>
<tr>
<th></th>
<th>Heparin plus Xigris (N =976)</th>
<th>Placebo plus Xigris (N = 959)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Bleeding (Serious and Non-serious) Events (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study drug infusion period</td>
<td>105 (10.8%)*</td>
<td>78 (8.1%)</td>
</tr>
<tr>
<td>28-day study period</td>
<td>121 (12.4%)</td>
<td>105 (10.9%)</td>
</tr>
<tr>
<td><strong>Serious Bleeding Events(^1) (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study drug infusion period</td>
<td>22 (2.3%)</td>
<td>24 (2.5%)</td>
</tr>
<tr>
<td>28-day study period</td>
<td>38 (3.9%)</td>
<td>50 (5.2%)</td>
</tr>
<tr>
<td><strong>CNS Bleeding Events(^2) (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study drug infusion period</td>
<td>3 (0.3%)</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>28-day study period</td>
<td>10 (1.0%)</td>
<td>7 (0.7%)</td>
</tr>
</tbody>
</table>
Serious bleeding events included any fatal bleed, any life threatening bleed, any CNS bleed, or any bleeding event assessed as serious by the investigator.

CNS bleeding includes any bleed in the central nervous system, including the following types of hemorrhage – petechial, parenchymal, subarachnoid, subdural, and stroke with hemorrhagic transformation.

*Statistically significantly different from placebo.

RESOLVE Paediatric study

Fatal CNS bleeding events, serious bleeding events (over the infusion period and over the 28-day study period), serious adverse events, and major amputations were similar in the Xigris and placebo groups in a placebo-controlled study in 477 paediatric patients. Xigris is not indicated for use in this patient population.

There was a higher rate of CNS bleeding in the Xigris group versus the placebo group. Over the infusion period (study days 0-6) the number of patients experiencing CNS bleeding was 5 versus 1 for the overall population (Xigris versus placebo, respectively). Four of the 5 events in the Xigris group occurred in patients aged ≤ 60 days or weighing ≤ 3 kg. Two of the 5 Xigris-treated patients and the placebo-treated patient who experienced CNS bleeding had violated protocol guidelines intended to limit the risk of an adverse bleeding event occurring.

Additional Information

Intracranial haemorrhage has been reported in patients receiving Xigris in non-placebo controlled trials with an incidence of approximately 1% during the infusion period. The risk of intracranial haemorrhage may be increased in patients with risk factors for bleeding such as severe coagulopathy and severe thrombocytopenia (see PRECAUTIONS – Bleeding).

DOSAGE AND ADMINISTRATION

Xigris should be used by experienced doctors in institutions skilled in the care of patients with severe sepsis.

Treatment should be started within 48 hours, and preferably within 24 hours, of the onset of the first documented sepsis-induced organ failure.

The recommended dose of Xigris is 24 microgram/kg/hr (based on actual body weight) 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 microgram/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, as no clinically significant differences in the plasma clearance of Xigris were detected with regard to age, gender, obesity, hepatic function or renal function or co-administration of low-dose heparin.

Paediatrics: Data from a placebo-controlled clinical trial in paediatric patients (the RESOLVE study) did not establish the efficacy of Xigris. Consequently, dosage recommendations cannot be given (see PRECAUTIONS).
**End stage renal disease:** There is insufficient data to support a dosage recommendation in patients with end stage renal disease (see PHARMACOLOGY - Pharmacokinetic Properties).

**Preparation and administration instructions:** Use aseptic technique.

1. Use appropriate aseptic technique during the preparation of Xigris for intravenous administration.

2. Calculate the dose and the number of Xigris vials needed. Each Xigris vial contains 5 mg of recombinant human Activated Protein C. The vial contains an excess of recombinant human Activated Protein C to facilitate delivery of the label amount.

3. Prior to administration, 5 mg vials of Xigris must be reconstituted with 2.5 mL of Sterile Water for Injection, resulting in a solution with a concentration of approximately 2 mg/mL recombinant human Activated Protein C. Slowly add the Sterile Water for Injection to the vial and avoid inverting or shaking the vial. Gently swirl each vial until the powder is completely dissolved.

4. The solution of reconstituted Xigris must be further diluted with sterile 0.9% Sodium Chloride Injection. Slowly withdraw the appropriate amount of reconstituted Xigris from the vial. Add the reconstituted Xigris into a prepared infusion bag of sterile 0.9% Sodium Chloride Injection. When adding the reconstituted Xigris into the infusion bag, direct the stream to the side of the bag to minimise the agitation of the solution. Gently invert the infusion bag to obtain a homogeneous solution. Do not transport the infusion bag between locations using mechanical delivery systems which may cause agitation.

5. Because Xigris contains no antibacterial preservatives, the intravenous solution should be prepared immediately upon reconstitution of Xigris in the vial(s). If the vial of reconstituted Xigris is not used immediately, it may be held at room temperature (15 to 30°C), but must be used within 3 hours. After the intravenous solution is prepared, the infusion of that solution must be completed within 12 hours.

6. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

7. When using a syringe pump to administer the drug, the solution of reconstituted Xigris should be diluted with sterile 0.9% Sodium Chloride Injection to a final concentration of between 100 microgram/mL and 200 microgram/mL. Invert and/or rotate the syringe to obtain a homogeneous solution, but avoid excessive agitation. When administering Xigris at low flow rates (less than approximately 5 mL/hr), the infusion set must be primed for approximately 15 minutes at a flow rate of approximately 5 mL/hr.

8. When using an intravenous infusion pump to administer the drug the solution of reconstituted Xigris should be diluted into an infusion bag containing sterile 0.9% Sodium Chloride Injection to a final concentration of between 100 microgram/mL and 200 microgram/mL.
9. Xigris should be administered via a dedicated intravenous line or a dedicated lumen of a multilumen central venous catheter. The ONLY other solutions that can be administered through the same line are 0.9% Sodium Chloride Injection, Lactated Ringer’s Injection, Glucose or Glucose and Saline mixtures.

10. Avoid exposing Xigris solutions to heat and/or direct sunlight. No incompatibilities have been observed between Xigris and glass infusion bottles or infusion bags and syringes made of polyvinylchloride, polyethylene, polypropylene or polyolefin.

11. Xigris contains no antibacterial preservatives. It is for use in a single patient with infusion completed within 12 hours of preparation.

OVERDOSAGE

In clinical trials and in post-marketing experience, there have been some reports of accidental overdosing. In the majority of cases no reactions have been observed. For the other reports, the observed events were consistent with known effects of the drug and/or sequelae of the underlying condition of sepsis.

There is no known antidote for Xigris. In case of overdose, immediately stop the infusion (see PHARMACOLOGY – Pharmacokinetic properties). In case of overdose, immediately contact the Poisons Information Centre 13 11 26 for advice.

PRESENTATION AND STORAGE CONDITIONS

Xigris is supplied as a sterile, lyophilised powder in 5 mg and 20 mg* strengths. Xigris should be stored in a refrigerator 2° to 8°C. Keep the vial in the outer carton in order to protect it from light.

*currently not available in Australia

NAME AND ADDRESS OF THE SPONSOR

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POSION SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

TGA Approval:
23 October 2009

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