EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Xigris

Procedural steps taken and scientific information after the authorisation

## Changes made after 1 October 2004

For procedures finalised before 1 October 2004, please refer to 'Procedural steps taken until cut-off date'

| No | Scope | Opinion/ Notification[1] issued on | Commission Decision Issued[2] / amended on | Product Information affected[3] | Summary |
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| IB/0030 | B.I.b.2.e - Change in test procedure for active substance or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate | 02/06/2010 | n/a | | |

[1] Notifications are issued for type I variations (unless part of a group or a worksharing application). Opinions are issued for all other procedures.
[2] No Commission Decision is issued for type IA and type IB variations or for type II variations and annual re-assessments that do not affect the annexes.
[3] SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).



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| S/0029 | Annual reassessment<br><br>Seventh annual reassessment of the benefit/risk profile for Xigris. | 22/04/2010 | n/a | | Please refer to the Assessment report "Xigris EMEA/H/C/396/S/29" for further information |
| S/0028 | Annual reassessment<br><br>Sixth annual reassessment of the benefit/risk profile for Xigris.<br><br>The MAH has also taken the opportunity to correct the contact detail of the Slovenian local representative. | 24/09/2009 | 08/12/2009 | SPC, PL | Please refer to the Assessment report "Xigris EMEA/H/C/396/S/28" for further information |
| II/0026 | Update of Summary of Product Characteristics<br><br>To update sections 4.2 "Posology and method of administration", 4.4 "Special warnings and precautions for use" and 4.9 "Overdose" of the SPC as follows:<br><br>- Section 4.2 is updated to provide further clarification on dosing in obese patients<br><br>- Section 4.4 is updated to reflect new information related to | 23/10/2008 | 04/12/2008 | SPC | This type II variation relates to changes proposed to ensure that the Xigris SPC wording remains accurate and reflects the availability of new clinical trial data. As there is no difference in the clearance, steady state concentration and half-life between patients weighing > 135 kg to those weighing ? 135 kg, section 4.2 of the SPC was updated to provide further clarification on dosing in obese patients. Section 4.4 of the SPC was updated to reflect new information related to readministration, together with a new methodology used to re-test stored samples from PROWESS, ENHANCE, ADDRESS and XPRESS studies. Retesting of these samples did not establish a difference in antibody development between Xigris and placebo |

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| | readministration, together with a new methodology used to re-test stored samples from clinical trials.<br>- Section 4.9 is updated to take into account additional cases of overdose in clinical trials. | | | | patients. Section 4.9 of the SPC was updated to reflect the occurrence of two additional cases of overdose in clinical trials which do not alter the overall conclusions to the overdose section of the Xigris SPC. |
| II/0027 | Change(s) to the test method(s) and/or specifications for the finished product,<br>Change(s) to the test method(s) and/or specifications for the active substance | 23/10/2008 | 04/12/2008 | SPC, PL | Introduction of a minor change to a test method, with associated tightening of release and end of shelf life specifications for drug substance and drug product. This change leads to minor revisions to section 6.6 of the SPC and to the leaflet. |
| S/0024 | Annual reassessment<br>Fifth annual reassessment of the benefit/risk profile for Xigris. | 24/01/2008 | 31/03/2008 | Annex II | The CHMP, having reviewed the data submitted by the Marketing Authorisation Holder, concluded that the benefit/risk profile for Xigris in the "treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care. The use of Xigris should be considered mainly in situations when therapy can be started within 24 hours after the onset of organ failure" remained unchanged. Nonetheless, since there was still a Specific Obligation that remained to be fulfilled, the Marketing Authorisation for Xigris will remain under exceptional circumstances. |

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| IA/0025 | 05_Change in the name and/or address of a manufacturer of the finished product | 08/02/2008 | n/a | | |
| R/0023 | Renewal of the marketing authorisation | 24/05/2007 | 20/07/2007 | SPC, Annex II, Labelling, PL | Based on the CHMP review of the available information, the CHMP was of the opinion that the quality, safety and efficacy of Xigris continued to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of Xigris remained positive. Nevertheless, the CHMP recommended that the Marketing Authorisation Holder (MAH) should continue to closely monitor the bleeding/central nervous system bleed reactions, thrombocytopenia, convulsions, events and serious bleeding events in paediatric patients 17 years of age and younger, and the use in pregnancy. Furthermore, the CHMP concluded that the MAH should continue to monitor serious bleeding events in connection with potential off-label use of Xigris through the collection and evaluation of data via a dedicated serious bleeding follow-up form. Additionally, the results of the upcoming placebo-controlled study of Xigris in its target population (see 4th annual re-assessment EMEA/H/C/000396/S/0021) fully justified the maintenance of Xigris under close scrutiny, i.e. under exceptional circumstances. Thus, based upon the safety profile of Xigris, which required the submission |

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| | | | | | of yearly PSURs, and considering that the Marketing Authorisation remained under exceptional circumstances, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time. |
| S/0021 | Annual reassessment<br><br>Fourth annual re-assessment of the benefit/risk profile of Xigris. | 22/02/2007 | 25/04/2007 | Annex II | The CHMP adopted a positive opinion on the fourth annual re-assessment of the benefit/risk profile of Xigris.<br><br>Nevertheless, the CHMP concluded that 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 heparin or did not receive any thrombosis prophylaxis) with severe sepsis and documented organ failure should be performed to further clarify the benefit/risk profile of Xigris. The Marketing Authorisation will remain under exceptional circumstances.<br><br>Please refer to the Scientific Discussion "Xigris-H-C-396-S-21" for further information. |

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| II/0020 | Update of Summary of Product Characteristics<br><br>Update of sections 4.2, 4.5 and 5.1 of the SPC with relevant data from the heparin/Xigris versus placebo/Xigris XPRESS study. Section 4.8 of the SPC was updated to include that serious bleeding rates were consistent with those observed in previous studies but the risk of non-serious bleeding was increased in prophylactic heparin compared with placebo. | 22/02/2007 | 02/04/2007 | SPC | Please refer to the Scientific Discussion "Xigris-H-C-396-II-20" for further information. |
| II/0022 | Update of Summary of Product Characteristics and Package Leaflet<br><br>To update sections 4.4 and 4.8 of the SPC with information on increased risk of serious bleeding events in surgical patients, following the CHMP's assessment of data on bleeding events in surgical versus non-surgical patients from the major studies with Xigris.<br><br>In addition the MAH completed the | 22/02/2007 | 02/04/2007 | SPC, PL | At the conclusion of the 3rd annual re-assessment, the CHMP requested the MAH to compare bleeding episodes [all, serious, fatal serious, Central Nervous System (CNS) and fatal CNS] in surgical patients versus medical (non surgical) patients in all the clinical trials in order to obtain more information regarding a possible increased risk in surgical patients. Therefore, the MAH submitted the requested data from 5 major studies: PROWESS, ENHANCE, ADDRESS, RESOLVE and XPRESS.<br><br>From the assessment of these data the CHMP concluded that the incidence of serious bleeding |

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| | list of local representatives in the PL to include the two new EU Member States (Bulgaria and Romania).<br><br>Finally the MAH took the opportunity to introduce minor editorial amendments into the Bulgarian and Danish Product Information. | | | | events with Xigris was higher in patients with recent (within 30 days) surgery than in "medical" patients and that the bleeding risk should be taken into account when considering the risk benefit for individual patients. During the infusion period in PROWESS and ENHANCE the incidence of serious bleeding events with Xigris was numerically higher in patients with recent (within 30 days) surgery than in patients without surgery (PROWESS: 3.3% vs 2.0%; ENHANCE: 5.0% vs 3.1% respectively; placebo rates in PROWESS 0.4% vs 1.2% respectively). |
| II/0019 | Change(s) to container | 27/04/2006 | 03/05/2006 | | |
| S/0017 | Annual reassessment<br><br>Third annual re-assessment of Xigris, as its approval was granted under exceptional circumstances. | 23/02/2006 | 24/04/2006 | SPC, Annex II | For the third annual re-assessment of Xigris, the MAH has submitted an update on clinical trials during the past 12 months, one-year follow-up supplemental report on the ADDRESS study and an update on spontaneous safety data from the market during the past 12 months.<br><br>The results of the one-year long-term follow-up data of the ADDRESS study demonstrated that Xigris has an acceptable safety profile at 1 year. There was no increased risk of death or evidence of harm at 1 year associated with the administration of Xigris.<br><br>Given that "increased risk of bleeding" is the only |

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| | | | | | adverse event known to be associated with treatment with Xigris, it is reassuring that the reporting rate of spontaneous CNS (Central Nervous System) and non-CNS bleeding events has been fairly stable across the Periodic Safety Update Reports (PSURs). Additionally, it was acknowledged that the spontaneous cases of serious bleeding events did not show any particular pattern across Europe and are compatible with rates observed in clinical trials. The frequency of spontaneous cases of serious bleedings has not increased since Xigris started to be used 3 years ago.<br><br>The CHMP requested the MAH to comment on any potential off-label use of Xigris in the EU, particularly in children and in patients who have undergone recent surgery. Since it is difficult to assess any potential off-label use of Xigris based on spontaneous reports, the MAH has proposed to implement a follow-up questionnaire for spontaneous reports of serious bleeding events to capture information about surgical status, timing of initiation of Xigris in relation to surgery, and number of organ dysfunctions present. The MAH has planned a communication strategy in order to discourage any off-label use of Xigris and to emphasise that<br><br>- Xigris should only be used in severe sepsis patients |

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| | | | | | with multiple organ dysfunction;<br>- Xigris is not recommended in children and therefore should not be used in children;<br>- the use of Xigris should be considered mainly in situations when therapy can be started within 24 hours after the onset of organ failure;<br>- Xigris should only be used by experienced doctors in institutions skilled in the care of patients with severe sepsis;<br>- Xigris should not be used in patients with single organ dysfunction, especially if they have had recent surgery (within 30 days).<br>The communication strategy aims to directly contact 300 hospitals (most frequent Xigris users) and to mail further 900 hospital intensive care units and additionally paediatric intensivists.<br>In order to emphasise that Xigris is not recommended in children, section 4.4 of the SPC was updated in order to include that Xigris is not recommended in children below the age of 18 and therefore it should not be used in children.<br>On the basis of the data submitted, the benefit/risk profile for Xigris in the indicated population remains |

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| | | | | | positive: "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". The CHMP agreed that the Marketing Authorisation should remain under exceptional circumstances. |
| II/0018 | Quality changes | 14/12/2005 | 19/12/2005 | | |
| II/0011 | Quality changes | 17/11/2005 | 25/11/2005 | | |
| II/0016 | Update of Summary of Product Characteristics<br><br>To update sections 4.2 and 4.4 of the SPC with relevant data from the RESOLVE study (F1K-MC-EVBP) in paediatric patients with severe sepsis, indicating that efficacy has not been established in the paediatric population. | 13/10/2005 | 15/11/2005 | SPC | Data from a placebo-controlled clinical trial did not establish efficacy of Xigris in paediatric patients suffering from severe sepsis, acute infection, systemic inflammation and respiratory and cardiovascular organ dysfunction. This trial was stopped for futility after 477 patients had received the study drug (out of 600 patients intended).<br><br>A planned interim analysis (with 400 patients enrolled) showed a low likelihood of demonstrating a significant difference in the primary endpoint of "Composite Time to Complete Organ Failure Resolution" (CTCOFR score of 9.8 versus 9.7 mean days over 14 days). There was also no difference in 28-day mortality (17.1% versus 17.3% in the Xigris |

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| | | | | | and placebo groups, respectively).<br><br>Investigators attributed 2 deaths in the Xigris group and 5 deaths in the placebo group to bleeding events. There was a higher rate of central nervous system (CNS) bleeding in the drotrecogin alfa (activated) versus the placebo group. Over the infusion period (study days 0-6) the number of patients experiencing CNS bleeding was 5 versus 1 (2.1% versus 0.4%) for the overall population (drotrecogin alfa (activated) versus placebo), with 4 of the 5 events in the drotrecogin alfa (activated) group occurring in patients =60 days old or =3.5 kg bodyweight. Fatal CNS bleeding events, serious bleeding events (over the infusion period and over the 28-day study period), serious adverse events, and major amputations were similar in the drotrecogin alfa (activated) and placebo groups.<br><br>Therefore no dosage recommendation can be made and the use of Xigris is not recommended in children below the age of 18. |
| II/0012 | Quality changes | 20/01/2005 | 31/01/2005 | | |

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| II/0014 | Update of Summary of Product Characteristics and Package Leaflet<br><br>Update of sections 4.2, 4.4, 4.8 and 5.1 of the SPC with relevant data from the ENHANCE study (F1K-MC-EVAZ).<br><br>Further, in line with the post-opinion commitment from variation EMEA/H/C/396/II/008, sections 4.2 and 6.6 of the SPC and the `Instructions for use and handling' in the PL have been updated.<br><br>Finally, minor typographical corrections in section 5.1 (`Clinical efficacy') of the SPC and two minor changes to the list of local representatives (Slovenia and Portugal) in the PL have been proposed. | 15/12/2004 | 25/01/2005 | SPC, PL | Following the assessment of the final study report of the ENHANCE study, the section 4.2 `Posology and method of administration' of the SPC has been updated to include that the treatment should be started within 48 hours, and preferably within 24 hours, of onset of the first documented sepsis-induced organ dysfunction. This information has been reflected in 5.1 `Pharmacodynamic properties' of the SPC. The section 4.8 `Undesirable effects' of the SPC has been updated and a table on "Serious bleeding events during the infusion period" has been included.<br><br>In line with the post-opinion commitment from variation EMEA/H/C/396/II/008, section 4.2 `Posology and method of administration' has been updated to include the recommendation that Xigris should be infused with an infusion pump to accurately control the infusion rate. The same recommendation has been included in section 6.6 `Instructions for use and handling' of the SPC and in the `Instructions for use and handling' of the Package Leaflet. |
| IB/0015 | 31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits | 11/01/2005 | n/a | | |