SAFETY REVIEW OF XIGRIS (DROTRECOGIN ALFA [ACTIVATED])

This New Drug FAX Sheet issue provides information from the FDA regarding an analysis of a recently published retrospective review of bleeding associated with drotrecogin alfa. Patients with baseline bleeding risk factors had an increased risk of serious bleeding and mortality when administered drotrecogin alfa. The verbatim communication from the FDA is provided below. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.

FDA is aware of a retrospective study (Gentry et al.: Adverse outcomes associated with the use of drotrecogin alfa (activated) in patients with severe sepsis and baseline bleeding precaution, Crit Care Med 2009), which reported an increased risk of serious bleeding events and of death in patients with sepsis (a severe illness related to a bloodstream infection) and baseline bleeding risk factors who received drotrecogin alfa (activated). Drotrecogin alfa (activated), marketed as Xigris, is a recombinant human activated protein C indicated for the reduction of mortality in adult patients with severe sepsis who have a high risk of death. The baseline bleeding risk factors as defined by this study are the same as those described in the Xigris prescribing information, under the Contraindications and the Warnings and Precautions sections of the package insert.

An editorial accompanying the Gentry et al. article stated that one approach to increasing the safety of Xigris would be to not administer it to any patients with sepsis and baseline bleeding risk factors, effectively changing a warning in the product labeling to a contraindication. Under FDA regulations, contraindications in the prescribing information describe situations where the risks are known (that is, are not theoretical) and where the risks of use clearly outweigh any possible benefit.

The study conducted by Gentry et al. was a retrospective medical record review of 73 patients who received Xigris. Serious bleeding events occurred in 7 of 20 patients (35%) who had a bleeding risk factor vs. only 2 of 53 (3.8%) patients without any bleeding risk factors. More patients with baseline bleeding risk factors died (13/20; 65%) compared to patients without any bleeding risk factors (13/53; 24.5%). The authors acknowledge that there are limitations to this study, such as its retrospective design and the small size of the patient population, that limit the ability to draw definitive conclusions from the data.

The current prescribing information for Xigris describes the increased risk of bleeding, and includes a statement in the Warnings and Precautions section that bleeding is the most common serious adverse reaction experienced by patients who received the drug. The Warnings and Precautions section also lists a number of risk factors for the increased risk of bleeding that should be taken into account when considering use of Xigris therapy. The Contraindications section states that Xigris is not to be used in the following clinical situations where bleeding could lead to significant morbidity or death:

- Active internal bleeding
- Recent (within 3 months) hemorrhagic stroke
- Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma
- Trauma with an increased risk of life-threatening bleeding
- Presence of an epidural catheter
- Intracranial neoplasm or mass lesion or evidence of cerebral herniation

Overall, the finding by Gentry et al. of an increased risk of death and serious bleeding events in patients treated with Xigris who also have baseline bleeding risk factors is consistent with the information in the current product label. Prescribers should refer to the product label for the specific contraindications, warnings, and, precautions and carefully weigh the increased risk of bleeding against the benefits of Xigris.

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FDA is working with the manufacturer to further evaluate the incidence of serious bleeding events and mortality in patients who received Xigris. FDA will communicate its conclusions and any resulting recommendations to the public when our review is completed, which may take several months.

This communication is in keeping with FDA’s commitment to inform the public about its ongoing safety reviews of drugs.

The FDA urges both healthcare professionals and patients to report side effects from the use of Xigris to the FDA’s MedWatch Adverse Event Reporting program:

- online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm);
- by returning the postage-paid FDA form 3500 available in PDF format at [www.fda.gov/medwatch/getforms.htm](http://www.fda.gov/medwatch/getforms.htm) to 5600 Fishers Lane, Rockville, MD 20852-9787;
- faxing the form to 1-800-FDA-0178; or
- by phone at 1-800-332-1088

3. APACHE II score >25. The APACHE II score (Acute Physiology and Chronic Health Evaluation II) is a commonly-used severity of disease classification system calculated for critically ill patients after admission to an intensive care unit.

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