Bundesamt für Sicherheit
im Gesundheitswesen

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Information des Bundesamts für Sicherheit im Gesundheitswesen über Maßnahmen zur Gewährleistung der Arzneimittelsicherheit und Sicherheit von Medizinprodukten

Betreff: Sicherheitsinformationen zu Risiken von Aprotinin in der Kardiochirurgie

In der Zeitschrift „New England Journal of Medicine" wurden am 26. Januar 2006 die Ergebnisse einer umfangreichen Beobachtungsstudie zur Sicherheit von Aprotinin bei herzchirurgischen Eingriffen publiziert (NEJM 345 (2006); 353-365). In dieser multinationalen, multizentrischen Studie wurden Ereignisse erfasst, die bei Patienten nach einem herzchirurgischen Eingriff während des Krankenhausaufenthaltes auftraten.

Die Häufigkeit kardialer, zerebrovaskulärer oder renaler Ereignisse in den Patientengruppen, die entweder Aprotinin, Aminocapronsäure, Tranexamsäure oder keine Behandlung erhielten, wurde miteinander verglichen. Die Ergebnisse dieser Studie weisen auf ein erhöhtes Risiko für das Auftreten von Herzinfarkten, Schlaganfällen oder Nierenfunktionsschädigungen einschließlich Nierenversagen im Zusammenhang mit der Anwendung von Aprotinin hin.

Die veröffentlichte Studie bedarf, wegen ihrer Komplexität und der Tatsache dass wichtige, für eine Bewertung notwendige Daten und Informationen nicht enthalten sind, einer eingehenden Bewertung. Diese schließt den Informationsaustausch mit dem pharmazeutischen Unternehmer, der Firma Bayer HealthCare, ein. Bei Aprotinin - haltigen Arzneimitteln wird derzeit das Nutzen/Risiko neu bewertet.

Aprotinin ist unter den Warenzeichen Trasylol® (Zulassungsinhaber: Bayer) und Pantinol® (Zulassungsinhaber: Gerot) zugelassen worden.

Die AGES PharmMed wird erneut darüber berichten, wenn die Bewertung der vorhandenen Daten abgeschlossen ist oder neue wichtige Zwischenergebnisse vorliegen.

Für das Bundesamt

Dr. Reinhard
Berger e.h.
für das Bundesamt
Wien
2006.02.15
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Beilage: vorgelegte Sicherheitsinformation der Fa. Bayer („dear doctor letter") englisch – 3 Seiten

Bayer HealthCare
Pharmaceuticals

IMPORTANT Trasylol Safety Information

February, 2006

Dear Healthcare Professional:

Bayer HealthCare would like to inform you that Bayer and European regulatory authorities are evaluating recent reports published in the medical literature concerning Trasylol® (aprotinin injection).

A study entitled, "The Risk Associated with Aprotinin in Cardiac Surgery" by Mangano et al., was published in the *New England Journal of Medicine*, (Mangano D, Tudor J, Dietzel C. N Eng J Med, 2006 (354) :353-65. www.nejm.org). The publication describes the findings from an observational study of 4,374 patients (1,295 treated with aprotinin) scheduled for coronary artery bypass graft (CABG) surgery in multiple centers in multiple countries. Patients received either no therapy for blood loss, or a drug therapy intended to reduce blood loss (aprotinin, aminocaproic acid, tranexamic acid).

The *NEJM* publication reported an association of aprotinin with increased risk of cardiovascular events (myocardial infarction or heart failure), cerebrovascular events such as stroke, encephalopathy or coma, and renal dysfunction or failure in patients undergoing CABG surgery. Patients were not randomized to these treatments. Instead, choice of study drug (or no treatment) was at physician discretion. Patients receiving aprotinin may have been at a higher risk to begin with for developing renal failure, myocardial infarction, heart failure or stroke compared to patients receiving no treatment or treatment with another drug intended to decrease bleeding. This possibility prevents a direct assessment of whether aprotinin altered the risk for serious adverse events. To try to adjust for known differences between the treatment groups, the study authors used statistical procedures (multivariable logistic regression and propensity score adjustments).

A study entitled, "A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery" by Karkouti et al. has been published in the journal *Transfusion* (Karkouti K, Beattie W, Dattilo K, McCluskey S, Ghannam M, Hamdy A, et al., Transfusion, on-line edition, 1/20/06. www.blackwellpublishing.com/journal.asp?ref=0041-1132). This was also an observational study that used statistical methodology to compare outcomes from patients undergoing CABG. Like the NEJM study, the patients in this study received, at physician discretion, either Trasylol or another drug intended to decrease the risk for perioperative bleeding.

The study in *Transfusion* has some of the same limitations as the NEJM publication. The study suggested that Trasylol administration increased the risk for renal dysfunction or failure. Renal

dysfunction and renal failure have previously been reported in patients receiving Trasylol. The study by Karkouti et al. did not find an increased rate of cardiovascular or cerebrovascular events in Trasylol-treated patients and reported comparable mortality rates between the control treatment group and the Trasylol group.

Relevant EU regulatory authorities have said that they will review these reports, data supplied by Bayer and the authors of the studies, other reports in the literature as well as adverse event reports submitted to regulatory authorities through established processes, to determine if any actions are warranted. Several regulatory authorities have or will issue guidance to physicians and patients in their respective markets. Bayer welcomes and supports both the review and evaluation of these published studies and posting of guidance to physicians and patients in various markets.

While the evaluation of these published reports and other relevant data continues, Bayer, European and other regulatory authorities worldwide are providing guidance for physicians, other health care professionals and patients. The U.S Food and Drug Administration (FDA) has posted an “Alert for Healthcare Professionals” and a “Public Health Advisory” concerning Trasylol on its website (www.fda.gov) along with questions and answers related to this issue. Bayer has also posted a press statement and letter to Healthcare Professionals on its websites (www.bayer.com, www.bayerhealthcare.com, www.bayerpharma.com, www.pharma.bayer.com, www.bayervital.de [insert local Bayer web address as appropriate] and www.trasylol.com). In the next days Bayer will mail its letter to healthcare providers who use the product e.g. cardiothoracic surgeons, anesthesiologists and hospital pharmacists.

Guidance from regulatory authorities, e.g. the U.S. FDA includes a recommendation that physicians carefully monitor patients receiving Trasylol for the occurrence of adverse events particularly related to the kidneys, heart, or central nervous system and promptly report any events to Bayer or their respective regulatory authorities. The guidance also suggests that while the evaluation continues, physicians should consider limiting Trasylol use to situations where the clinical benefit of reduced blood loss is essential for medical management of the patient and outweighs potential risks.

Bayer supports these actions. We have been working and will continue to work closely with regulatory authorities in countries where Trasylol is marketed to address questions regarding product safety. We share the company’s data on Trasylol with regulatory authorities on an ongoing basis and welcome their evaluation of these published reports. Bayer believes that Trasylol is a safe and effective treatment when used in accordance with the product labeling.

If you wish to request further information, please contact your local Bayer HealthCare Medical Department.

Sincerely,

Franz-Josef Wingen, MD

Head Medical Science, Europe

Bayer HealthCare, Pharmaceuticals