1-1-2008

Pharmacy & Therapeutics Update: Drug Information for Health Care Professionals

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Update

Drug Information for Health Care Professionals

January 2008

Market Suspension of Aprotinin (Trasylol®) due to Potential Safety Concerns

On November 5, 2007, FDA announced the marketing suspension of aprotinin (Trasylol®) by Bayer Pharmaceutical Corporation. This suspension was at the request of FDA pending a detailed review of preliminary results from a Canadian study that suggested an increased risk for death associated with aprotinin compared with other agents.

Aprotinin is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery. It has been on the market since the early 1990s and has been used widely during cardiothoracic surgery in both adult and pediatric patients.

On October 19, 2007, FDA was notified that the Data and Safety Monitoring Board (DSMB) recommended to stop patient enrollment in the aprotinin treatment group in the BART (*Blood conservation using antifibrinolytics: A randomized trial in a cardiac surgery population)* study. The preliminary findings suggested that aprotinin increases the risk of death when compared with the antifibrinolytic drugs, aminocaproic acid and tranexamic acid. The BART study was designed to show that aprotinin was superior to aminocaproic acid and tranexamic acid in decreasing the occurrence of massive bleeding associated with cardiac surgery. The study had planned to enroll approximately 3,000 adult patients who were to undergo various types of cardiac surgery that placed them at high risk for bleeding.

Information from the interim analyses performed by the DSMB is limited, but the following was sent to FDA:

- the 30-day mortality in the aprotinin group nearly had reached conventional statistical significance at the interim analysis when compared with the other agents;
- a trend toward increased mortality in the aprotinin group had been observed throughout the study;
- the use of aprotinin was associated with less serious bleeding than the other agents; however, more deaths due to hemorrhage had been observed among patients receiving aprotinin;

- the DSMB concluded that continued enrollment of patients into the aprotinin group was unlikely to significantly change the study findings.

FDA determined that these preliminary data support the findings from observational studies that also suggested increased risks for mortality when aprotinin was compared to other antifibrinolytic drugs. FDA will work will the study sponsor to fully evaluate the data and determine the risk and benefits of aprotinin. This may lead to additional labeling or other regulatory action. During the review period, FDA recommends that health care providers review the risks and benefits of aprotinin outlined in the label and in the information provided by the manufacturer and discuss the information with their patients.

There are limited treatment options for patients at risk for excessive bleeding during cardiac surgery. Therefore, FDA is working with Bayer to phase aprotinin out of the marketplace in a way that does not cause shortages of other drugs used for this purpose. Until FDA can review the data from the terminated study it is not possible to determine and identify a population of patients undergoing cardiac surgery for which the benefits of aprotinin outweigh the risks. Understanding that individual doctors may identify specific cases where benefit outweighs risk, FDA is exploring ways for physicians to have continued but limited access to aprotinin.

After reviewing the literature regarding alternatives, there is limited literature to support aminocaproic acid and tranexamic acid in certain patients at high risk for bleeding. Therefore, after consultation with the Department of Anesthesiology and the Division of Cardiothoracic Surgery, the Pharmacy and Therapeutics Committee has maintained aprotinin on the *MUSC-MC Formulary of Accepted* with use restricted by prescribing service (ie, Anesthesiology, Pediatric Cardiothoracic Surgery, Adult Cardiothoracic Surgery) **AND** per the clinical criteria listed in Figure 1. The guidelines are posted on the *Formulary and Drug Information Resources* page under *Medication Use Policies/Guidelines.*

FDA and Bayer will be working together to create a program during the temporary suspension under which physicians in these markets might request and receive aprotinin for treatment of certain surgical patients with an established medical need. The company will work with the FDA, Health Canada, and any other authorities who wish to institute similar programs, to outline appropriate patient profiles and the specific details. Until the FDA and manufacturer develop a process for distribution, aprotinin use will be determined by availability from the distributor. Once current stock is depleted, it will be unavailable for use.

Figure 1. Clinical Guidelines for Aprotinin (Trasylol®)

Due to the current marketing suspension for aprotinin by the Food and Drug Administration and the manufacturer, Bayer, the use of aprotinin has been restricted to the following clinical indications:

For adult patients, aprotinin is approved for the following:
- Complex aortic surgery requiring profound hypothermic circulatory arrest
- Explantation of a mechanical assist device for cardiac recovery or heart transplantation
- Redo sternotomy for cardiac transplantation
- Redo sternotomy for endocarditits
- Any cardiac procedure performed on a patient who has received clopidogrel within 3 to 5 days prior to surgery

For pediatric patients, aprotinin is approved for the following:
- Open-heart cases for neonates (patients less than 1 month of age)
- Complex re-operative surgery (ie, third time or greater "re-do's," patients on ECMO or a ventricular assist device at the time of surgery)

If a patient does not meet one of the indications stated above, approval for aprotinin use must be obtained by an attending physician from the Chair or Secretary of the Pharmacy and Therapeutics Committee per policy C-82.

Strengthened Boxed Warnings for Erythropoiesis-Stimulating Agents

FDA approved revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs) [epoetin alfa (Procrit®, Epogen®), darpoetin (Aranesp®).] These agents are approved for the treatment of anemia in patients

with chronic kidney failure and anemia caused by chemotherapy in certain patients with cancer. Epoetin alfa products are also approved for use in certain patients with anemia who are scheduled to undergo major surgery to reduce blood transfusions during or shortly after surgery and for the treatment of anemia caused by zidovudine therapy in HIV patients.

The revised statements address the risks that ESAs pose to patients with cancer and patients with chronic kidney failure. The labeling changes, which incorporate advice from FDA advisory committees and expand upon labeling changes made in March 2007, also include a statement that symptoms of anemia, fatigue, and quality of life have not been shown to improve in patients with cancer who are treated with ESAs.

For patients with cancer, the new boxed warnings emphasize that ESAs caused tumor growth and shortened survival in patients with advanced breast, head and neck, lymphoid and non-small cell lung cancer when they received a dose that attempted to achieve a hemoglobin concentration of 12 g/dL or greater. The warnings also emphasize that no clinical data are available to determine whether there is a similar risk of shortened survival or increased tumor growth for patients with cancer who receive an ESA dose that attempts to achieve a hemoglobin concentration of less than 12 g/dL.

An earlier boxed warning, approved in March 2007, described the results of 6 studies demonstrating that survival was shorter and time to tumors progression was faster when ESAs were used to achieve hemoglobin concentrations above 12 g/dL in cancer patients. The current warning clarifies that ESAs should only be used in patients with cancer when treating anemia specifically caused by chemotherapy and not for other causes of anemia. Additionally, it states that ESAs should be discontinued once the patient's chemotherapy course has been completed.

For patients with chronic kidney failure, the new warning states that ESAs should be used to maintain a hemoglobin concentration between 10 and 12 g/dL. Maintaining higher hemoglobin concentrations in patients with chronic kidney failure increases the risk for death and for serious cardiovascular reactions such as stroke, heart attack, or heart failure. Additionally, the new labeling provides specific instructions for dosage adjustments and hemoglobin monitoring for chronic kidney failure patients who do not respond to ESA treatment with an adequate increase in their hemoglobin concentrations.

The new labeling also emphasizes that there are no data from controlled trials demonstrating that ESAs improve symptoms of anemia, quality of life, fatigue, or patient well-being for patients with cancer or for patients with HIV undergoing AZT therapy.

Early this month, FDA issued another statement regarding the safety of ESAs. An additional 2 studies were reviewed, which demonstrated similar results to the previous 6 studies reviewed by the agency. When taken together, all 8 studies show more rapid tumor growth or shortened survival in patients with breast, non-small cell lung, head and neck, lymphoid, or cervical cancers who received ESAs compared with patients who did not receive treatment. All in patients receiving ESAs, the goal hemoglobin was greater than 12 g/dL, although many patients did not reach that level.

FDA will continue to analyze data and do plan to revisit the risk and benefits at a public advisory meeting in the near future.

The current labeling for both ESAs is included in Table 1. It is important that health care professional follow the labeling set forth by the FDA and to monitor patients very closely for increases in hemoglobin greater than 12 g/dL. For more information, see the FDA communication at the following URL:
www.fda.gov/cder/drug/early_comm/ESA.htm.

Direct Thrombin Inhibitor (DTI) Preprinted Order Form and Protocol

At the November Pharmacy and Therapeutics Committee meeting, a direct thrombin inhibitor (DTI) preprinted order form and dosing protocol was approved. The purpose of form and protocol is to set guidelines that ensure the appropriate use, dosing, and monitoring of DTIs (ie, argatroban, bivalrudin) in the adult population. This protocol excludes patients in

Table 1. Dosing Recommendations for Erythropoiesis-stimulating Agents (ESAs)

	Epoetin alfa (EPOGEN®/PROCRIT®)[5,6]	Darbopoetin alfa (ARANESP®)[7]
FDA indications and recommended starting doses ***Please see package insert for additional information regarding when to increase/decrease dose and maintenance dosing***	**Anemia of Chronic Renal Failure** ▪ Adults: 50 to 100 units/kg TIW ▪ Pediatrics: 50 units/kg TIW **Anemia in Cancer Patients Receiving Chemotherapy** ▪ Adults: 150 units/kg SC TIW or 40,000 units SC weekly ▪ Pediatrics: 600 units/kg IV weekly (maximum = 40,000 units) **Anemia in zidovudine-treated HIV patients** (serum erythropoietin concentrations < 500 mUnits/mL) ▪ 100 units/kg TIW IV or SC x 8 weeks **Reduction of Allogeneic Blood Transfusion in Surgery Patients** ▪ 300 units/kg/day SC for 10 days prior to surgery, on the day of surgery, and for 4 days post-surgery ▪ Baseline Hgb should be >10 to <13 g/dL	**Anemia of Chronic Renal Failure** ▪ Adults: 0.45 micrograms /kg IV or SC weekly ▪ Pediatrics: not studied **Anemia in Cancer Patients on Chemotherapy** ▪ Adults: 2.25 micrograms/kg SC weekly or 500 micrograms SC once every 3 weeks ▪ Pediatrics: not studied
Black-Box Warnings	**INCREASED MORTALITY, SERIOUS CARDIOVASCULAR AND THROMBOEMBOLIC EVENTS, AND TUMOR PROGRESSION** ***Renal Failure:*** ▪ Patients experienced greater risks for death and serious cardiovascular events when administered ESAs to target higher versus lower Hgb concentrations (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in 2 clinical studies. ▪ Individualize dosing to achieve and maintain Hgb concentrations within the range of 10 to 12 g/dL ***Cancer:*** ▪ ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid, and non-small cell lung malignancies when dosed to target a Hgb of ≥ 12 g/dL. ▪ The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a Hgb of < 12 g/dL. ▪ To minimize these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusions. ▪ Use only for treatment of anemia due to concomitant myelosuppressive chemotherapy. ▪ Discontinue following the completion of a chemotherapy course. ***Perisurgery:*** ▪ Increased the rate of deep venous thromboses in patients not receiving prophylactic anticoagulation. Consider deep venous thrombosis prophylaxis.	
Contraindications	▪ Uncontrolled hypertension ▪ Known hypersensitivity to mammalian cell-derived products ▪ Known hypersensitivity to albumin	▪ Uncontrolled hypertension ▪ Known hypersensitivity to active substance or any of the excipients
Adverse Effects (most common)	Hypertension Headache Tachycardia Nausea/vomiting Edema Clotted vascular access Shortness of breath Hyperkalemia Diarrhea Pyrexia	Fatigue Edema Nausea/vomiting Diarrhea Fever Dyspnea Hypertension
Monitoring/ Recommendations	▪ Closely monitor and aggressively control blood pressure ▪ Decrease dose if Hgb increase exceeds 1 gm/dL in any 2-week period ▪ Monitor transferrin saturation and serum ferritin at baseline and during therapy (Goal: transferrin > 20% and ferritin at least 100 ng/mL) ▪ Iron supplementation is recommended to maintain iron stores ▪ Frequent monitoring of Hgb/hematocrit, especially during initiation (*twice weekly*)	

TIW: three times weekly; Hgb: hemoglobin; SC: subcutaneous; IV: intravenous

FORMULARY UPDATE FOR OCTOBER 2007

The Pharmacy and Therapeutics Committee recently approved the actions listed below. The formulary effective date was November 15, 2007.

Additions:

Rosuvastatin (Crestor®) is an HMG-CoA reductase inhibitor similar to other medications within this class. Rosuvastatin is less than 10% metabolized by CYP2C9 liver enzymes, but increased plasma concentrations may be found in patients with severe renal impairment and/or hepatic disease. The adverse effects associated with rosuvastatin are similar to others within the class. Serum cholesterol and liver function should be monitored on a regular basis in patients receiving rosuvastatin. Cost analysis shows that rosuvastatin is less expensive when compared with atorvastatin directly.

5-, 10-, 20-, 40-mg tablets

Hepatitis B Immunoglobulin (HepaGamB™) is indicated for post-exposure to hepatitis B. Compared to the current product on formulary (Nabi-HB®), HepaGamB™ has an additional indication for prevention of hepatitis B recurrence following liver transplantation. For this indication, HepaGamB™ should be administered intravenously (IM administration for both products is indicated for post-exposure to hepatitis B). HepaGamB™ is formulated with maltose; therefore, diabetic patients should be monitored closely for changes in blood glucose. Additionally, there is a cost-savings associated with switching from Nabi-HB® to HepaGamB™.

1-, 5-mL vials

Line Extensions:

Sodium bicarbonate 5% [500-mL bottle]

Hydroxyzine hydrochloride [25-mg/mL extemporaneous solution]

Deletions:

Hepatitis B Immunoglobulin (Nabi-HB®) [1, 5 mL vials]

Meperidine [50-mg tablet]

Amino-Cerv cream [77.9-g tube]

Deletions (continued):

Ergocalciferol [500,000-IU/mL intramuscular injection]

Quinine sulfate [260- and 325-mg tablets and capsules]

Other Action Items:

All mixed insulin products will be restricted from use and cannot be ordered through the nonformulary process. Additionally, patients are prohibited from using their own home supply. The products affected include the following:

- NovoLIN® 70/30 (NPH/regular)
- NovoLOG® 70/30 (aspart protamine/aspart)
- HumuLIN® 70/30 (NPH/regular)
- HumalLOG® 75/25 Mix (lispro protamine/lispro)

For patients admitted on a mixed insulin product, separate orders must be written for basal insulin [insulin glargine (Lantus®) or insulin NPH (Novolin® N)] and prandial insulin [insulin aspart (Novolog®)]. The Diabetes Management Service has posted a insulin conversion resource on the clinical order form page to assist with conversions.

the Children's Hospital and DTIs ordered for other indications (including cardiac catheterization).

Additionally, the protocol describes the role of a credentialed pharmacist to make decisions in dosage adjustments of the DTIs. Within the preprinted form, the physician will have the option of choosing the "Pharmacy to Dose" protocol. This protocol allows the pharmacist to manage DTI therapy without contacting the physician after the initial order is placed.

Based on new policy changes (see page 7), pharmacy will also be able to give verbal/telephone orders to nurses without the physician's cosignature. The nurse will write the order with the credentialed pharmacists name and specific "Pharmacy to Dose". The pharmacist will cosign the order within 48 hours per policy.

The DTI program began this month and will be piloted with 3 credentialed pharmacists. As more pharmacists undergo the credentialing process, a list will be maintained online of the approved pharmacists. The DTI program provides 24-hr coverage for these patients. There, if a physician selects the "Pharmacy to Dose" pro-

FORMULARY UPDATE FOR NOVEMBER 2007

The Pharmacy and Therapeutics Committee recently approved the actions listed below. The formulary effective date was December 17, 2007.

Not Added:

Omeprazole/sodium bicarbonate (Zegerid®) is formulated to prevent omeprazole from being degraded in the stomach prior to absorption. Other advantages include the antacid effect seen with the sodium bicarbonate, faster onset of action, and higher omeprazole plasma concentrations. With the acquisition cost for Zegerid® being significantly higher than other PPIs on formulary, the Committee felt that Zegerid could be reserved for outpatient treatment.

Posaconazole (Noxafil®) was not added to the formulary based on similarities between posaconzaole and formulary azole antifunals, limitations in dosage form and administration, and cost.

Line Extensions:

- Antihemophilic factor VIII (Helixate®) injection
- Hydromorphone syrup [1-mg/mL]
- Multiple vitamins liquid (AquADEK®)
- Amphetamine/ dexamphetamine (Adderall XR) [5-mg capsule]
- Aripiprazole (Abilify®) liquid [1-mg/mL]
- Valproic acid syrup [500 mg /10-mL unit dose cups]

Deletions:

- Aprotinin (Trasylol®) injection
- Antihemophilic factor VIII (Kogenate®) injection
- Multiple vitamins (ADEK®) pediatric drops
- Japanese encephalitis vaccine (JE-Vax®)
- Valproic acid syrup [250-mg/5-mL unit dose cups]

Other Action Items:

Direct Thrombin Inhibitor Policy and Pharmacy Dosing Protocol was approved to be piloted in early 2008. The preprinted order form creates a standardized format for ordering argatroban and bivalrudin in patients with heparin induced thrombocytopenia (HIT). (See story on page 7)

Intravenous (IV) Push Medication Administration Charts have been updated for adult and pediatric patients. The charts are posted on the *Formulary and Drug Information Resource* Web page under Medication Policies/Guidelines. (See story on page 6)

Policy C78: Medication Orders. has been updated to reflect changes to the use of range orders (See story below).

tocol, a credentialed pharmacist will be paged to assess the patient. A physician may choose not to participate in the "Pharmacy to Dose" DTI program, but must still use the preprinted order form to order DTIs.

Changes to Medication Order Writing Policies

Updated Intravenous (IV) Push Medication Administration Policy and Charts

The purpose of the IV push medication policy (C-151) is to ensure that medications administered to patients via the IV push route are evaluated for safety from the standpoint of the medication and the health care professional administering the medication. The published IV push charts serve as the official guideline regarding IV push administration of medications in all patients. The charts define in which patient care units and under what circumstances individual medications may be administered via IV push. Some patient care units have special monitoring capabilities or have nursing personnel with specific credentials; thus, the IV push administration of certain medications may be allowed in some patient care areas and prohibited in others. The direct links are provided in Figure 2 and can be found at the following locations:

- *Formulary and Drug Information Resources* Web page
- Nursing Tool Box under Pharmacy Links

Figure 2. Links for Adult and Pediatric IV Push Administration Charts

MUSC-MC Adult IV Push Medication Administration Chart :
www.musc.edu/pharmacyservices/forms-charts/ivpushadultcurrent.pdf.
MUSC Children's Hospital IV Push Medication Administration Chart:
www.musc.edu/pharmacyservices/forms-charts/ivpushpedcurrent.pdf.

If a medication is not listed on the chart, the medication cannot be given IV push, as the safety has not been evaluated. Requests for changes to the charts can be forwarded to the Drug Information Center at 2-3896.

Revisions to Range Order Section of Policy C78: Medication Orders

A range order can be defined as a medication order in which the dose of medication can vary depending on the patient's status and provider assessment, within a specified time frame (ie, morphine 2 - 4 mg every 2 –3 hrs prn).

The Joint Commission states that range orders should only be allowed if there are clear criteria provided in the order. Guidelines for dosing assures that the order will be interpreted consistently from staff member to staff member and that each practitioner has a clear understanding of how the patient will be treated.

The policy provides guidelines for writing range orders, where if a dosing range is used then the prescriber must include clear guidelines for dosing so that it can be interpreted consistently among all staff members. For the previous morphine example, the order should also include guidelines for when to give 2 mg versus 4 mg (ie, 2 mg for moderate pain; 4 mg for severe pain),

Time interval ranges (ie, 2-4 hrs) are ***not*** permitted. If ranged time intervals are written, the shortest time interval will be used in transcribing and acting upon the order. Therefore, the shortest time interval will be placed on the MAR (eg, *every 2-4 hours prn* will be placed on the MAR as *every 2 hours prn*).

Standard Administration Times

Recently, the standardized administration times (SATs) were changed so that the frequency of BID is reflected in a 9 AM and 5 PM schedule (it was formerly an 8 AM and 8 PM schedule). This new time is consistent with typical dosing in the outpatient setting, where the patient should take the medication twice a day within waking hours.

There are some medications that should be given using a 12 hour interval. Therefore, the medication order should be written using either BID or Q12hr, depending on the medication. If a medication should be given with a 12-hr interval the order should use Q12h.

If the health care practitioner acting upon an order written for BID feels that there is a clinical reason to have a 12-hr interval, the change should be made. Therefore, pharmacists entering the order may change the BID to a Q12 hr interval and nurses may also request a change if the medication requires Q12 hr interval.

The approved SATs can be found on the *Formulary and Drug Information Resources* web site under "Medication Charts and Other Documents" or at: www.musc.edu/pharmacyservices/medusepol/SATimes.pdf. The SATs are important to provide consistency across the organization for dispensing and administering medications. These times should be followed in all patients unless there is a clinical justification for deviating from the policy.

"Pharmacy-to-Dose Protocols:" Changes to Policy C56 and C78

With the approval of the direct thrombin inhibitor (DTI) "Pharmacy to Dose" protocol, MUSC policy C78: *Medication Orders* has been changed to include orders written by pharmacist who are credentialed to participate in the "Pharmacy to Dose" program. The wording "Pharmacy to Dose" when specified in physician orders will serve as a written agreement between the prescriber and the Department of Pharmacy Services to authorize a credentialed pharmacist to initiate, modify or discontinue the specified medication.

Protocols eligible (eg, aminoglycosides, vancomycin, direct thrombin inhibitors) for "Pharmacy-to-Dose" will be reviewed and approved by the Pharmacy and Therapeutics Committee. The Department of Pharmacy Services will ensure that competencies are maintained for credentialed pharmacists who are allowed to participate in Pharmacy to Dose protocols."

In addition, MUSC policy C56: *Verbal Orders* has been changed to INCLUDE the "Pharmacy to Dose" program where a credentialed pharmacist can give a nurse a verbal/telephone order for DTI management as ordered by the prescriber on the preprinted form. The order will be signed by the pharmacist within 48 hours.