

DRUG UPDATE

Volume 24, Number 2

February 2007

FORMULARY UPDATE

The P&T Committee met on January 22, 2007. The following is a summary of the business conducted:

ADDED:

- ◆ Ranibizumab (Lucentis™)
- ◆ Bivalirudin (Angiomax®)
- ◆ Zoster Vaccine Live (Zostavax®)

DELETED:

- ◆ Bepidil (Vascor®)
- ◆ Edrophonium (Reversol®)
- ◆ Nalidixic acid (Neggram®)
- ◆ Plicamycin (Mithracin®)

CRITERIA FOR USE:

- ◆ Doxercalciferol (Hectorol®)
- ◆ Human Papillomavirus Vaccine (Gardasil®)
- ◆ Zoster Vaccine Live (Zostavax®)
- ◆ Varicella-Live Vaccine (Varivax®)
- ◆ Iron Sucrose (Venofer®)

Ranibizumab (Lucentis™) was added to the *Formulary* for the treatment of neovascular (wet) age-related macular degeneration (AMD). This agent is considered a vascular endothelial growth factor (VEGF) inhibitor. Similar VEGF inhibitors, bevacizumab (Avastin™) and pegaptanib (Macugen®) are listed in the Shands Jacksonville *Formulary*. Only pegaptanib has an FDA-approved ophthal-

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Medication Safety/Prescribing

Preprinted forms must be used when ordering certain high-risk medications

In an effort to promote patient safety, the Pharmacy and Therapeutics Committee approved the revision of Policy for Guidelines for Writing Medication Orders (Rx-11-044). Medications with preprinted forms will be required when ordering medications in the hospital.

Preprinted order forms are designed to assist prescribers in ordering medications for the appropriate use, the correct dose, dosage adjustments (if necessary), and recommended monitoring parameters. These order forms are designed to prevent errors and ensure patient safety.

Order forms will be required for the following medications:

- ◆ acetylcysteine IV (Acetadote®)
- ◆ oral acetylcysteine
- ◆ chemotherapy (for regimens available on pre-printed forms)
- ◆ argatroban
- ◆ alteplase (TPA)
- ◆ dihydroergotamine
- ◆ drotrecogin (Xigris®)
- ◆ insulin correction scale

- ◆ insulin infusion
- ◆ heparin (low dose no bolus)
- ◆ heparin drip (Medicine/Surgery/Critical Care Areas)
- ◆ pediatric vaccines (i.e., haemophilus B vaccine, hepatitis B immune globulin)
- ◆ Patient controlled analgesia (PCA) and epidurals will require the analgesia order form

When orders for these medications are written without a form, the prescriber will be contacted by the pharmacist for clarification.

Preprinted order forms are designed to assist prescribers in ordering medications for the appropriate use, the correct dose, dosage adjustments (if necessary), and recommended monitoring parameters.

An electronic, web-based forms program will soon be available to allow greater accessibility to all hospital forms. Please contact your liaison pharmacists if you have any

questions regarding the completion of the required forms.

IN THIS ISSUE

- ◆ Contrast induced adverse effects
- ◆ Argatroban monitoring

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mology indication, bevacizumab only carries a labeled indication for systemic use in the treatment of colorectal cancer. Data and clinical experience show that pegaptanib successfully stabilizes visual acuity; however, few patients demonstrate visual improvements. In comparison, bevacizumab and ranibizumab have demonstrated significant improvements in visual acuity.

Ranibizumab is a new monoclonal antibody fab fragment of bevacizumab that is safe and effective compared to photodynamic therapy (PDT). PDT, until recently, was considered the standard of care for well-defined lesions (i.e., classic). Study results demonstrate potential advantages with ranibizumab when given in combination with PDT and as monotherapy in the treatment of less well-defined lesions (i.e., occult). There are no published trials that directly compare ranibizumab, bevacizumab, and pegaptanib.

Ranibizumab appears to be well-tolerated; however, there is concern for systemic VEGF effects such as hypertension. Its use should be avoided in this population.

Recently, an FDA Medwatch described an increased risk of stroke in patients receiving ranibizumab. The causality of this risk is under review; however, patients should be informed of the risk. Ranibizumab should be used with caution in patients with a recent history of stroke.

Ranibizumab is significantly more expensive than bevacizumab and pegatinib. The advantage of ranibizumab over bevicizumab is its FDA approved indication for the treatment of AMD, which allows reimbursement by third party agen-

cies such as Medicare. Bevacizumab is not approved for this indication, but because of its lower cost, it may be an option for the uninsured patient. Ranibizumab and bevacizumab are both manufactured by Genentech and it is unlikely that future studies will be sought for AMD labeling for bevacizumab. Both medications are effective at maintaining or improving visual acuity in patients experiencing symptoms of neovascular central vision loss. Pegaptanib will remain in the *Formulary* and its use will be reassessed in six months.

Bivalirudin (Angiomax[®]) is a direct thrombin inhibitor (DTI) added to the *Formulary* specifically for use in patients undergoing percutaneous coronary interventions (PCI) who are unable to tolerate heparin or glycoprotein (Gp) IIb/IIIa inhibitors secondary to thrombocytopenia or heparin-induced thrombocytopenia (HIT). All DTIs have been studied in the setting of PCI to different degrees (bivalirudin has the most data). In order to reduce the incidence of ischemic events, patients undergoing PCI procedures typically receive clopidogrel, aspirin, heparin (as either low molecular weight [LMWH] or unfractionated) and a GpIIb/IIIa inhibitor. It is theorized that a DTI will be efficacious due to its short half-life (bivalirudin = 24 minutes; argatroban = 39 minutes). Other agents such as enoxaparin and heparin have significantly longer half-lives (IV enoxaparin 2-4 hours, subcutaneous enoxaparin 3-6 hours, heparin dose-dependent).

According to the 2005 ACC/AHA guidelines for PCI, DTIs are an advantageous option in the setting of HIT. In addition, DTIs may be used in place of unfractionated heparin and GpIIb/IIIa inhibitors in

otherwise low-risk patients undergoing elective PCI. According to the results of the REPLACE-2 trial, bivalirudin plus *provisional* GpIIb/IIIa inhibitors compared to heparin plus *planned* GpIIb/IIIa inhibitors was found to be non-inferior in terms of incidence of ischemic events but was associated with reduced bleeding rates. Despite the advantages reported and a comparatively shorter half-life, there is no antidote for emergency reversal of bivalirudin.

Of note, bivalirudin currently lacks significant data for use in HIT patients outside the setting of PCI. Thus, argatroban should be used in patients with HIT who are not undergoing PCI.

Adding bivalirudin to the *Formulary* may have a significant cost impact. If bivalirudin is administered daily to two PCI patients, yearly hospital expenditures may increase by approximately \$200,000. Judicious use of bivalirudin is essential, thus the Criteria for Use will reflect recommendations for limited use.

Criteria for Use for doxercalciferol (Hectorol[®]) reflect its indication for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. This includes both pre-dialysis (stage 3 and 4) as well as current dialysis patients.

Criteria for Use for Human Papillomavirus Vaccine (Gardasil[®]) were approved for prophylaxis against HPV infection that may lead to condyloma acuminata (genital warts), cervical cancer, and precancerous lesions. It is indicated for use in women 9 to 26 years of age and should be administered in the ambulatory care clinics

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due to the nature of its three dose schedule.

Criteria for Use for Zoster Vaccine Live (Zostavax[®]) reflect its indication to reduce the risk for the development of herpes zoster (shingles) and post-herpetic neuralgia (PHN) in immunocompetent patients 60 years of age or older. Zoster-live vaccine is not indicated as a treatment for shingles or PHN or for prevention of primary varicella infection (chickenpox). The administration of this vaccine will also be limited to the Ambulatory Care Clinics.

Criteria for Use for Varicella-Live Vaccine (Varivax[®]) were created to reduce confusion with the zoster-live vaccine. Varivax is indicated for prophylaxis against varicella infection (chickenpox) in patients ≥ 12 months of age. Varicella-live vaccine is not indicated for prevention or treatment of herpes zoster (shingles) or post-herpetic neuralgia.

The Criteria for Use for iron sucrose (Venofer[®]) was revised to recommend treatment of iron deficiency anemia in patients with higher serum ferritin levels than previously recommended (i.e., 200 ng/mL vs. 100 ng/dL). This update is proposed to mirror the new National Kidney Foundation KDOQI guidelines.

Medication Safety

Serious adverse events after use of gadolinium-based contrast agents

On December 22, 2006, the FDA released a MED-WATCH alert to health care providers regarding an association between Nephrogenic Systemic Fibrosis or Nephrogenic Fibrosing Dermopathy (NSF/NFD), and patients with moderate to end-stage kidney disease who have received a Magnetic Resonance Imaging (MRI) or Magnetic Resonance Angiography (MRA) scan where a gadolinium-based contrast agent was used. The gadolinium-based contrast agent used most commonly at Shands Jacksonville, is Magnevist[®].

NSF/NFD is a relatively new disorder, first diagnosed in 1997. It is associated with fibrosis of the skin, connective tissues and organs. Thickening of the skin is thought to inhibit flexion and extension of joints resulting in contractures. NSF/NFD is a progressive disorder and may be fatal. Although the exact cause is unknown, it has been associated with moderate to severe renal impairment. Diagnosis is made by skin biopsy. Gadolinium has been found in the skin biopsies of some patients with NSF/NFD.

At the time of the alert, the FDA received 90 reports of chronic kidney disease patients (CrCL $<$ 60 mL/min) developing NSF/NFD after an MRI or MRA procedure where gadolinium was used. Another 215 cases have been reported worldwide. A total of 75 of those cases

had been reviewed in detail and all patients received a gadolinium-based contrast agent. In case reports, onset of the NSF/NFD began 2 days to 18 months after exposure to the contrast agent. Although many of the patients reported to the FDA had received high doses of gadolinium; some cases of NSF/NFD occurred after only one dose.

NSF/NFD should be suspected in patients with areas of tight, rigid skin, and organ scarring. Other symptoms may include burning, itching, swelling, hardening and tightening of the skin; red or dark

patches on the skin; yellow spots on the whites of the eyes; stiffness in joints with trouble moving or straightening the arms, hands, legs, or feet; pain deep in the hip bones or ribs; and muscle weakness. Currently, the FDA is recommending that gadolinium-based contrast agents should be avoided when possible in patients with moderate to end-stage kidney disease.

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patches on the skin; yellow spots on the whites of the eyes; stiffness in joints with trouble moving or straightening the arms, hands, legs, or feet; pain deep in the hip bones or ribs; and muscle weakness. Currently, the FDA is recommending that gadolinium-based contrast agents should be avoided when possible in patients with moderate to end-stage kidney disease. If this is not possible, prompt dialysis following the MRI or MRA should be considered. For additional information, please see the FDA's Information for Healthcare Professionals available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/gcca_200612HCP.pdf. Any suspected cases of NSF/NFD should be reported as an adverse drug reaction (ADR) by calling 244-4185 or contacting your liaison pharmacist.

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Argatroban Monitoring—Correction

In the November/December 2006 Drug Update, the Criteria for Use for argatroban was summarized in the Formulary Update section. It was erroneously stated that:

“Argatroban produces a laboratory test interaction that results in a falsely elevated INR. Argatroban does not have any clinical effect on the vitamin K dependent coagulation factors. Thus, it is recommended to monitor INR daily.”

This statement refers to the monitoring of argatroban as oral anticoagulation therapy is initiated.

Argatroban should be monitored using the aPTT. The aPTT should be obtained two hours after initiation of infusion, and titrated as needed to obtain a steady-state aPTT of 1.5 to 3 times the initial baseline value (not to exceed 100 seconds).

When patients are ready for oral anticoagulation, argatroban and warfarin therapy should be overlapped to ensure continuous anticoagulation

and to avoid prothrombotic events when initiating warfarin. There is a laboratory test interaction that produces prolongation of the PT/ INR during argatroban infusion, without clinical effects on vitamin-K dependent coagulation factors. Therefore, **INR should be measured daily when warfarin is initiated**, and the following procedure should be used to determine the timing of argatroban discontinuation:

If warfarin is co-administered with argatroban at an infusion rate less than or equal to 2 mcg/kg/min:

- ◆ Argatroban may be discontinued when INR during combined therapy exceeds 4; however, the INR should be repeated 4 to 6 hours after discontinuation, to ensure that anticoagulation from warfarin alone is sufficient to maintain a therapeutic INR.
- ◆ If the INR is subtherapeutic 4 to 6 hours after argatroban discontinuation, the argatroban infusion should be resumed and the proce-

cedure repeated daily until desired therapeutic range on warfarin alone is reached.

If argatroban is coadministered with warfarin at a rate exceeding 2 mcg/kg/min:

- ◆ temporarily reduce the rate of argatroban infusion to 2 mcg/kg/min and repeat the INR 4 to 6 hours after dose reduction.
- ◆ If INR remains above 4, follow the recommendations described above for discontinuing argatroban at rates less than or equal to 2 mcg/kg/min.

If patients have hepatic impairment, it may take longer than 4 hours for full reversal of anticoagulant effects after argatroban discontinuation, due to impaired clearance of the drug.

Argatroban is a drug that should be ordered using the preprinted order form. The form indicates the appropriate monitoring, dosage adjustments, and recommendations for bridge therapy with oral anticoagulants.