

Drugs & Therapy

B ♦ U ♦ L ♦ L ♦ E ♦ T ♦ I ♦ N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met June 19, 2001. 2 drugs were added in the *Formulary*; 2 drugs were deleted. 1 drug was evaluated but not added.

◆ ADDED

Factor VIIa, Recombinant (NovoSeven® by Novo Nordisk)*

Fibrin Sealant (Tisseel® by Baxter)

*Restricted to Hematology Consult

◆ DELETED

Aspirin/Oxycodone (eg, Percodan®)

Thyrotropin alfa (Thyrogen® by Genzyme)

◆ EVALUATED BUT NOT ADDED

Fluticasone/Salmeterol (Advair® by GlaxoSmithKline)

Recombinant factor VIIa was added in the *Formulary*, but it was restricted to use in patients who have had a Hematology Consult. Recombinant factor VIIa (rFVIIa) is a coagulation product used for the treatment of bleeding episodes in patients with hemophilia A or B who have inhibitors to factor VIII or factor IX, respectively. It is used in patients with elevated anti-human and anti-porcine coagulation factor inhibitors.

Porcine factor VIII (Hyate® C) is an alternative to recombinant factor VIIa. This product is most beneficial in patients with acquired inhibitors to factor VIII. Supply problems have occurred with porcine factor VIII because of the foot-and-mouth disease epidemic, which has limited the source used to manufacture this product.

(continued on page 2)

ADVERSE DRUG REACTION PROGRAM

Is this patient allergic to penicillin?

Penicillin is currently withheld from many patients who could benefit from its use. This leads to the overuse of alternative antibiotics, particularly vancomycin. Carbapenems (eg, imipenem) or monobactams (eg, aztreonam) are beta-lactam antibiotics that have been shown to cross-react in patients with true penicillin allergies and are also avoided in patients who have been labeled as penicillin-allergic.

In the May 16, 2001 issue of *JAMA*, Salkind and colleagues published a systematic review of the literature of the likelihood of penicillin allergy in patients with a "history" of penicillin allergy.¹ They conclude that only 10 to 20% of patients reporting a history of penicillin allergy are truly allergic when assessed by skin testing.

A detailed history may allow the exclusion of a true allergy, which would allow patients to receive penicillins or similar agents. Patients with a history that suggests a type I (ie, immediate type) penicillin allergy should be skin tested before receiving penicillin.

The following questions are recommended for patients with a history of penicillin allergy:

- What was the patient's age at the time of the reaction?
- Does the patient recall the reaction? If not, who informed them of it?
- How long after beginning penicillin did the reaction begin?
- What was the route of administration?
- Why was the patient taking penicillin?
- What other medications was the patient taking? Why and when were they prescribed?
- What happened when the penicillin was discontinued?
- Has the patient taken antibiotics similar to penicillin (eg, amoxicillin,

ampicillin, cephalosporins) before of after the reaction? If "yes," what was the result?

The importance of documenting the nature of the patient's penicillin allergy cannot be stressed enough. Despite the fact that most patients with a "penicillin allergy" appear to be able to tolerate penicillin or a penicillin derivative, it would be imprudent to prescribe penicillin or a related drug without explaining the rationale for this decision.

If a patient has a history of exfoliative dermatitis of Stevens-Johnson syndrome from penicillin, they should never receive penicillin. They should not be skin tested. Further, they should wear a Medic Alert bracelet indicating a severe reaction to penicillin.

If a patient has had a thorough history and the likelihood of penicillin allergy is high, these patients should also wear a Medic Alert bracelet. Although hospital and community pharmacy computer systems are getting better, they are not integrated. As patients move throughout the healthcare system, it is important that warning methods like Medic Alert bracelets be used to help prevent unnecessary patient harm.

REFERENCE

1. Salkind AR, Cuddy PG, Foxworth JW. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA* 2001;285:2498-2505.

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- ◆ Clonidine abuse?

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Another alternative to recombinant factor VIIa is anti-inhibitor factor complex (ie, Feiba®). Anti-inhibitor complex has undergone in vitro activation resulting in an increased amount of activated and precursor vitamin K-dependent clotting factors (factors II, VII, IX, and X). It is used as coagulation factor bypass therapy in patients with hemophilia with inhibitors or in patients with acquired inhibitors to other clotting factors. This product has been associated with serious thrombotic complications (ie, myocardial infarction, limb thrombosis).

Recombinant factor VIIa is considered a safer alternative “bypass” product in patients with inherited hemophilia who have developed antibodies to exogenous factor supplementation or in patients who have developed acquired hemophilia with autoimmune depletion of factor VIII. Recombinant factor VIIa activates factor X to Xa and IX to IXa. Factor Xa, in complex with other factors, converts prothrombin to thrombin, which leads to a hemostatic plug by converting fibrinogen to fibrin. Factor VIIa also activates factors IX and X on the surface of activated platelets to restore the formation of thrombin by platelets. This contributes thrombin to the fibrin network, even in the absence of an optimal initial platelet plug.

Because rFVIIa is a recombinant product, it is considered safer than products that come from pooled plasma. It is generally well-tolerated.

At typical dosages, recombinant factor VIIa costs over \$60,000 for the first day of therapy. Patient selection and dosing are critically important. Accepting hospital to hospital transfers for treatment with rFVIIa will require careful consideration, especially when patients are referred from outside of the Shands at UF catchment area.

Fibrin sealant (Tisseel®) was added in the *Formulary* 1 year ago for an evaluation. Fibrin sealants have been used for decades; however, the FDA approved Tisseel® in 1998. Tisseel® is a 2-component fibrin sealant. The main ingredient of the 1st component syringe is fibrinogen that has been stabilized with aprotinin. The 2nd component syringe contains thrombin and calcium. These 2 component syringes are mixed in a common joining piece and applied at the wound site like epoxy glue. The sealed parts must be held in position for 3 to 5 minutes to assure that the sealant adheres firmly.

Tisseel® has labeled indications for use as an adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of splenic injuries due to blunt or penetrating trauma to the abdomen, when control of bleeding by conventional surgical techniques (eg, sutures, ligatures, and cautery) are ineffective or impractical. However, fibrin sealants may be an alternative to fibrin glue in the treatment of bronchopulmonary fistulas and maybe useful in laparoscopic surgeries where sutures, ligature, and cautery is impractical.

When Tisseel® was added in the *Formulary* for an evaluation; a case report form was required with each use. 41 Tisseel® kits were used in 11 months. The 5-mL kits were most often used in a variety of settings. Neurosurgery and Cardiothoracic Surgery were the primary users, however. All case report forms listed a satisfactory response. The 41 kits used cost approximately \$25,000; however, this level of use was considered reasonable. Rather than use a case report form, the use of Tisseel® will now be monitored by standard reports.

Since fibrin sealant is a blood product, prescribers should discuss the theoretical risk of viral contamination with their patients. Patients getting Tisseel® during surgery do give consent for blood products. It should be noted, however, that after 20 years of use in Europe, no cases of hepatitis or HIV have been associated with the use of this product. Further, since Tisseel® is a product derived from pooled plasma, prescribers should discuss this with any patient with the potential to have religious objections to the use of blood products.

The P&T Committee deleted **aspirin plus oxycodone** (ie, Percodan®) combinations as part of this class review. Although listed in the *Formulary*, this combination product is not used.

Thyrotropin alfa (Thyrogen®) is recombinant human thyrotropin stimulating hormone (TSH). It has a labeled indication for use as an adjunctive diagnostic tool in patients with well-differentiated thyroid cancer. Thyrotropin alfa activates thyroid iodine uptake and the synthesis of thyroglobulin like native TSH. This helps identify residual thyroid tumor, metastases, or recurrence of thyroid tumors in patients who have had thyroid ablation.

Since thyrotropin alfa was added in the *Formulary* 1 year ago, none has been used. Several vials have went out-of-date and had to be returned. A carton of 2 vials costs approximately \$900. Because of the high inventory

cost and low use, thyrotropin alfa was deleted from the *Formulary*.

Advair® is a fixed-dose combination of **fluticasone** and **salmeterol** that is in dry-powder inhalation device (ie, Diskus™). This combination is used in patients with moderate to severe asthma who continue to be symptomatic on inhaled corticosteroids alone. It is not indicated for patients with mild disease. The P&T Committee decided not to add this product in the *Formulary* at this time.

Inhaled corticosteroids like fluticasone have become the cornerstone of the management of asthma, which is an inflammatory disease. Anti-inflammatory therapy prevents chronic symptoms, maintains pulmonary function, maintains activity levels, and prevents exacerbations that require emergency department visits or hospitalizations.

Salmeterol is a long-acting selective beta-2-agonist. Unlike albuterol, it is not effective during acute exacerbation because its onset of effect is long. Salmeterol is used as chronic therapy because of its long duration of effect. It is used in patients who experience exercise-induced asthma or nocturnal asthma who do not have an adequate response to corticosteroids alone.

The evidence shows that the use of the fixed-dose combination of fluticasone and salmeterol is as effective as the individual agents when used concomitantly. The purpose of a fixed-combination is to improve compliance. A fixed-dosage product, however, is not ideal for dosage titration in patients who are admitted for an exacerbation of their disease. Further, patients started on Advair™ in the hospital will receive a 30-day supply. Since there is no current mechanism to legally label these products to send home with the patient, most of this inhaler would be wasted.

If Advair™ is started on a hospitalized patient, it is recommended that the patient's family fill a prescription before discharge. This could allow for patient education while the patient is still hospitalized. Alternatively, placebos are available from the manufacturer that can be used to train patients while they are hospitalized.

Counterfeit-proof Rx Pads Required by September

The Florida Legislature has mandated that all prescriptions written for patients covered by Medicaid be written on counterfeit-proof prescription pads. This legislation goes into effect July 1, 2001. Fortunately, pharmacies can continue to accept prescriptions written on traditional blanks through September 30, 2001.

Prescriptions that are transmitted via facsimile, telephone, electronic prescribing, and transfers are exempt from the counterfeit-proof-blank requirements. However, this will not work for Schedule II controlled substances, which must be written prescriptions by law. Drugs like opioids for pain control must be written on the new prescription blanks.

Pharmacies that do not follow this new law face considerable financial penalties. If the Agency for Healthcare Administration audits a pharmacy and finds that 50% of its Medicaid prescriptions are not on these counterfeit-proof forms, the State could require that pharmacy to return the payment for 50% of all of the Medicaid prescriptions that it has filled that year. This threat of a hefty financial penalty will

assure that pharmacists will not fill prescriptions that are not written on the new counterfeit-proof blanks.

The State has mandated these counterfeit-proof blanks because it is perceived that counterfeit prescrip-

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tions are a major reason that Medicaid drug expenditures are so much higher in Florida compared with other states. Fraud and abuse are easy targets for prescription cost savings. However, the magnitude of this problem is not really known.

A counterfeit-proof prescription blank prevents photocopying or scanning of prescriptions that would allow them to be altered. These prescription blanks are like payroll checks that show "VOID" when they are photocopied. All practitioners who prescribe drugs to Medicaid recipients are responsible for obtaining the new counterfeit-proof blanks from an approved vendor before the September deadline.

The State has posted lists of approved vendors for these new prescription blanks on its website at www.floridamedicaid.consultec-inc.com in the Provider Support section. (Go to Provider Support, then click on "Counterfeit-proof prescription Pads" on the lower left-hand corner of the page. Select the pdf file shown.)

Additional information can also be obtained by calling the Agency for Health Care Administration's Bureau of Pharmacy Services at (850) 487-4441 or the Consultec Pharmacy Help Desk at (800) 603-1714. Or call Georgina Kassebaum, Director of Publication Services, Shands HealthCare, at 377-0849 for assistance.

DRUG INFORMATION FORUM

Clonidine abuse?

We recently received a question in the Drug Information Center about whether clonidine can be abused. This question was prompted when a caller noticed that a patient with a history of drug abuse was demonstrating drug-seeking behavior for clonidine.

Although not widely appreciated, there are several cases of clonidine abuse reported in the medical literature.^{1,4} Clonidine is traditionally used as an antihypertensive agent; however, it is also used for inpatient and outpatient opioid detoxification and the treatment of nicotine dependence. Some abusers of clonidine have stated that clonidine enhances central nervous system effects when taken in combination with opioids or benzodiazepines. High doses of the clonidine alone have sedative or euphoric effects. The abuse of clonidine is an example of a drug being used for adverse effects that are usually considered dysphoric.

Clonidine abuse has been likened to benzodiazepine intoxication. Some patients describe the effects as "getting a nod," feeling drowsy, or being more relaxed. Dosages ingested to achieve this effect range from 0.1 to 3 mg at a time. There is even a case

report of patient ingesting a 5-mg patch.² These doses put individuals at significant risk for adverse drug effects (eg, hypotension).

Prescribers should be aware that clonidine may be sought out for its abuse potential or street value. Some patients use clonidine to manage their withdrawal symptoms. Patients interviewed in 1 study indicated a street purchase price for clonidine ranging from \$0.50 to \$3.00 per 0.3-mg tablet.⁴

Clonidine abuse is usually seen in patients with a history of opiate abuse. A high index of suspicion and careful patient education and questioning can help determine whether clonidine abuse is occurring. Clonidine may be abused like other atypical drugs of abuse (eg, antihistamines or amitriptyline). Access is a major factor in drug abuse. Clonidine is easier to access than controlled substances, especially when its abuse potential is not appreciated.

REFERENCES

- Schaut J, Schnoll SH. Four cases of clonidine abuse. *Am J Psychiatry*. 1983;140:1625-6.
- Raber JH, Shinar C, Finkelstein. Clonidine patch ingestion in an adult. *Ann Pharmacother* 1993;27:719-22.
- Dy EC, Yates WR. Atypical drug abuse: a case report involving clonidine. *Am Fam Physician* 1996;54:1035-8.
- Beuger M, Tommasello A, Schwartz R, et al. Clonidine use and abuse among methadone program applicants and patients. *J Subst Abuse Treat* 1998;15:589-93.

To Report an Adverse Drug Reaction

**Call the ADR Hotline:
5-ADRS (5-2377)**

PROVIDE:

- Patient's name
- Patient's location
- Suspected drug(s)
- Type of reaction
- Whether the reaction was: — probable, possible, or definite
- Your name and pager # or extension

And we'll do the rest!

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 **ADR HOTLINE: 5-ADRS**

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SHANDS

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POLICIES AND PROCEDURES

In case you don't know...The Rules

- 1. Drug Reps:** You may not be aware of this, but drug reps are guests. There are rules that sales reps must follow to continue to be able to visit the hospital. Reps must 1st register and get a name badge each time they visit. They must have a specific appointment. Drug reps cannot roam around, visit informally in call rooms, or show up at conference rooms unannounced. They cannot promote nonformulary drugs to housestaff, be in patient care areas, or leave promotional items (eg, pens, pads) in hospital areas—this includes all geographic boundaries of Shands at the University of Florida (eg, hallways, conference rooms). If you notice these policies being violated, please notify the Director of Pharmacy (265-0404).
- 2. Pharmaceutical Samples:** No inpatient area of the hospital is approved to use samples. Drug manufacturers' sales representatives who leave samples for in-hospital use are violating JCAHO regulations and are subject to disciplinary action. The Outpatient Burn Unit Clinic, Occupational Health, Emergency Department, and the GI Laboratory are the only Shands areas approved to use and store samples.
- 3. Patients' Own Medications:** Patients can take their own medications during their hospital stay **only** if it is not listed in the *Formulary*. Patients' medications that are controlled substances cannot be used. An order for each "own med" must be written including drug name and dosage. Patients cannot take their own injectables, oral liquids, compounded topicals, ophthalmics, otic preparations, or tramadol.
- 4. Dietary Supplements:** Patients can take their own supply of dietary supplements if they bring an **unopened** container. These products are difficult to identify. The pharmacy will only obtain nonformulary supplements that meet national standards (unfortunately none do right now).
- 5. Chemotherapy:** Chemotherapy must be ordered using a Chemotherapy Order Form. Only oncology attendings, fellows, PAs, or pharmacists who are credentialed to do so may order chemo.
- 6. Maintenance IVs:** Orders for large volume parenterals must be rewritten each day. This reduces waste and alerts the pharmacy to prepare the next IV.
- 7. TPN:** Adult and pediatric TPNs must be written on TPN Order Forms. These must be complete. Please check the previous day's order. Orders must be written AND faxed by 1 pm.
- 8. Pre-operative Antibiotics:** Pre-operative antibiotics should be written as "give in pre-operative holding" NOT "on call to OR." This assures that antibiotics are given just prior to surgery.
- 9. Investigational Drugs:** The Investigational Drug Service (4-4237) must handle all investigational drugs used within Shands at UF. Patients on investigational drugs from an outside institution must also meet specific requirements before they can be used.