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SHANDS at the University of Florida

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# Drugs & Therapy

## B • U • L • L • E • T • I • N

## FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met May 18, 2004. 4 drugs were added in the *Formulary* and no drugs were deleted. A restriction was removed from 1 drug.

### ◆ ADDED

**Enfuvirtide** (Fuzeon® by Trimeris)

**Fosamprenevir** (Lexiva® by GlaxoSmithKline)

**Memantine** (Namenda® by Forest Pharmaceuticals)

**Polyethylene glycol 3350** (MiraLax® by Braintree Laboratories)

### ◆ DELETED

**None**

### ◆ CRITERIA FOR USE CHANGES

**Argatroban** (Argatroban Injection by GlaxoSmithKline)*

*No longer requires Hematology's approval

**Enfuvirtide** was first evaluated for addition in the *Formulary* in June 2003. At that time, it was not added because it could not be stocked. The manufacturer would not sell their drug to hospitals. Patients were forced to use their own supply of injectable drug during their hospitalization. Enfuvirtide can now be stocked in the hospital and has been added in the *Formulary* for the few patients taking this drug during their hospitalizations.

Enfuvirtide is the first drug in a new class of anti-HIV drugs called fusion inhibitors. This is the first new class of drugs approved for the treatment of HIV since 1996.

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DIETARY SUPPLEMENTS

## Glucosamine and shellfish allergy

Can patients take glucosamine to treat arthritis if they are allergic to shellfish? The Drug Information and Pharmacy Resource Center has received this question several times. It is based on a warning found on some bottles of glucosamine and in some dietary supplement references. What is the basis for this warning?

Glucosamine is a dietary supplement used "to treat" osteoarthritis. It is a naturally occurring amino-sugar found in the body as a component of ligaments and cartilage. The theory of using glucosamine in patients with osteoarthritis is based on the assumption that providing substrate aids in the formation of cartilage and prevention of the progression of disease.

**The warning to not use glucosamine in patients with shellfish allergy is based on the assumption that patients allergic to shellfish might also be allergic to glucosamine, since glucosamine is derived from shellfish.**

There is published clinical evidence that suggests that glucosamine may be effective at preventing the progression of osteoarthritis.[1-2] This evidence and promotion in the lay media led to widespread use of glucosamine. Although the evidence is promising, whether glucosamine is safe and effective is still undetermined.

The National Institutes of Health's (NIH) Glucosamine or Chondroitin Arthritis Intervention Trial (GAIT) is an ongoing multicenter clinical trial testing the effects of glucosamine and chondroitin for treatment of knee osteoarthritis. This trial will study whether glucosamine and chondroitin used separately or in combination are effective in reducing pain and improving functional ability in patients with knee osteoarthritis. GAIT includes an additional study component that will assess whether glucosamine and chondroitin can reduce or halt the progression of knee osteoarthritis. If glucosamine is found to be effective in this study, it could lead to even more widespread use of this dietary supplement.

The shells of shellfish are a common raw material used to manufacture glucosamine. The warning to not use glucosamine in patients with shellfish allergy is based on the assumption that patients allergic to shellfish might also be allergic to glucosamine, since glucosamine is derived from shellfish.

This warning appears to be conservative, since the antigens in crustaceans (eg, shrimp, lobster, crabs) and mollusks (eg, oysters and clams) are proteins and not derivatives of their shells. Also, there have been no published reports about patients with shellfish allergies cross-reacting to glucosamine supplements.

There are, however, case reports of patients experiencing hypersensitivity to glucosamine.[3-4] Neither of the patients in these reports were described as being allergic to shellfish. Like all patients who are allergic to foods or drugs, there is always the possibility of a patient being independently allergic to glucosamine and shellfish, but the reactions not be directly related.

*(continued on page 3)*

### INSIDE THIS ISSUE

***Formulary update,*** *from page 1*
Enfuvirtide binds to a region of the HIV envelope and prevents viral fusion with cell membranes.

Enfuvirtide has a labeled indication for the treatment of advanced HIV infections in adults and children greater than 6 years old. It must be administered subcutaneously twice a day, which is inconvenient and is associated with adverse effects. Therefore, enfuvirtide is reserved for patients with advanced disease who are often resistant to several other therapies.

Evidence supporting the effectiveness of enfuvirtide includes 2 randomized, open-label trials in patients with high viral loads and extensive previous exposure to antiretroviral therapy or documented resistance. Patients received enfuvirtide in addition to their background HIV regimen. Treatment resulted in clinically significant reductions in viral loads. These data are supported by additional observational data.

The most common adverse effect associated with the use of enfuvirtide is injection site reactions. Nodules at the injection site occurred in up to 98% of patients in clinical trials. Other symptomatic adverse effects may include insomnia, headache, dizziness, and nausea.

**Fosamprenevir** is a phosphate ester prodrug of the protease inhibitor amprenavir (Agenerase®). Like amprenavir, fosamprenavir has a labeled indication for the treatment of HIV infection in combination with other antiretroviral drugs.

Fosamprenavir is more soluble than amprenavir, which enables patients to take fewer capsules per day and lower their "pill burden." Lower pill burden is associated with better compliance and improved patient response in the treatment of HIV.

Clinical studies in antiretroviral-naïve and experienced patients have shown comparable efficacy compared with other antiretroviral agents. In treatment-naïve patients, approximately 65% of patients achieved undetectable viral loads. For experienced patients, boosted regimens with fosamprenavir achieved responses similar to lopinavir-ritonavir-based regimens.

The appropriate conversion from amprenavir to fosamprenavir is not clear; therefore, amprenavir will remain in the *Formulary*, at least for a while. It is anticipated that experience will determine the appropriate conversion method and allow the deletion of amprenavir from the *Formulary*.

The most frequent adverse effects associated with the use of fosamprenavir include gastrointestinal effects (nausea, vomiting, diarrhea), rash, and headache. As with other protease inhibitors, increased liver function tests, serum lipase, hypertriglyceridemia, and neutropenia are possible.

**Memantine** is the first agent in a new category of drugs used to treat patients with Alzheimer's disease. Evidence suggests that Alzheimer's disease may be caused by excessive activation of the N-methyl-D-aspartate (NMDA) receptor by glutamate. Glutamate is the main excitatory neurotransmitter in the regions of the brain associated with cognition and memory. Cortical neuronal loss may be related to either increased sensitivity or increased levels of glutamate. Excessive glutamate stimulation may eventually cause cell death. Memantine selectively blocks the effects of glutamate at the NMDA receptor (ie, NMDA-receptor antagonist).

Memantine has a labeled indication for the treatment of patients with moderate to severe Alzheimer's disease. It is the only marketed drug with a labeled indication for severe Alzheimer's disease. The cholinesterase inhibitors (eg, donepezil [Aricept®], galantamine [Reminyl®]) have labeled indications for mild to moderate Alzheimer's disease.

There is published evidence that shows that memantine improves cognitive function and memory using standard subjective dementia scales. There is also evidence that the use of memantine slows the progression of Alzheimer's disease and decreases the workload of caregivers of patients with Alzheimer's disease.

There have been few adverse effects associated with the use of memantine. Memantine has been available in Europe for over 20 years. Thus far, no rare or serious adverse effects have been associated with the use of memantine.

Although expensive, memantine costs slightly less than cholinesterase inhibitors used to treat Alzheimer's disease. There are limited data on the use of memantine in combination with a cholinesterase inhibitor (ie, donepezil), which show improvement and/or delay in the decline of memory and cognition.

Memantine should be gradually started with an initial dosage of 5 mg per day for 1 week, 5 mg twice a day for 1 week, 5 mg in the morning and 10 mg in the evening for 1 week, then 10 mg twice a day. The increases in dosages should be at least a week apart. A "titration pack" is available for outpatient use and is designed for a 1-week interval between dosage titrations.

Dose reductions in moderate renal impairment should be considered. Memantine has not been evaluated in patients with severe renal impairment and is not recommended. The exact definitions of "moderate" and "severe" renal impairment have not been established.

**Polyethylene glycol 3350** (PEG 3350) is a commonly used nonformulary osmotic laxative. It is used as an alternative to fiber, lactulose, or sorbitol.

The number 3350 is the molecular weight of this form of PEG. PEGs are widely used in pharmaceuticals, foods, and cosmetics. The larger the number the more solid a PEG becomes and less water-soluble it is. PEGs are considered inert.

There are limited published data supporting the use of PEG 3350 for the treatment of constipation. There are data showing that it is superior to placebo for the treatment of constipation, but at the recommended doses (eg, 17 grams for an adult) the time to response is slow. Large doses (eg, 64 grams in an adult) have been used for overnight relief of constipation.

There are no published data showing superior efficacy for PEG 3350 over other laxatives. An open-label study in children found that PEG 3350 and lactulose were equally effective by most measurements of efficacy. The overall "effectiveness" of PEG 3350 was rated higher by parents or guardians of children in this study, but the reason for this rating was not clear. The results of this study are limited by the open-label design and relatively low dose of PEG 3350 used.

PEG 3350 is considerably more expensive than other osmotic laxatives. The main reported reason for choosing PEG 3350 over other choices (eg, lactulose) is patient acceptance. It is tasteless and can be taken in 8 ounces of any beverage. This may be the reason that it was rated subjectively more "effective" than lactulose in the only published comparative trial.

Patient acceptance was deemed justification for adding PEG 3350 in the *Formulary*.

**Argatroban** is a direct thrombin inhibitor with a labeled indication for the prophylaxis and treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). This intravenous anticoagulant reversibly inhibits the catalytic site of thrombin, neutralizing the actions of thrombin.

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MEDICATION SAFETY

# A warning about contraindications?

According to the *The American Heritage® Dictionary of the English Language, Fourth Edition,* a contraindication is "A factor that renders the administration of a drug or the carrying out of a medical procedure inadvisable: A previous allergic reaction to penicillin is a contraindication to the future use of that drug." But the astute clinician looks at this definition and realizes that there are situations where giving a penicillin to a patient with a history of a penicillin allergy is required. This has led to the use of the terminology "relative contraindication."

The term "relative contraindication" suggests there are circumstances when a contraindication does not apply. The administration of the contraindicated drug is forbidden in most circumstances, but there are possible exceptions. Unfortunately, these exceptions are not always explicitly stated…yet the contraindication is explicitly stated. This has led to many lawsuits, including arguing on whether the contraindication is truly "relative." There is no FDA-approved definition for a "relative contraindication," but it appears in many references.

When treating an infection in a patient with an allergy to penicillin, the prescriber may have several options. If the "allergy" is not a true allergy (ie, nausea), then the use of penicillin is acceptable. If an alternative antibiotic is available, then it may be used. If penicillin is the only option, then the patient may require desensitization and then therapeutic doses. Not treating the infection may not be an option. Thus, penicillin is not always contraindicated in a patient with a history of a penicillin allergy whose only therapeutic option is penicillin.

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**Contraindications often do not consider off-labeled uses of drugs or every possible clinical situation for which a drug might be useful.**

Contraindications are an important section in a drug product's official labeling. According to Federal Law (21 CFR 201.57), "Contraindications are those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, eg, if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state, 'None known'."

Unfortunately, labeled contraindications do not sufficiently describe all clinical "situations." Contraindications often do not consider off-labeled uses of drugs or every possible clinical situation for which a drug might be useful.

However, when a drug is used when it may appear to be inadvisable (ie, despite a contraindication), the prescriber should have good evidence to support this use. Ideally, this would include evidence from well-done clinical trials. This, however, would be unusual. Guidelines and position statements are helpful and may be available. Even observational research and case series or reports are preferred to individual expert opinion.

It is advisable to document the rationale for a decision to use a "contraindicated" drug. This documentation should explain why it is not contraindicated in this particular circumstance.

Thus, contraindications that exclude descriptions of specific clinical situations are not "relative." Either a drug should or should not be used in a particular patient. There are circumstances when the use of a drug appears inadvisable, yet it is the best (or only) therapeutic option. The key is finding evidence to support your decision.

***Formulary update,*** *from page 2*

Argatroban was added in the *Formulary* in January of 2001, but it was restricted to use in patients who had been approved by the Hematology Service. The diagnosis of HIT is difficult and the dosing and monitoring of argatroban can be difficult. The data show that argatroban's use is sporadic, and the number of patients receiving it per year is not great.

The restrictions on the use of argatroban were removed, since Hematology no longer supports approving argatroban before it can be used for a particular patient. However, the volume of argatroban use will continue to be monitored. A Hematology consult is recommended for patients with a suspected diagnosis of HIT.

***Dietary supplements,*** *from page 1*

A patient with a shellfish allergy was not automatically excluded from the NIH's glucosamine trial. Patients were evaluated based on the severity of their allergic reaction to shellfish. For example, a patient would have been excluded from the study if their allergic reaction to shellfish was anaphylaxis. However, patients were included if the allergic reaction to shellfish was less severe, such as gastrointestinal distress, minor skin rash, or pruritus. Shellfish intolerance, especially gastrointestinal intolerance, may not be an allergic reaction. Patients may experience GI intolerance from shellfish because of toxins or infectious agents.

Thus, cross-reactivity with glucosamine and shellfish is unlikely. However, it still needs to be considered before using this dietary supplement, especially if the shellfish allergy is anaphylaxis. Even if the cross-reactivity is not based on scientific evidence, there are medical-legal concerns.

There are alternatives to glucosamine for the "treatment" of osteoarthritis with dietary supplements. Chondroitin alone has been used to treat osteoarthritis. However, if you use the same logic as with glucosamine and shellfish, you would make sure your patient is not allergic to beef (since chondroitin usually comes from bovine cartilage).

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## QUOTABLE QUOTES

**"There is, therefore, both clinical and physiologic evidence to support the use of [metered-dose inhaler] therapy in place of nebulization. Why is this idea met with incredulous stares by clinicians...? Old therapies, it seems, tend to linger in the mind in much the same way as old melodies...We regale our house staff with tales of asthma treated with IV aminophylline and subcutaneous epinephrine. Perhaps they will, in turn, spin tales for the residents of tomorrow of children treated with clouds of bronchodilator mist. And thus, we may be listening to the nebulizer's last refrain."**

*Charles W. Callahan, DO, FCCP*
*Chief, Pediatric Pulmonary Division*
*Tripler Army Medical Center*
Wet Nebulization in Acute Asthma: The Last Refrain? Chest 2000;117:1226-8.

## 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!*

**ADR HOTLINE: 5-ADRS**

## BEST WISHES...

**To all students, residents, and fellows finishing their training at Shands at UF. If you are moving to a new practice site and would like to continue to read the *Drugs & Therapy Bulletin*, it is available on the Internet through the shands.org website at www.shands.org/professional/drugs/bulletin.htm.**