

# Drugs & Therapy

B ♦ U ♦ L ♦ L ♦ E ♦ T ♦ I ♦ N

## FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met on June 17, 2003. 4 drugs or dosage forms were added in the *Formulary*. 2 drugs were deleted and 6 products were designated not available. 1 drug was evaluated but not added in the *Formulary*, and significant changes were made in the Criteria for Use of 1 drug.

### ◆ ADDED

**Escitalopram**  
(Lexapro® by Forest)

**Levofloxacin Ophthalmic**  
(Quixin® by Santen)

**Meropenem**  
(Merrem® by AstraZeneca)\*

\*Restricted to ID Approval

**Pramipexole**  
(Mirapex® by Pharmacia)

### ◆ DELETED

**Ciprofloxacin Ophthalmic**  
(Ciloxan® by Alcon)

**Citalopram** (Celexa® by Forest)

### ◆ NONFORMULARY AND NOT AVAILABLE

**Ampicillin-Sulbactam**  
(Unasyn® by Pfizer)

**Ciprofloxacin ER**  
(Cipro® XR by Bayer)

**Citalopram** (Celexa® by Forest)

**Gatifloxacin Ophthalmic**  
(Zyma® by Allergan)

**Moxifloxacin Ophthalmic**  
(Vigamox® by Alcon)

**Ofloxacin Ophthalmic**  
(Ocuflox® by Allergan)

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## NEWS

### P&T Committee Action 2002-03

The P&T Committee's year goes from July to June. Thus, another productive year was just completed. The P&T Committee is the medical staff committee that is the formal line of communication between the medical staff and Shands at UF. Therefore, formulary activities, drug use policies, adverse drug reaction monitoring, and medication safety are most of the activities.

34 new drugs were added in the *Formulary* this year. Three additional drugs were added for 12-month evaluations. There were only 6 new drugs requested, the rest of the additions were the result of reviewing non-formulary drugs, drug category reviews, and the proactive review of new products.

19 drugs were deleted from the *Formulary*. 29 drugs were designated nonformulary and not available. "Not available" drugs cannot be requested through the nonformulary process.

Several therapeutic interchanges were approved this year (see related article on pages 3-4). For example, this month's *Formulary Update* lists the interchange of insulin aspart for insulin lispro.

Drugs that are being used nonformulary are reviewed. High-volume non-formulary drugs are reviewed to determine whether they should be added in the *Formulary*, added with restriction, or designated "not available." High-priority, nonformulary drugs are those drugs that a delay could result in patient harm, like antibiotics, pain medications, hypotensive agents, and ophthalmic agents. These agents are reviewed for formulary consideration.

As part of the normal function of the P&T Committee, several drug-use policies were reviewed throughout the year. The following is a partial list of policy changes.

■ **Comfort Medications:** A policy was established that allows nursing staff

to administer local anesthetic agents in order to improve patient comfort during selected procedures (eg, IV or urinary catheter placement).

■ **Compounded Pharmaceuticals from an External Vendor:** In order to assure content and purity, standards for external vendors of compounded pharmaceuticals were established.

■ **Dose Ranges:** Changes were made to the policy on the appropriate ordering of medications, including the appropriate interpretation of dosage ranges (eg, 2 to 4 mg every 4 to 6 hours).

■ **Standardized Heparin Protocols:** Based on data that shows anticoagulants are associated with a high incidence of adverse events, an ad hoc committee recommended protocols that were endorsed by P&T.

■ **Standardized Insulin Protocol:** Similar to heparin, insulin is frequently associated with adverse events, and an ad hoc committee recommended a standardized protocol.

■ **Patients' Own Medications:** Changes were made to allow the use of MDIs, and injectable drugs available only through limited distribution networks.

The *Drugs & Therapy Bulletin* is the primary method for communicating P&T activities throughout the year. In most years the P&T Committee meets 10 times and a *Bulletin* is published after each meeting.

Dr. Gonzalez-Rothi chairs the P&T Committee. This is his 4<sup>th</sup> year leading this medical staff committee. If you have questions or comments about the activities of the committee, contact Dr. Gonzalez-Rothi by e-mail at RothiRJ@medicine.ufl.edu.

## ◆ INSIDE THIS ISSUE

◆ Therapeutic interchange update

◆ **EVALUATED BUT NOT ADDED**

**Enfuvirtide**

(Fuzeon® by Trimeris)\*\*

\*\*Patients must use their own supply

◆ **THERAPEUTIC INTERCHANGES**

**Insulin aspart** (Novolog®) for

**Insulin lispro** (Humalog®)\*\*\*

\*\*\*Automatic interchange on a unit-per-unit basis

◆ **CRITERIA REVISIONS**

**Bivalirudin** (Angiomax® by The Medicines Company)\*\*\*\*

\*\*\*\*Restricted to Hematology approval AND PCI with severe renal dysfunction

**Escitalopram** is a selective serotonin reuptake inhibitor (SSRI). It was evaluated because of high nonformulary use. Escitalopram is the S-isomer of citalopram.

The equivalent dose of escitalopram compared with citalopram is in the 1:2 to 1:4 range. The usual dosage of escitalopram is 10 mg per day. Dosage equivalencies must be considered when reviewing the published data comparing escitalopram and citalopram.

The published literature does not directly compare escitalopram and citalopram, but suggests that escitalopram is as effective as citalopram. Escitalopram has some theoretical safety advantages compared with citalopram. However, the current data do not show that escitalopram is more effective, more rapid acting, or less likely to cause adverse effects compared with citalopram or other SSRIs.

Citalopram currently costs 13% more than escitalopram. Because escitalopram is less expensive, it was added in the *Formulary* while citalopram was deleted and designated nonformulary and not available. If costs change, however, this issue will be re-evaluated.

**Levofloxacin ophthalmic** has been selected as the only ophthalmic fluoroquinolone listed in the *Formulary*. **Ciprofloxacin ophthalmic** was deleted. **Ciprofloxacin, gatifloxacin, moxifloxacin, and ofloxacin ophthalmic** were all designated not available. These actions were taken after a class review by the Anti-Infective Subcommittee with input from the Department of Ophthalmology.

Levofloxacin ophthalmic solution provides sufficient ophthalmic concentrations to treat common ocular pathogens. There are 3 primary intraocular infections in the hospital setting: the treatment of bacterial conjunctivitis, the prevention of post-operative endophthalmitis, and the treatment of any infection following ocular surgery. Because these infections are caused by many of the same bacteria, they can usually be treated with the same agents.

Topical fluoroquinolones represent the newest class of antibacterial agents available for the treatment of ocular infections. These drugs exhibit activity against a broad spectrum of ocular pathogens. Levofloxacin is active against gram-positive organisms exhibiting activity against bacteria that are resistant to ciprofloxacin and ofloxacin. In addition, levofloxacin ophthalmic solution provides effective concentrations to adequately cover many gram-negative infections.

The most common adverse reactions with levofloxacin ophthalmic are transient itching and burning, decreased vision, foreign body sensation, ocular pain, chemical conjunctivitis-keratitis, and photophobia.

**Meropenem** is an intravenous carbapenem antibiotic similar to imipenem. Meropenem was last reviewed in May 2002 for formulary addition. At that time, meropenem and imipenem were deemed comparable. Since meropenem costs more, it remained nonformulary and imipenem was selected as the carbapenem in the *Formulary*.

Recently, nonformulary use of meropenem has increased secondary to the presence of multiply resistant organisms for which meropenem sensitivity was maintained compared with imipenem. Meropenem was re-considered by the Anti-Infective Subcommittee to determine the appropriate formulary status for this agent.

Meropenem was added in the *Formulary*, but its use is restricted to patients that have been approved by the Infectious Diseases Service. The recommended criteria for use are nosocomial bacterial meningitis caused by organisms resistant to other beta-lactam antibiotics and other serious nosocomial infections due to multi-drug resistant (including imipenem) gram-negative bacilli. (ie, *Pseudomonas*, *Enterobacter*, and *Acinetobacter* sp).

**Pramipexole** is a direct dopamine agonist that is used to treat early Parkinson's disease (instead of levodopa-carbidopa). Pramipexole is also used as an add-on to levodopa-carbidopa to lower the dose of levodopa when patients are refractory

to therapy or when patients are experiencing intolerable dopaminergic adverse effects. It was reviewed because of high nonformulary use.

The published evidence suggest that pramipexole has fewer dopaminergic adverse effects compared with levodopa, but that levodopa has superior efficacy for the activities of daily living. All patients should be alerted that somnolence is a common adverse effect associated with the use of pramipexole.

Pramipexole is equivalent to bromocriptine, another direct dopamine agonist that is already listed in the *Formulary*. Pramipexole has not been compared with pergolide or ropinirole.

Pramipexole is priced similarly to ropinirole and is less expensive than bromocriptine or pergolide. Pramipexole was added in the *Formulary* because there is sufficient evidence to support its efficacy.

Pramipexole therapy should be started with dosages of 0.125 mg 3 times a day. This dosage should be titrated slowly to avoid adverse effects. Pramipexole may be taken with food to avoid stomach upset.

**Ampicillin-sulbactam** is a combination of a penicillin (ampicillin) and a beta-lactamase inhibitor (sulbactam). The beta-lactamase inhibitor broadens the spectrum of ampicillin to cover organisms that would normally be resistant. It was considered for formulary addition because it has been occasionally requested for nonformulary use. Most nonformulary anti-infectives are considered "high-priority" and are evaluated to determine whether they are needed in the *Formulary*. After a thorough review, ampicillin-sulbactam was designated nonformulary and not available.

Ticarcillin-clavulanate (Timentin®) and piperacillin-tazobactam (Zosyn®) are formulary alternatives to ampicillin-sulbactam. A possible niche for ampicillin-sulbactam is for the treatment of multiply resistant *Acinetobacter* infections. There are limited data (ie, case series) that suggests that ampicillin-sulbactam is useful in this setting. It is possible that sulbactam has a unique utility for resistant *Acinetobacter*. Based on information from the Clinical Laboratory at Shands at UF, multiply resistant *Acinetobacter* infections are not a concern at this time.

**Ciprofloxacin extended-release** is a long-acting oral version of ciprofloxacin with a labeled indication for the treatment of urinary tract infections (UTIs). Clinical trials have shown no clinical benefit for Cipro® XR over ciprofloxacin immediate-

release (IR). The only benefit for Cipro<sup>®</sup> XL is once-daily administration.

The costs of therapy for ciprofloxacin IR and XR are comparable. Ciprofloxacin IR is scheduled to be available as a generic after December 2003. A year from now, it is estimated that the cost of ciprofloxacin immediate-release should decrease dramatically.

Currently, ciprofloxacin IR and gatifloxacin are available in the *Formulary* for the treatment of cotrimoxazole-resistant UTIs. Therefore, ciprofloxacin extended-release was designated nonformulary and not available.

**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. It must be administered subcutaneously twice a day. Enfuvirtide will be used in patients with advanced disease who are often resistant to several other therapies. It was reviewed because it is a high-priority non-formulary drug.

Because enfuvirtide is available only through a limited distribution network (ie, the Fuzeon "Progressive Distribution Program"), it cannot be stocked in the hospital. Since it cannot not be "readily available," it cannot be listed in the *Formulary*. This could be problematic for a medication used to treat HIV, where missing doses could encourage the development of resistance.

Patients will be able to use their own supply of enfuvirtide while they are hospitalized. Last month, the *Patient Medications Brought into Shands at the University of Florida*

policy was modified to allow the use of injectable medications available only through limited distribution networks.

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

**Bivalirudin** is a synthetic bivalent analog of hirudin. Its anticoagulant effect is the result of direct thrombin inhibition, which is reversible and transient. The onset of anticoagulant effect is immediate following direct intravenous injection of bivalirudin. Coagulation times return to normal approximately 1 to 2 hours after an infusion of bivalirudin is stopped.

The FDA-labeled indication for bivalirudin is for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA). However, it was added in the *Formulary* for therapeutic anticoagulation in patients with a history of heparin-induced thrombocytopenia-thrombosis (HITT). It requires Hematology's approval for use as a therapeutic anticoagulant. The criteria for the use of bivalirudin were reviewed after the publication of the *Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events-2* (REPLACE-2).

The review of the REPLACE-2 results only led to minor changes in the bivalirudin criteria for use at Shands at UF. The primary endpoint of REPLACE-2 was a combination of efficacy (death, MI, urgent revascularization) and safety (bleeding). A triple-endpoint using just the efficacy components was a secondary analysis. A drug that is less efficacious, but safer

would look better using the quadruple-endpoint.

Bivalirudin could be no more than 9% worse using the quadruple-endpoint. However, the trend with the triple-endpoint favored heparin plus a GP IIb/IIIa inhibitor. Bivalirudin could be as much as 32% less effective using the triple-endpoint, which only measured efficacy. There were also more non-Q-wave MIs in the bivalirudin-treated patients.

Bleeding was lower in the bivalirudin group, but the "drivers" in this finding were vascular access puncture and GI bleeding. The bleeding endpoint included major and minor bleeding. If only major bleeding was used, the bleeding between the groups would have been similar.

Whether bivalirudin should replace heparin in "low-risk" patients or heparin plus a GP IIb/IIIa depends on the interpretation of the quadruple-endpoint, the definition of bleeding, the dosage range of heparin used, and an economic consideration. The REPLACE-2 data are not strong enough to justify the increased cost from shifting from heparin and not convincing enough to decrease the use of a GP IIb/IIIa, which would decrease expenses.

Bivalirudin's criteria for use were extended to include patients undergoing PCI with significant renal dysfunction, as defined as a creatinine clearance less than 20 mL per minute. For patients with a creatinine clearance less than 20 mL/min, the labeling states that bivalirudin's dosage should be reduced by 60% initially, and then adjusted based on activated clotting time (ACT). Patients on hemodialysis should have their initial dosages reduced by 90%.

## POLICIES AND PROCEDURES

# Therapeutic interchange — Update

**A** drug is ordered, but a different drug is dispensed and administered. The drug that is dispensed is not a generic equivalent of the ordered drug, but it is a "therapeutically equivalent" product. A single drug product is selected and listed in the *Formulary* for a therapeutic class. The drugs are not the same, but they are so similar that there is no clinically significant difference among the drugs in a class. All non-selected drugs are changed to the formulary class representative. The non-selected drugs are nonformulary and are not available — with a few exceptions.

This is therapeutic interchange. Therapeutic interchange is the substitution of various therapeutically

equivalent drug products by pharmacists under arrangements of the authorized prescribers who have agreed on the conditions for the change.

Therapeutic interchange is reviewed and approved by the medical staff by the Pharmacy and Therapeutics Committee, which is a medical staff committee. Representatives from various medical specialties participate in the P&T Committee. If a particular drug class is used by a specific medical specialty and a representative from that medical specialty is not on the P&T Committee, the department head is contacted to solicit input on that particular interchange.

Therapeutic interchange has been practiced for over 20 years at Shands

at UF. When it was first initiated, it was considered controversial. However, this practice is now well accepted. Feedback from both attendings and housestaff consistently support the concept of interchanging to a product that is currently available, rather than frequently paging to have a new order written. Some institutions list only 1 agent in the class and contact the prescriber to change the order to the formulary agent.

Since the medical staff are not contacted to write a new order, there has to be a mechanism to notify the medical staff and nursing when an interchange occurs. This article will review how to find out which drugs  
(continued on next page)

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<http://shands.org/professional/drugs/bulletin.htm>

*Policies and procedures, from page 3* are being interchanged at Shands at UF and explain the policy for notifying practitioners when an interchange has occurred.

When a drug is prescribed that is interchanged, documentation of the interchange is placed in the chart. This documentation is placed in both the Physician Orders section of the chart and the Progress Notes section. The notation in the Orders section notifies the patient's nurse of the change. The note in the Progress Notes notifies the medical staff. An example of an order is:

*"Change Insulin Lispro 5 units 15 minutes before morning and evening meals to Insulin Aspart 5 units 15 minutes before morning and evening meals"*

*"Authorized Therapeutic Interchange"*

*Signature of Pharmacist*

There can be exceptions made to the interchange policy. If the patient has a rational reason not to receive the interchanged drug (ie, allergic to a dye

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in the interchanged product), the change can be overruled. Experience has shown that these situations are very rare.

A continuously updated version of a list of the drugs that are interchanged can be found on the Shands intranet at <http://intranet.shands.org/pharm/therapeu.htm>. When new drugs are added to the list, there is usually a 1-month transition period.

Usually, prescribers are notified that beginning the next month, an interchange will occur. This gives prescribers an opportunity to change their habits.

Most prescribers use the preferred agents in the table. Interchanges are relatively infrequent—once the house-staff and other prescribers know the drug that is listed as the "class representative."

## 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**