

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met June 20, 2006. 2 drugs were added in the *Formulary* and 1 drug was deleted. 3 drugs were designated nonformulary and not available.

◆ ADDED

Moxifloxacin Ophthalmic
(Vigamox® by Alcon)

Temozolomide
(Temodar® by Schering Plough)

◆ DELETED

Levofloxacin Ophthalmic
(Quixin® by Vistakon)*

*Nonformulary and not available

◆ NONFORMULARY AND NOT AVAILABLE

Raloxifene (Evista® by Eli Lilly)

Varicella Zoster Immune Globulin
(VZIG® by Massachusetts Public Health Biologic Laboratories)*

*Previously available from the Blood Bank

Moxifloxacin ophthalmic solution was added in the *Formulary* and all other ophthalmic fluoroquinolones, including **levofloxacin ophthalmic**, are nonformulary and not available and will automatically be converted to moxifloxacin. Like all therapeutic interchanges, this will be documented in the Progress Notes and Orders section of the chart as a *P&T-Authorized Interchange*.

Moxifloxacin is a fourth-generation fluoroquinolone antibiotic with enhanced *in-vitro* activity against gram-positive pathogens while retaining similar efficacy against commonly encountered gram-negative ocular pathogens. *In vitro* sensitivity analyses have demonstrated activity of moxifloxacin against ciprofloxacin-
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PRESCRIBING

The legality and ethics of self-prescribing

Whether self-prescribing is legal and ethical is a debate influenced by the culture and perceptions of practitioners. Many recognize that family- and self-prescribing are common among licensed practitioners and typically do not question the practice. Although there may be a perception that self-prescribing is acceptable, the reality is that it is unacceptable and illegal in most instances.

Laws governing physicians differ significantly from state to state. The State of Florida's statutes regarding self-prescribing are applicable to physicians and pharmacists. Florida Statute 458.331(q) provides a listing of grounds for disciplinary action for physicians. This statute lists under grounds for disciplinary action, "Prescribing... a legend drug, including any controlled substance, inappropriately or in excessive or in inappropriate quantities is not in the best interest of the patient and **is not in the course of the physician's professional practice**, without regard to his or her intent." Based on this statute, is self-prescribing considered part of a physician's professional practice? Self-prescribing or prescribing to an individual not considered a patient, as defined by a valid patient chart or record, is not considered part of a physician's professional practice.

Pharmacy statute 465.016(s) states, "Dispensing any medicinal drug... when the pharmacist knows or has reason to believe that the purported prescription **is not based upon a valid practitioner-patient relationship**" is grounds for denial of a license or disciplinary action. Based on this statute, pharmacists in Florida are at risk when dispensing medications to a physician who has prescribed for himself or herself or a family member. Arguments that laws such as these are put on the books to deter the prescribing of controlled substances to one's self or

family have been used as a method to rationalize the practice.^{1,2} However, the interpretation of these statutes is not debatable. Is self-prescribing or filling a prescription which is not based on a valid physician-patient relationship really worth the potential repercussions?

In addition to the legal aspects of this question, the ethics of self-prescribing has produced further debate due to concern about physician health practices. The American Medical Association (AMA) has been a staunch supporter of education on the pitfalls of self-prescribing and has taken a stance to deter physicians from this practice unless in an emergency situation. The AMA code of ethics states, "Physicians should not treat or write prescriptions for themselves or immediate family members."

Again, many argue that much of the information and literature about self-prescribing is focused primarily on controlled substances with the non-controlled substances, such as antibiotics and contraceptives, being in a gray area. The counter debate is that even non-controlled medications should not be self-prescribed due to lack of objectivity and professional distance that typically exists in a practitioner-patient relationship.³ Furthermore, lack of objectivity and self-treatment can translate to potential delays in diagnosis and untimely treatment of many disease states.³

In a 2001 Penn State press release, Jason Christie, MD, was quoted as saying "A physician who treats himself has a fool for a patient. This may not

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- ◆ Ordering cytotoxic drugs

Formulary update, from page 1
resistant *Staphylococcal* species. Since 41% of the clinical *Staphylococcus aureus* isolates at Shands at UF are resistant to ciprofloxacin, resistance must be considered when selecting a topical fluoroquinolone. For gram-negative isolates, ophthalmic fluoroquinolones are considered equipotent.

Although ophthalmic fluoroquinolones have labeled indications for bacterial conjunctivitis, they are also used off-label for the prevention of post-operative endophthalmitis, and the treatment of other ocular infections following ocular surgeries. Most of the published evidence for these ophthalmic antibiotics is for bacterial conjunctivitis.

Tolerability among ophthalmic fluoroquinolone products is similar with ocular discomfort, itching, and burning being the predominant complaints. This may be associated with the preservative benzalkonium chloride. Moxifloxacin does not contain benzalkonium chloride.

The cost of third- and fourth-generation ophthalmic fluoroquinolones is similar. These agents are used sparingly, thus switching to moxifloxacin will have little impact on pharmaceutical expenditures.

The Anti-Infective Subcommittee recommended that moxifloxacin ophthalmic be added in the *Formulary*, that levofloxacin ophthalmic be deleted from the *Formulary*, and that ciprofloxacin ophthalmic (Ciloxan®),

ofloxacin ophthalmic (Ocuflox® and generics), gatifloxacin ophthalmic (Zymar®), and levofloxacin ophthalmic be automatically interchanged to moxifloxacin. Regardless of the dosage of these ophthalmic fluoroquinolones, they will be interchanged to 1 drop of moxifloxacin in each affected eye every 8 hours.

Temozolomide was evaluated for possible formulary addition as part of the ongoing review of oncology agents listed in the *Formulary*. Temozolomide is an oral alkylating agent. Temozolomide and dacarbazine (DTIC) are metabolized to the same active compound.

Temozolomide has significant activity in malignant gliomas, including anaplastic astrocytoma and glioblastoma multiforme, and melanoma. Patients with previously treated anaplastic astrocytoma or glioblastoma multiforme had overall response rates of 62% and 46-51%, respectively, following treatment with temozolomide. All patients experienced increases in quality of life parameters. The use of temozolomide in combination with radiation therapy in the treatment of newly diagnosed glioblastoma multiforme resulted in a statistically significant improvement in median overall survival (14.6 months) compared to radiation therapy alone (12.1 months).

Temozolomide received accelerated FDA approval for the treatment of recurrent anaplastic astrocytoma in August 1999. This indication is based on response rates. The FDA approved labeling for temozolomide for the treatment

of newly diagnosed glioblastoma multiforme on March 15, 2005. Temozolomide is also currently under standard review by the FDA for the treatment of metastatic melanoma. Temozolomide has an orphan drug designation for the treatment of malignant gliomas and advanced metastatic melanoma.

There are 4 strengths of temozolomide available (5 mg, 20 mg, 100 mg, and 250 mg) permitting appropriate dosing for brain tumors. The cost of maintenance therapy assuming a 1.73-m² patient is \$166 per day. Cost of treatment for a dose of 150 mg/m²/day is \$1729.45 per cycle and the cost of treatment for a dose of 200 mg/m²/day is \$2421.80 per day.

Temozolomide is effective for the treatment of relapsed anaplastic astrocytoma, as well as the initial treatment for glioblastoma multiforme—both diseases historically with a poor outcome. There are few alternatives for this disease, and the use of an oral agent that is well-tolerated permits a better quality of life for patients with this disease. Therefore, temozolomide was added in the *Formulary*.

Raloxifene was evaluated to determine its appropriate formulary status in the inpatient setting because of its high volume of nonformulary use. Because of its prevalence, raloxifene is frequently requested for nonformulary use to continue home medications. Raloxifene is widely used for the treatment and prevention of osteoporosis.

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Prescribing, from page 1

be a problem when self-treating for minor or self-limited conditions, but a loss of objectivity means also that one can lose sight of when the line has been crossed."⁴

From the legal standpoint, self-prescribing or prescribing to an individual outside of a valid physician-patient relationship is against Florida law. Ethically, risks associated with a lack of objectivity that result in poor health outcomes should be a deterrent. Common sense would dictate based on legal, ethical, and overall health concerns, an objective provider is a necessity regardless of the profession and barriers to access of the individual.

By Brandi Beyhan, PharmD

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MEDICATION SAFETY

Variety of insulin product vendors selected

Based upon the recommendations of the Medication Safety Committee, beginning August 1, 2006, there will be an increased variety of vendors and dosage forms stocked for insulin products. When all insulin products are purchased from the same company, the vials and their labels tend to look similar. By selecting different companies' insulin products, different products look "different." Also, pre-filled insulin pens will be added into stock, along with the retention of some vials. This adds more variety and, thus, more differentiation among the products. The goal is to decrease the chances for medication errors because products look similar.

Insulin aspart (Novolog®) and insulin aspart plus insulin aspart protamine (Novolog® 70/30 Mix) will be available as pre-filled "pens" (FlexPen®) instead of vials. Dosages from 1 to 60 units can be "dialed-in" using the Novolog® FlexPen®. No Novolog® vials will be stocked. For larger doses, more

than 1 injection may be necessary. For patients in isolation, all pens will be placed in a plastic bag and returned to the medication cart for storage.

Novolin® R brand of regular insulin will be removed from the *Formulary*. This "sound-alike" brand is too close to Novolog® and could cause confusion. Regular insulin will be switched to Humulin® R pens. These pens look distinctly different than the Novolog® pens. We will continue to use Novolin® N vials.

Novolin® 70/30 vials, which is a mixture of NPH insulin 70 units per milliliter and 30 units of regular insulin per milliliter, will be replaced with Humulin® 70/30 vials.

Pens were selected for the more frequently used products because of their ease of use. Although pens from different vendors work slightly differently, they are easy to use and there will be an educational effort to explain the differences between the products.

Formulary update, from page 2

Raloxifene is a selective estrogen receptor modulator. By selectively activating estrogen receptors, raloxifene retains the beneficial effects of estrogen on bone without adversely affecting uterine or breast tissue. Raloxifene appears to have anti-estrogenic effects on breast tissue similar to tamoxifen and does not appear to have estrogenic stimulatory effect on the uterus (unlike tamoxifen).

Clinical trials evaluating the effectiveness of raloxifene for the treatment of osteoporosis show that it decreases the incidence of vertebral fractures, but not hip fractures. The American Association of Clinical Endocrinologists and the American College of Endocrinology guidelines recommend raloxifene as a second-line option for patients with hip osteoporosis who cannot tolerate oral bisphosphonate therapy. Other recommended options include a parenteral bisphosphonate, teriparatide, or calcitonin. For patients with ongoing bone loss and vertebral fractures, raloxifene is a first-line agent. Other first-line options are an oral bisphosphonate or calcitonin.

Recently released data from the National Cancer Institute's large, randomized comparison of raloxifene and tamoxifen for the prevention of breast cancer in high-risk women shows that raloxifene is equally effective and is associated with less venous thromboembolism and uterine dysplasia than tamoxifen. These data suggest that raloxifene will be a drug of choice for breast cancer prevention in high-risk women. This could increase the non-formulary demand for raloxifene.

Raloxifene is often well-tolerated, with the most common adverse effects associated with its use being hot flashes and leg cramps. Increased risk of venous thromboembolism is the major serious adverse effect associated with raloxifene therapy. The *Warnings* section of the official labeling recommends that raloxifene be stopped for 72 hours before prolonged immobilization, like post-operative recovery or prolonged bed rest. This describes most of the patients who would receive raloxifene as an inpatient at Shands at UF.

Because of the risk of venous thromboembolism associated with raloxifene, it was designated nonformulary and not available. This recommendation is based on the difficulty assessing each patient admitted on raloxifene to determine whether the warnings about venous thrombosis risk in immobilized patients outweigh the short-term benefits for osteoporosis or breast cancer prevention. It is anticipated that missing a few doses of raloxifene is less of a risk than the increased risk for thromboembolism. This risk-to-benefit assessment is similar to the precedent set by the nonformulary and not available status for oral bisphosphonates.

Varicella zoster immune globulin is a hyperimmune IgG immune globulin used for passive prevention of varicella-zoster infections in susceptible patients. Roughly a year ago, Massachusetts Public Health Biologic Laboratories published notice that they stopped making VZIG[®] brand of varicella zoster immune globulin. VZIG[®] has long been dispensed by the Blood Bank at Shands at UF instead of the Pharmacy Department. Unfortunately, their supply has been exhausted. There is no longer any

commercial supply of VZIG[®] available for use at Shands.

There is an investigational product from Canada, which may eventually be marketed. If this investigational product is marketed, the P&T Committee will evaluate it as a pharmacy product. Since we currently do not have access to VZIG[®], it was designated nonformulary and not available.

The investigational product is available via a treatment IND. However, there will be logistical issues surrounding the acquisition of the investigational product (VariZIG[®] by Cangene), if it is needed before the product comes to market. It can be obtained by contacting FFF Enterprises at 800-843-7477. It can be obtained for immune compromised pediatric and adult patients, neonates and infants less than 1 year of age, premature infants, pregnant women, and newborns whose mothers had varicella infection less than 5 days prior to delivery to less than 2 days after delivery. Acyclovir prophylaxis is an alternative to using varicella zoster immune globulin for some patients.

VariZIG[®] can only be accessed under the investigational protocol for an emergent, 1-time use with approval from the IRB Chair or Vice-Chair. If an investigator agrees to sponsor the IRB protocol, VariZIG[®] still cannot be stocked and there will be a delay before therapy can be started. In order for varicella zoster immune globulin to be effective, it must be administered within 96 hours of an exposure.

POLICIES AND PROCEDURES

Changes to the chemotherapy ordering process

For more than 2 decades, Shands at UF has required the use of a chemotherapy order form for parenteral cytotoxic chemotherapy for oncology indications. At the June meeting, the Pharmacy and Therapeutics Committee approved several policy changes that will improve patient safety by enhancing the processes used to order and dispense cytotoxic chemotherapy. Now, all oral and parenteral cytotoxic chemotherapy must be ordered using a chemotherapy order form for both oncology and non-oncology uses. There will also be a 5:00 pm cut-off time for all chemotherapy orders.

The P&T Committee actually approved a 9-point plan to improve the ordering and handling of cytotoxic chemotherapy (see Table 1, next page). This plan establishes a process that allows a small number of specially

trained pharmacists to process all orders for cytotoxic drugs. A high-level review of each order based on patient characteristics, including indication for use, patient size, protocol, etc., will enhance the current safety processes.

The 5:00 pm cut-off time was created to enable this new program to be staffed. Since most chemotherapy is not an emergency, proper planning will allow the "chemotherapy pharmacists" to handle chemotherapy orders during the day shift, 7 days a week.

There will, however, be a process for emergency or "off-hours" chemotherapy orders. These orders will be processed only if a delay in treatment would be a threat to the patient's health. The decision to process and administer off-hours chemotherapy will occur only after a clinical pharmacy oncology specialist consults with the

prescriber and there is consensus that a delay would not be in the best interest of the patient.

The most controversial change made with these new chemotherapy policies is the inclusion of cytotoxic chemotherapy for non-oncology indications on the Chemotherapy Order Form. However, if these cytotoxic drugs are ordered by multiple procedures (ie, Chemotherapy Order Form for Oncology uses and regular Physicians Orders for non-oncology uses), it increases the likelihood that errors could slip through the enhanced safety net.

The new process will also promote the use of pre-printed orders for cytotoxic chemotherapy for non-oncology uses. All pre-printed orders will be reviewed and approved by the P&T Committee. Pre-printed orders will
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Policies and procedures, from page 3 promote standardization and safety. In addition to assuring appropriate dosing and administration, pre-printed orders facilitate appropriate supportive care and monitoring. The mandated pre-printed orders for rituximab and cyclophosphamide will be prototypes for this process.

The drugs that must be ordered on a Chemotherapy Order Form are listed in Table 2. Some changes to this list are anticipated as new drugs are approved. There are several drugs on this list that are used for non-oncology uses (eg, cyclophosphamide, methotrexate, mitomycin, mitoxantrone, and thalidomide). There will be an effort to work with the various medical services that use these drugs to establish pre-printed orders to facilitate the safe use of these cytotoxic drugs for non-oncology uses.

Cytotoxic chemotherapy drugs are high-risk, but when used appropriately, they can have significant positive impact on a patient's care. However, there is a broad range of acceptable doses for these drugs depending on the indication, and the additional information provided by the Chemotherapy Order Form helps identify potential problems. This information, combined with the process of funneling these enhanced orders to specially trained pharmacists for screening, should result in improved patient safety.

TABLE 1. CHEMOTHERAPY PROCESS IMPROVEMENTS

1. 5:00 pm Daily Cut-off Time for All Chemotherapy Orders
2. Collaborative Process for Emergency Off-hours Chemotherapy Processing
3. All Cytotoxic Chemotherapy for Both Oncology and Non-oncology Uses Must Use a Chemotherapy Order Form
4. Pre-printed Chemotherapy Order Forms for Rituximab and Cyclophosphamide Must Be Used for Non-oncology Uses
5. Cumulative Lifetime Doses Must Be Documented On Chemotherapy Order Forms for Bleomycin, Daunorubicin, Doxorubicin, Epirubicin, and Idarubicin
6. Authorized Oncology Prescribers Must Provide a Reference or Other Supportive Information for Chemotherapy Orders for All Oncology Uses
7. Prescribers Must Provide a Reference or Other Supportive Information for Chemotherapy for Non-oncology Uses
8. Credentialed Oncology Attending Physicians Must Sign or Co-sign All Orders for Oncology Uses
9. An Attending Physician Must Sign or Co-sign All Orders for Chemotherapy for Non-oncology Uses

TABLE 2. DRUGS THAT MUST BE ORDERED ON A CHEMOTHERAPY ORDER FORM

Aldesleukin	Cytarabine	Idarubicin	Podoflox
Alemtuzumab	Dacarbazine	Ifosfamide	Podophyllum resin
Arsenic Trioxide	Dactinomycin	Imatinib mesylate	Procarbazine
Asparaginase	Dasatinib	Irinotecan	Rituximab
Azacitidine	Daunorubicin	Leflunomide	Sorafenib
Bacillus Calmette-Guerin	Decitabine	Lenalidomide	Streptozocin
Bevacizumab	Denileukin	Lomustine	Sunitinib
Bexarotene	Docetaxel	Mechlorethamine	Teniposide
Bleomycin	Doxorubicin	Melphalan	Thalidomide
Bortezomib	Epirubicin	Methotrexate	Thioguanine
Busulfan	Erlotinib	Mitomycin	Thiotepa
Capecitabine	Estramustine Phosphate	Mitotane	Topotecan
Carboplatin	Etoposide	Mitoxantrone	Tositumomab
Carmustine	Floxuridine	Nab-paclitaxel	Trastuzumab
Cetuximab	Fludarabine	Nelarabine	Valrubicin
Chlorambucil	Fluorouracil	Oxaliplatin	Vinblastine
Cisplatin	Gemcitabine	Paclitaxel	Vincristine
Cladribine	Gemtuzumab ozogamicin	Pegaspargase	Vinorelbine
Clofarabine	Hydroxyurea	Pemetrexed	
Cyclophosphamide	Ibrutinomab tiuxetan	Pentostatin	