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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met March 21, 2006. 7 products were added in the *Formulary,* and 5 were deleted and designated not available. A restriction was removed from 1 product.

◆ ADDED

Dexmethylphenidate Extended-Release
(Focalin® XR by Novartis)*

Lansoprazole Capsule & Injection
(Prevacid® by TAP)

Methylphenidate Extended-Release
(Metadate® CD by Celltech Pharmaceuticals)*

Olanzapine Injection
(Zyprexa® IntraMuscular by Lilly)†

Theophylline Suspension
(compounded)

Tigecycline
(Tygacil® by Wyeth)‡

Vinorelbine
(eg, Navelbine® by GlaxoSmithKline)¶

**Restricted to Shands Vista*

†Restricted to the ED, Psychiatry Service, & Shands Vista

‡Restricted to Infectious Diseases or Anti-Infective Stewardship approval

¶Restricted to credentialed chemotherapy prescribers

◆ DELETED

Didanosine Chewable Tablets
(Videx® by Bristol-Myers Squibb)**

Gatifloxacin (Tequin® by Bristol-Myers Squibb)**

Lindane ("Kwell" generics)**

Pantoprazole Tablets & Injection
(Protonix® by Wyeth)**

Saquinavir (Fortovase® by Roche)**

***Nonformulary and Not Available*

◆ CRITERIA FOR USE CHANGES

Levofloxacin
(Levaquin® by Ortho-McNeil)+

+No longer restricted

(continued on next page)

NEWS

Joint Commission report & medication use management

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) visited Shands at UF the week of March 20-24, 2006. The results of the survey were outstanding, and there were only 5 areas that did not meet the current standards and, thus, received Requirements for Improvement (RFIs). These RFIs require a written report, Evidence of Standards Compliance (ESC), to be submitted within 45 days of receipt of the final survey report.

JCAHO visited Shands at UF the week of March 20-24, 2006. The results of the survey were outstanding, and there were only 5 areas that did not meet the current standards.

The RFIs received relate to the following standards: pain re-assessment; verbal order "read back;" banned abbreviations; medication reconciliation; and documentation of laboratory test reference ranges for waived tests.

Comprehensive pain assessments (and re-assessments) are required for all patients and the reassessment must be documented. When verbal orders are taken from prescribers, the order must be written down and read back to the prescriber to verify the accuracy of the transcription. Although we have accomplished much in the area of decreasing the use of banned abbreviations, a single pre-printed order was found that contained banned abbreviations. Pre-printed orders will receive additional attention and must be formally approved by the Patient Records Committee. Although we instituted the new medication reconciliation process this year, only 30% of the charts reviewed contained a completed Home Medication Reconciliation form. Finally, there were results documented in the medical records that did not list reference ranges for waived (bedside) glucose testing.

The ESC report will be filed within 45 days. During this time we will be re-educating both employees and members of the medical staff and closely monitoring documentation to ensure full standards compliance within the 45-day timeframe.

4 of the RFIs have medication use implications. Pain assessment is necessary to make sure patients are receiving adequate pain control, which often includes changing pain medications. Verbal orders for medications are given and can be a source of medication errors; thus adding to the justification for the "read back" requirement. Banned abbreviations are often included in medication orders, which can result in errors. The medication reconciliation process is about evaluating all medications as patients transition through the various levels of care. Our current process documents patients' admission medications, medications as patients are transferred from a different level of care (eg, from an ICU to a general ward), and provides patients' current medications to compare to their admission medications so that appropriate discharge prescriptions can be written based on the patient's current condition and their previous therapy.

INSIDE THIS ISSUE

The Clinical Practice Bulletin is not included in this issue but will return in May.

Formulary update, *from page 1*

Dexmethylphenidate and **Metadate® CD** are stimulants added in the *Formulary* for use at Shands Vista to treat patients with attention deficit disorder. A high percentage of patients admitted to Shands Vista are on Medicaid and are taking these medications. Dexmethylphenidate and Metadate® CD are listed in the Medicaid Preferred Drug List and were added to promote continuity of care. The decision to add these agents was not based on therapeutic superiority. These products will not be available at Shands at UF.

Methylphenidate and its active isomer dexmethylphenidate are thought to block the reuptake of dopamine and norepinephrine and increase the release of both monoamines into the extraneuronal space. Catecholamine dysfunction, specifically dysregulation of dopamine and norepinephrine, is thought to play a role in the pathophysiology of attention deficit disorder.

Dexmethylphenidate has been shown to be effective in the treatment of attention deficit disorder. Since dexmethylphenidate is the active isomer of racemic methylphenidate, it is at least twice as potent on a milligram-per-milligram basis. Evidence indicates that dexmethylphenidate has equal efficacy and a slightly longer duration of effect compared to methylphenidate. There have been no randomized, prospective studies that demonstrate therapeutic superiority to extended-release methylphenidate.

Metadate® CD is 1 of many extended-release formulations of methylphenidate. These products differ in their mechanisms of drug release and their serum-concentration-time profiles. Metadate® CD provides higher methylphenidate serum concentrations during the day, but lower levels in the evening. Concerta®, the extended-release methylphenidate listed in the *Formulary* at Shands at UF, provides more constant serum levels throughout the day.

The adverse effect profiles for these medications are very similar. The most common adverse events are nervousness and insomnia. Other adverse events that occurred with a frequency of greater than 5% include headache, abdominal pain, anorexia, nausea, and fever. Other more serious adverse events include growth suppression with long-term use and the potential for drug dependence and abuse.

Although pharmacokinetic evidence has shown that Metadate® CD has different serum concentration versus time blood levels, Concerta® doses can be supplemented with immediate-release methylphenidate or the dosage can be increased to achieve similar blood levels.

Lansoprazole capsules and **injection** were added in the *Formulary* and **pantoprazole tablets** and **injection** were deleted and designated nonformulary and not available. Lansoprazole will be the only proton-pump inhibitors (PPIs) dispensed. The P&T Committee has approved equivalent dosages for the interchange of esomeprazole, omeprazole, pantoprazole, and rabeprazole to lansoprazole *(see table on page 4)*.

Lansoprazole was chosen to replace pantoprazole because of a dramatic increase in cost scheduled for pantoprazole. The injectable price was increased 6-fold and the oral tablets were increased 16-fold. Lansoprazole was chosen to represent this class of drugs because it offers a full line of products (ie, oral capsule, dissolvable tablet [SoluTabs®], a compounded oral suspension, and an injectable). This facilitates conversion between the intravenous an oral formulations. The P&T Committee has previously approved automatic IV-to-PO interchange. Patients receiving intermittent IV lansoprazole can be converted to oral therapy (ie, suspension, SoluTabs®, or capsule) if they are receiving other oral medications or food orally.

Lansoprazole can be given as an intravenous infusion for patients with a gastrointestinal bleed. There are also good data on the use of lansoprazole in children.

Lansoprazole will be interchanged for other PPIs using the following ratios: esomeprazole (3:2), omeprazole (2:3), pantoprazole (3:4), and rabeprazole (3:2). See the article on Therapeutic Interchange in this issue of the *Bulletin* for more details.

Olanzapine injection is the second intramuscular atypical antipsychotic marketed with a rapid onset of action. Ziprasidone intramuscular injection, which is listed in the *Formulary*, was the first atypical, rapidly acting antipsychotic.

Olanzapine's efficacy in schizophrenia is attributed to a combination of dopamine and serotonin type 2 antagonism. The mechanism of action of olanzapine in the treatment of acute manic episodes associated with bipolar disorder is unknown. Olanzapine also has anticholinergic effects, including causing sedation. Olanzapine's alpha blocking effects are related to its propensity to cause hypotension.

Olanzapine intramuscular injection has labeled indications for the treatment of agitation associated with schizophrenia and bipolar mania. It has been used off-label for agitation in dementia and agitation in other medical conditions including in critical care patients.

Studies show greater efficacy than placebo for the labeled indications. There are no published studies directly comparing olanzapine injection with ziprasidone injection. There are, however, studies comparing olanzapine injection with haloperidol in schizophrenia and medical agitation and lorazepam in bipolar mania. There is no evidence that olanzapine has superior efficacy to haloperidol, but it is associated with less extrapyramidal adverse effects. Olanzapine has been shown to be superior to lorazepam in patients with bipolar mania.

There is no evidence that intramuscular olanzapine is superior to haloperidol for agitation in dementia or medical patients (eg, critical care setting). Concerns about the risk of sudden death in elderly patients with dementia should prevent its use in these patients until this issue has been studied more extensively.

Like other antipsychotics, olanzapine has been associated with neuroleptic malignant syndrome. Hypotension is the most common serious potential adverse effect. Olanzapine should be used with particular caution in patients with known cardiovascular disease, cerebrovascular disease, and conditions that predispose patients to hypotension.

Intramuscular olanzapine is 6-12 times more expensive than haloperidol injection and twice as expensive as ziprasidone injection. If benztropine is routinely used to prevent EPS, olanzapine is 50-80% more expensive. Olanzapine injection is restricted to the Psychiatry Service and the Emergency Department.

A compounded **theophylline suspension** was added in the *Formulary* for use in adults and children. Theophylline is used in infants with apnea that is not responsive to caffeine. A liquid form of theophylline is used in some adults with bradycardia that need their medication administered down a tube. Theophylline elixir has been previously designated nonformulary and not available because there was concern that it would inadvertently be given to small children.

A theophylline suspension will be prepared when needed from sustained-release theophylline tablets. This formula is based on a recently published article assuring 90-day stability for the suspension.

Tigecycline is a bacteriostatic minocycline derivative that inhibits bacterial protein synthesis by binding to a site on the 30S ribosome within the bacterial cell, similar to the action of other tetracycline-class agents. Tigecycline has a 5-fold stronger affinity for binding to the ribosome site compared to other tetracyclines, such as tetracycline and minocycline. It is thought that this stronger binding affinity allows tigecycline to overcome certain resistance mechanisms seen with other tetracyclines.

Tigecycline exhibits a broad spectrum of activity against gram-positive and gram-negative organisms, including some resistant strains, such as: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), extended-spectrum beta-lactamase producing Enterobacteriaceae, *Acinetobacter baumannii,* and *Stenotrophomonas maltophila.*

Due to this unique expanded spectrum of activity, tigecycline may serve an important role in the treatment of multidrug-resistant bacterial infections. Unfortunately, efflux mutations have already been identified, capable of enhancing the transport of tigecycline out of the bacterial cell, which may eventually result in resistance to tigecycline when the drug gains widespread clinical use.

(continued on next page)

Formulary update, *from page 2*

Clearly tigecycline must be used appropriately as it represents 1 of the last line agents in the management of multidrug-resistant pathogens. Therefore, tigecycline was added in the *Formulary* and restricted to approval by the Infectious Diseases consult service or the Anti-Infective Stewardship Program.

Vinorelbine is a synthetic vinca alkaloid. It has a labeled indication for combination treatment with other established therapies, including cisplatin for the treatment of non-small-cell lung cancer (NSCLC). Although associated with a greater incidence of adverse effects such as neutropenia, leukopenia, and thrombocytopenia, multiple phase III clinical trials have shown increased survival benefit and decreased disease progression for vinorelbine plus cisplatin compared with cisplatin monotherapy. The adverse effects associated with vinorelbine appear to be less than other treatments like docetaxel monotherapy. Current National Comprehensive Cancer Network (NCCN) guidelines recommend vinorelbine as a first-line therapy for the treatment of NSCLC in combination with cisplatin.

NCCN guidelines also recommend vinorelbine monotherapy as first-line therapy for the treatment of metastatic breast cancer. Although not established in clinical guidelines, combination therapy including vinorelbine is also used for the treatment of refractory non-Hodgkin's lymphoma.

Vinorelbine was added in the *Formulary* and restricted to credentialed chemotherapy prescribers.

Didanosine is an oral nucleoside reverse transcriptase inhibitor. Bristol-Myers Squibb announced that all strengths of Videx® Chewable Tablets have been discontinued. Therefore, all strengths of didanosine chewable tablets will be deleted from the *Formulary* and designated nonformulary and not available. Videx EC® 200-mg and 400-mg capsules as well as didanosine 10-mg/mL liquid remain in the *Formulary*.

Gatifloxacin was deleted from the *Formulary* when the FDA announced on February 15, 2006 that it is now contraindicated in patients with diabetes. In addition, the existing warnings regarding hypoglycemia and hyperglycemia have been updated to include information identifying other risk factors for developing low blood sugar and high blood sugar associated with gatifloxacin use, including advanced age, renal insufficiency, and concomitant glucose-altering medications. Because there are equally effective fluoroquinolones without these warnings, a change was deemed necessary for safety reasons.

Levofloxacin is listed in the *Formulary* and the previous restriction requiring Infectious Diseases approval has been lifted. The recommended dosage for levofloxacin is 750 mg IV or orally daily. In patients with impaired renal function (ie, creatinine clearance less than 50 mL/min), the dosage interval is prolonged to 48 hours. Ciprofloxacin also remains in the *Formulary*.

Lindane is a topical insecticide that has been used since 1947 for the treatment of pediculosis (lice) and scabies. It has been used less in recent years because of its potential to cause neurotoxicity and because of the availability of safer and more effective alternatives. Permethrin is the preferred agent and is listed in the *Formulary*.

An FDA advisory recommends against the use of lindane in children less than 1 month of age. Children with thin skin and for whom a large percentage of the body is exposed to lindane are more prone to develop toxicity. Lindane is also not recommended in patients less than 50 kilograms.

Since lindane is no longer a first-line agent and it is not particularly effective in the treatment of resistant pediculosis, it was removed from the *Formulary*.

Saquinavir is a protease inhibitor that has been used for the treatment of patients infected with HIV. The soft-gel formulation of saquinavir, Fortovase®, was discontinued by the manufacturer because of decreasing demand for this product.

Saquinavir remains available as a film-coated tablet, Invirase®, for use as an alternative treatment regimen when "boosted" with ritonavir. Ritonavir is a potent inhibitor of the metabolism of saquinavir in the gut and the liver, which allows sufficient serum concentrations to be a viable treatment option. Ritonavir co-administration allows less frequent dosing of Invirase® and decreases the development of resistance.

POLICIES AND PROCEDURES

Therapeutic interchange – 2006

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 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. Feedback from both attendings and housestaff consistently support the concept of interchanging to a product that is currently available, rather than constantly paging to have a new order written. Some institutions only list 1 agent in the class and constantly 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. 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 Pantoprazole 40 mg PO daily to Lansoprazole 30 mg PO daily"
"Authorized Therapeutic Interchange"
[Pharmacist Signature]

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

A continually updated version of the drugs that are therapeutically interchanged can be found on the intranet at http://intranet.shands.org/pharm/therapeu.htm. When a new product is added to the list, 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. Interchanges are relatively infrequent—once the housestaff and other prescribers know the drug that is listed as the "class representative."

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Policies and Procedures, from page 3

Combination products will also be interchanged when the ingredients are listed in the *Formulary* and the exact amount of each ingredient is available. For example, an order for Vytorin® 10/10 will be changed to Ezetimibe 10 mg [Zetia®] and Simvastatin [Zocor®] 10 mg. The same documentation as for the therapeutic interchanges will occur.

As stated in the *Formulary Update* in this issue of the *Bulletin,* the change in the proton-pump inhibitor (PPI) in the *Formulary* is a major change. The table below provides an explicit list of interchanges that will take place. The P&T Committee also authorized the automatic changing of pre-printed orders containing pantoprazole to lansoprazole.

CONVERSION OF OTHER PPIS TO LANSOPRAZOLE

DRUG	DOSAGE	DRUG DISPENSED§	DOSAGE DISPENSED*†
Esomeprazole	20 mg PO daily	Lansoprazole	30 mg PO daily
Esomeprazole	40 mg PO daily	Lansoprazole	60 mg PO daily
Esomeprazole	20 mg IVPB daily	Lansoprazole	30 mg IVPB daily
Esomeprazole	20 mg IVPB daily	Lansoprazole	30 mg PO daily‡
Esomeprazole	40 mg IVPB daily	Lansoprazole	60 mg IBPB daily
Esomeprazole	40 mg IVBP daily	Lansoprazole	60 mg PO daily‡
Esomeprazole	40-80 mg load, then 4-8 mg IV/hour	Lansoprazole	60 mg load, then 6 mg IV/hour (titrated)¶
Omeprazole	10 mg PO daily	Lansoprazole	15 mg PO daily
Omeprazole	10 mg PO BID	Lansoprazole	30 mg PO daily
Omeprazole	20 mg PO daily	Lansoprazole	30 mg PO daily
Omeprazole	20 mg PO BID	Lansoprazole	30 mg PO BID
Omeprazole	40 mg PO daily	Lansoprazole	60 mg PO daily
Omeprazole	40 mg BID	Lansoprazole	60 mg PO BID
Pantoprazole	40 mg PO daily	Lansoprazole	30 mg PO daily
Pantoprazole	40 mg PO BID	Lansoprazole	30 mg PO BID
Pantoprazole	40 mg IVPB daily	Lansoprazole	30 mg IVPB daily
Pantoprazole	40 mg IVPB daily	Lansoprazole	30 mg PO daily‡
Pantoprazole	80 mg load, then 8 mg IV/hour	Lansoprazole	60 mg load, then 6 mg IV/hour
Rabeprazole	20 mg PO daily	Lansoprazole	30 mg PO daily
Rabeprazole	40 mg PO daily	Lansoprazole	60 mg PO daily

§All PPIs will be interchanged to Lansoprazole. Patients may use their own medication supply, if they do not wish to interchange. Esomeprazole [Nexium®], Omeprazole [Prilosec®], Pantoprazole [Protonix®], and Rabeprazole [AcipHex®] are nonformulary and not available.

*Oral (PO) Lansoprazole can be the oral capsule, the dissolvable tablets (SoluTabs®), or the bicarbonate suspension depending on patient needs.

† Recommended conversion ratios: lansoprazole for esomeprazole 3:2; lansoprazole for omeprazole 2:3; lansoprazole for pantoprazole 3:4; and lansoprazole for rabeprazole 3:2.

‡ Convert IV to oral Lansoprazole (oral solid, SoluTabs®, or suspension) if patients taking other oral medications or food (ie, IV to PO switch).

¶ Continuous infusion of PPIs should only be used for gastrointestinal bleeding.