

Drugs & Therapy

B ♦ U ♦ L ♦ L ♦ E ♦ T ♦ I ♦ N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met April 17, 2001. 4 drugs or dosage forms were added in the *Formulary* and no drugs were deleted. 3 of the drugs were added only for 6-month evaluations. 3 drugs also have limitations put on their use (ie, restrictions).

◆ ADDED

Botulin toxin type A
(**Botox®** by Allergan)*

Caspofungin
(**Cancidas®** by Merck)

Restricted: ID approval required*

Itraconazole intravenous
(**Sporanox®** by Ortho Biotech)
Restricted: ID approval required*

Thalidomide
(**Thalidomid®** by Celgene)
Restricted to registered prescribers

◆ DELETED

None

*added for a 6-month evaluation period

Botulinum toxin type A (BTX-A) is a purified pharmaceutical form of the neurotoxin from *Clostridium botulinum*. It is approved by the FDA for strabismus, blepharospasm, 7th-nerve disorders, and cervical dystonia. It is used extensively for off-labeled uses because of its prolonged neuromuscular blocking effects. The evidence to support these uses ranges in quality; however, there is reasonable evidence for some off-label uses.

There are 7 antigenically distinct strains of BTX, which are designated by the serotypes of A through G. All serotypes are similar and interfere with neural transmission
(continued on next page)

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 or the ordered drug, but it is a “therapeutic 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 non-formulary 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 particularly 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 nearly 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 constantly paging to have a new order written. Some institutions list only 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 way to notify the medical staff and nursing when an interchange occurs. This article will review the interchanges that are being done 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 and Progress Notes section of the chart. 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 Famotidine 20 mg IV BID to Ranitidine 50 mg IV Q 8 hrs”
“Authorized Therapeutic Interchange”
Signature of Pharmacist

There can be exceptions 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 overruled. Experience has shown that these situations are very rare.

The table on page 4 lists the therapeutic interchanges that are currently done at Shands at UF. When new drugs are added to the list, there is always a 1-month transition. 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 housestaff and other prescribers know the drug that is listed as the “class representative.” (continued on page 4)

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Formulary, from page 1

by blocking the release of acetylcholine, which is the main neurotransmitter at the neuromuscular junction. When synaptic transmission is blocked by BTX, muscles become clinically weak and atrophic. This blockage is irreversible and only “recovers” when new nerve terminals and synaptic contacts develop. This usually takes 2 to 3 months; however, it may be longer. BTX may also be useful for smooth muscle inhibition (eg, achalasia) or the inhibition of glandular function (eg, hyperhidrosis). There are data that suggest that units are not equivalent between different strains of BTX. A patient may develop antibodies to a serotype of BTX, which would cause that product to lose its effectiveness. A different strain of BTX may still be effective.

The dosage of BTX-A will vary, primarily based on the mass of the muscle that is to be affected. However, there is also considerable inter-patient variability in required dose. Lower doses may be needed in patients with pre-existing weakness, in women, and in smaller patients.

Local injections of BTX-A are associated with few serious adverse effects. For most patients these tend to be localized to the area of injection. Overweakening of muscles by too much BTX-A may occur or by inadvertent injection into adjacent areas. There have been rare reports of death, sometimes associated with dysphagia, pneumonia, and/or significant debility after treatment with BTX-A. There have also been rare reports of cardiovascular events including arrhythmias and myocardial infarctions, some with fatal outcomes—although the exact relationship with BTX-A use has not been established.

In the inpatient setting, most reimbursement schemes are not designed to compensate for the increased expense of BTX-A. In the Florida Surgical Center (FSC), where BTX-A has been used nonformulary for approximately 6 months, the reimbursement has been poor. Poor reimbursement rates may be improved by better coding or collection strategies. This is currently being investigated.

Restricting this product to just FSC was considered; however, there may be CMS patients who cannot be treated at FSC and who may need to be treated inpatient at Shands at UF. Botulinum toxin type A was added in the *Formulary* for a 6-month evaluation. At the end of this period, reimbursement and usage will be re-evaluated.

Caspofungin is the 1st antifungal approved in the US in the category of echinocandins. Caspofungin inhibits the fungal cell wall formation by inhibiting the glucan synthase enzyme. It has in vitro activity against *Aspergillus*, *Candida*, and other fungi. It also has activity against *Pneumocystis*.

There are limited published data on caspofungin. The labeled indication is for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (ie, amphotericin B, lipid formulations of amphotericin B, and/or itraconazole). It has not been studied as initial therapy for invasive aspergillosis.

◆

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most reimbursement
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toxin type-A.

There are limited data published about drug interactions, but caspofungin has been shown to decrease tacrolimus (ie, FK506) levels. Cyclosporine has been shown to decrease caspofungin levels. Some patients who have received caspofungin have experienced increased liver function tests (LFTs).

Caspofungin can only be used after the approval of the ID Service or in the Bone Marrow Transplant Unit. Criteria for use will have to be developed as more data become available; however, the only approved criteria will be for refractory aspergillosis in patients who are refractory to or intolerant of other therapies (ie, amphotericin B, lipid formulations of amphotericin B, and/or itraconazole). It may be difficult to define what “refractory to amphotericin B” means, but the ID Service will help with this determination. After 6-months, caspofungin’s formulary status will be re-considered and criteria for use will be finalized.

Itraconazole is a broad-spectrum azole antifungal. The oral dosage form has been listed in the *Formulary* for several years. The intravenous dosage form may be useful in some patients who are unable to take itraconazole orally.

Itraconazole is used for the treatment of blastomycosis, histoplasmosis, and aspergillosis in patients who are intolerant to or who are refractory to amphotericin B therapy. The Bone Marrow Transplant service uses intravenous itraconazole when patients

have persistent fevers on fluconazole prophylaxis. Amphotericin B is an alternative, but it has the risk of nephrotoxicity.

A major concern with itraconazole is drug interactions. Itraconazole inhibits the CYP 3A4 isoenzyme system in the liver. Other drugs metabolized by this enzyme system can have their metabolism dramatically decreased, which can result in dose-dependent toxicities. Safety is a major concern for this rarely needed dosage form. Therefore, the use of intravenous itraconazole will be restricted to use in patients who have been approved by the ID Service or to patients in the Bone Marrow Transplant Unit. After 6 months, the formulary status of injectable itraconazole will be re-evaluated. At that time, criteria for use will be finalized.

Thalidomide was approved in 1998 for the acute treatment, prevention, and suppression of the cutaneous manifestations of leprosy. It is also an orphan drug for severe aphthous stomatitis and recurrent aphthous ulcers in severely immunocompromised patients, HIV-associated wasting syndrome, primary brain malignancies, clinical manifestation of mycobacterial infections, and for the prevention and treatment of graft-versus-host disease. It has been used “off-label” at Shands at UF and is among the top nonformulary drugs used. When thalidomide was first approved, it could not be stocked by the hospital pharmacy; and, thus, was ineligible for formulary status. This policy was subsequently changed and the pharmacy may now stock this product.

Because of the risks of birth defects, which are well-known with thalidomide, patients must sign informed consent before it can be used. Institutions must register a patient before the drug can be dispensed. Pharmacies and physicians must also be registered before they can dispense and prescribe thalidomide.

Because there is sufficient evidence for the use of thalidomide in some patient populations (eg, resistant chronic graft-versus-host disease and multiple myeloma) and because of the complexity of the distribution system, it was added in the *Formulary* with a “restricted” status. It will be restricted to prescribers who are registered with the manufacturer to prescribe thalidomide. The complete policy for the distribution of thalidomide can be found on the intranet at <http://shands.org/pharm/pdf/06-05-46.pdf>

More problems with medication supply

As previously reviewed in the *Bulletin*, shortages can be caused by changes in production by a drug manufacturer, marketing decision, or increased use patterns for drug products. Changes in production can be caused by a shortage of raw materials, damage to a production plant, or, most often, quality control problems that cause the FDA to stop production. Voluntary or mandatory recalls can cause havoc when there are few and/or less desirable alternatives. An example of a marketing decision causing a shortage is when a manufacturer stops making a rarely used and unprofitable product. Increased use of a drug can cause a shortage when new information stimulates prescribing for a particular "new" indication. Production may not be able to meet this new demand.

When the word spreads that a critical drug is in short supply, matters worsen. Managing the natural tendency to "hoard" drugs in supply is a reason that the FDA has gotten involved in the issue of drug shortages.

The FDA only considers a drug shortage to exist when the drug is "medically necessary" and not when a patient inconvenience alone exists. Anyone can report a shortage to the FDA by calling (888) INFOFDA or (888) 463-6332. More information on the FDA's shortage program can be found on the Internet at www.fda.gov/cder/drug/shortages.

The FDA may take many different steps to help resolve a drug shortage. If the shortage was caused by a manufacturer's noncompliance with quality control standards, the FDA may weigh the risks of the "non-compliant" drug product with the risk of not having drug to treat a condition. They may facilitate the importation of a foreign source of a drug product when they can assure the foreign manufacturer meets adequate quality control standards.

The FDA (and some manufacturers) have tried to address the effect that hoarding has on shortages. The FDA encourages the establishment of limited access programs that only release drugs based on specified criteria. These criteria may be based on the amount that can be obtained at 1 time or based on the reason that the patient needs the drug.

Institutions, like Shands, often establish their own "rationing" program. The goal of rationing is to reserve the limited drug supply for the most crucial patients. Medical staff experts may be appointed to review the merits of different indications.

The following brief summary gives the status of some shortages that have had an impact on Shands at UF. Future articles in the *Bulletin* will give you updates as the situations change. However, you will receive most information on shortages by e-mail because it is more timely.

Thiamine Injection

There is a national shortage of thiamine injection. There is no alternative source. The shortage was supposed to last through the beginning of May—at the earliest. The very limited supply of injectable thiamine will be reserved for the prevention of Wernicke's encephalopathy in patients with altered mental status of unknown origin who cannot take oral thiamine. Thiamine tablets are readily available and should be used whenever possible. Oral tablets can be crushed and administered via NG tub or feeding tubes. Patients who only require maintenance vitamin therapy may receive oral thiamine or an injectable multivitamin. Multivitamin injection (MVI-12®) contains 3 mg of thiamine and most oral multivitamins have 1.5 mg thiamine.

Dexamethasone Injection

The shortage of injectable dexamethasone sodium phosphate injection has been caused by manufacturing difficulties. There is also a shortage of raw material caused by a switch from an animal protein source to a plant source. This process change requires regulatory approval. This shortage may last up to a year.

Whenever possible, oral dexamethasone should be used. There is no shortage of oral dexamethasone

Betamethasone Injection

The shortage of injectable betamethasone is reportedly caused by an

increased demand, which is at least partly caused by the dexamethasone shortage. It will be reserved for mothers in preterm labor to accelerate fetal lung maturity. Injectable methylprednisolone may be acceptable for some indications; however, this product is also currently in short supply.

Succinylcholine

Succinylcholine is on backorder because of increased demand and a delay in the supply of the raw material at the manufacturer. There is no projected date for the resolution of this shortage.

Succinylcholine is a short-acting neuromuscular blocking agent with a quick onset. It is especially valuable for emergent intubations. There is no neuromuscular blocking agent on the market with as quick an onset. Other agents also have a much longer duration of effect.

Isoproterenol Injection

As of February 27, 2001, the manufacturer has exhausted their emergency supply of isoproterenol injection. Injectable isoproterenol was especially valuable at Shands at UF for the treatment of post-transplant bradycardia and for diagnostic purposes in electrophysiology testing. There is no good substitute for this product.

Naloxone

The shortage of naloxone started when a manufacturer stopped making naloxone. The remaining manufacturers cannot meet the increased demand. The FDA recently approved a Canadian company (ie, Sabex Inc) to sell naloxone during this shortage. The Sabex naloxone contains methylparaben and propylparaben and cannot be used intrathecally.

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

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EDITOR,
DRUGS & THERAPY BULLETIN
Randy C. Hatton, PharmD

DIRECTOR,
PHARMACY SERVICES
Alan Knudsen, MS, RPh

CHAIRMAN,
PHARMACY & THERAPEUTICS
COMMITTEE

Ricardo Gonzalez-Rothi, MD

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Gainesville, FL 32610-0316

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Policies, from page 1

THERAPEUTIC INTERCHANGES 2001		
Drug Ordered	Drug Dispensed	Drug / Dosage Dispensed
Allegra®-D	Loratidine + Pseudoephedrine	Loratidine 10 mg qd + Pseudoephedrine 60 mg qid
Amino Acid (on TPN order)	Travasol 10%	
Claritin®-D Claritin®-D 24 hour	Loratidine + Pseudoephedrine	Loratidine 10 mg qd + Pseudoephedrine 60 mg qid
Dakins Solution	Oxycloresene	
Depakene (Valproic Acid)	Depakote	Same Dose
Docusate Calcium (Surfak®)	Docusate Sodium (Colace®)	Docusate Sodium 100 mg for: Docusate Calcium 240 mg
Famotidine (Pepcid®) Injection	Ranitidine Injection	Ranitidine 50 mg q8h for: Famotidine 20 mg q12h
Famotidine (Pepcid®) Oral Liquid	Ranitidine Oral Liquid	Ranitidine 150 mg bid for: Famotidine 20 mg bid
Famotidine (Pepcid®) Tablets Ranitidine (Zantac®) Tablets	Nizatidine (Axid®) Oral Capsule	Nizatidine 150 mg bid for: Ranitidine 150 mg bid Famotidine 20 mg bid
Fat (on TPN order)	Intralipid® 10%, 20%	
Fexofenadine (Allegra®) Cetirizine (Zyrtec®)	Loratidine	Loratidine 10 mg qd for: Fexofenadine 30 mg qd Fexofenadine 60 mg qd Fexofenadine 180 mg qd Fexofenadine 30 mg bid Fexofenadine 60 mg bid Cetirizine 5 mg qd Cetirizine 10 mg qd Loratidine 5 mg qd for: Cetirizine 2.5 mg qd
Granisetron (Kytrel®) Dolasetron (Anzemet®)	Ondansetron	Ondansetron 8 mg q12h for: Granisetron 1 mg q12h Granisetron 2 mg q12h Dolasetron 50 mg Dolasetron 100 mg
Hydroxyzine, Hydrochloride or Pamoate	Hydroxyzine	Same Dose
Lansoprazole (Prevacid®) Capsule Omeprazole (Prilosec®) Capsule Rabeprazole (AcipHex®) Tablet	Pantoprazole Tablet	Pantoprazole 40 mg qd for: Omeprazole 10 mg, 20 mg, or 40 mg qd Omeprazole 20 mg bid Lansoprazole 15 mg or 30 mg qd Lansoprazole 15 mg bid Rabeprazole 20 mg or 40 mg qd Pantoprazole 40 mg bid for: Omeprazole 40 mg bid Lansoprazole 30 mg bid
Micro-K®	K-Dur®	K-Dur® 10 meq for: Micro K 8 meq
MS Contin®	Oramorph®	Same Dose
Mylanta®, Maalox®, Gelusil®	Maalox® TC	Maalox® TC 15 mL for: Mylanta®, Maalox®, Gelusil® 30 mL
Nafcillin or Methicillin	Oxacillin	Same Dose
TPN order for patient 11yrs of age or older	MVI-12 Vitamin Infusion	
TPN order for infant weighing 3.5kg or less	MVI-Pediatric 3.3 mL	
TPN order for infant weighing >3.5kg & < 11yrs old	MVI-Pediatric 5 mL	