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B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met January 21, 2003. 7 drugs or dosage forms were added in the *Formulary*. 2 drugs were deleted and 2 drugs were designated not available.

◆ ADDED

Hydrocortisone suppositories (generic)

Niacin ER (Niaspan® by KOS)

Opium Tincture (generic)*

*Restricted to Pharmacy Administrative Approval

Secretin (SecreFlo® by ChiRhoClin, Inc.)

Sildenafil (Viagra® by Pfizer)

Urokinase (Abbokinase® by Abbott)**

**Cannot be used for catheter clearance

Ziprasidone intramuscular (Geodon® IM by Pfizer)***

***Restricted to Psychiatric Unit & Emergency Department)

◆ DELETED

Liposomal Daunorubicin (DaunoXome® by Gilead)

Milk of Magnesia with Cascara (generic)

◆ NONFORMULARY AND NOT AVAILABLE

Amoxicillin-Clavulanate (Augmentin® XR by Glaxo SmithKline)

Insulin lispro-Insulin lispro protamine (Humalog® Mix 75/25 by Eli Lilly)

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NEWS

New drugs approved in 2002

There were fewer new drugs approved by the FDA in 2002 compared to historical standards. The 17 new molecular entities (NMEs) approved in 2002 was the lowest total since 1983 when only 14 NMEs were approved *(see Table on page 4)*. Last year, 24 NMEs were approved, while between 20 and 30 NMEs has been typical.

The decrease in NMEs last year is attributed to a low number of submissions by pharmaceutical companies. FDA rejections or deferrals do not explain the decrease.

In 2002, the FDA approved 48 first-time generic ingredients, which was a large increase from the 17 approved in 2001.

It is expected that 2003 will rebound to historic levels based on the number of new drug applications that have been filed and deadlines for review that the FDA must meet. For example, 4 new drugs for the treatment of patients infected with HIV (ie, atazanavir, fosamprenavir, emtricitabine, and enfuvirtide) are anticipated — 2 of these agents are protease inhibitors (ie, atazanavir and fosamprenavir), 1 a nucleoside reverse transcriptase inhibitor (ie, emtricitabine [Coviracil®]), and the first in a new category of drugs called fusion inhibitors (ie, enfuvirtide [Fuzeon®]). Other new drugs that may be approved in 2003 include duloxetine (Cymbalta®) for depression, rosuvastatin (Crestor®) for hyperlipidemia, tadalafil (Cialis®) for erectile dysfunction, telithromycin (Ketek®) an antibiotic for respiratory infections, and vardenafil (Levitra®) for erectile dysfunction. Most of the new drugs in 2003 are anticipated in the second half of the year.

The number of new biologicals (ie, biological license applications or BLAs) continues to increase. The table includes some of the significant new biologicals that were approved in 2002. It is anticipated that more BLAs will be approved each year based on the "drugs" in the pipeline and the trends of the last few years.

Biologicals that may be approved in 2003 include agalsidase alfa (Replagal®) for Fabry's disease, agalsidase beta (Fabrazyme®) for Fabry's disease, efalizumab (Raptiva®) for psoriasis, laronidase (Aldurazyme®) for mucopolysaccharidosis, and tositumomab (Bexxar®) for non-Hodgkin's lymphoma.

The number of generics approved in 2002 was significantly increased. The FDA approved 48 first-time generic ingredients, which was a large increase from the 17 approved in 2001. These approvals can provide some relief to patients who pay for their prescriptions "out of their pockets" and will decrease co-pays for patients with insurance coverage. In 2000, the average price of a brand name drug was over $72, while the average price of a generic drug was less than $17 — a more than 4-fold difference in price. The price of most generic products drops 70% once the second generic version is marketed. Because the first generic gets a short period of exclusivity, the price usually takes a few months to reach the eventual market price.

Important generics approved in 2002 include metformin (equivalent to Glucophage® for type 2 diabetes), isotretinoin (equivalent to Accutane® for acne), and amoxicillin-clavulanate (equivalent to Augmentin®). Generic omeprazole

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INSIDE THIS ISSUE

Formulary update, *from page 1*

Hydrocortisone suppositories are used for inflamed hemorrhoids, proctitis, pruritus ani, and other inflammatory conditions of the anorectum. The primary active ingredient of hemorrhoidal suppositories with hydrocortisone is hydrocortisone. Regular hemorrhoidal suppositories only contain emollients (eg, vegetable oil or starch).

Generic hydrocortisone suppositories will be automatically interchanged for orders for Anusol® HC, which also contains 25 mg of hydrocortisone. They will also be interchanged for any order for hydrocortisone-containing hemorrhoidal suppositories. This automatic interchange of any order for a hemorrhoidal suppository with hydrocortisone will be documented as an authorized P&T Committee interchange.

Hydrocortisone is a corticosteroid, which must be considered. The typical dosage is 1 suppository in the morning and at night. This is a low dosage (ie, 25 mg BID), but there is some systemic absorption of hydrocortisone. Systemic effects are, therefore, possible. Higher dosges have been used (eg, 1 TID or 2 BID). Therapy is usually limited to 2 weeks, but up to 8 weeks of use has been reported for proctitis.

Niacin extended-release (ER) is a commonly dispensed nonformulary drug at Shands at UF. Niacin is vitamin B3. It is popular in the ambulatory setting for the treatment of hyperlipidemias. Immediate-release niacin has been listed in the *Formulary*, but it is associated with a high incidence of common adverse effects (eg, flushing).

The National Cholesterol Education Program (NCEP) guidelines on detection, evaluation, and treatment of high blood cholesterol in adults list niacin (including extended-release niacin) as a treatment option for hypercholesterolemia. Many studies, as well as the NCEP guidelines, support the use of immediate-release (IR) niacin in the treatment of hyperlipidemia. Niacin lowers LDL-cholesterol, but not as much as HMG-CoA reductase inhibitors (eg, atorvastatin or simvastatin). Niacin also lowers triglycerides and increases HDL-cholesterol.

The use of IR niacin is limited due to the frequent occurrence of cutaneous flushing and itching. A published study comparing IR niacin to Niaspan® demonstrated a lower number of flushing events experienced per patient per month with Niaspan®. Another limitation of the use of IR niacin is the need to administer it 2 or 3 times daily.

Extended-release niacin does cause flushing and itching. These reactions may decrease with continued use. Taking an aspirin 30 minutes before a dose can reduce the incidence of flushing. Taking the dose with a low-fat snack at bedtime will reduce gastrointestinal distress. The starting dosage for niacin ER is 500 mg a day. This dosage must be increased slowly. The typical maintenance dosage is 1000 mg to 2000 mg per day.

Extended-release niacin has been associated with liver dysfunction. Liver dysfunction is usually reversible if niacin is stopped. Thus, liver function tests should be monitored. Niacin should be used with caution in patients who consume substantial quantities of alcohol or who have a past history of liver disease.

Elevations in creatine kinase, creatine phosphokinase (CPK), and myopathy have been reported in patients receiving niacin alone or in combination with other drugs used to treat hypercholesterolemia. Rare cases of rhabdomyolysis have been reported with higher dosages of niacin in combination with HMG-CoA reductase inhibitors. Periodic CPK monitoring should be considered.

Opium tincture is a potent form of oral opium (ie, anhydrous morphine) that is only used to treat patients with resistant chronic diarrhea. Many institutions have made opium tincture nonformulary and not available in order to prevent medication errors and confusion with camphorated opium tincture (Paregoric®). However, there are a small number of patients who may benefit from opium tincture at Shands at UF. Rather than have opium tincture remain nonformulary, the P&T Committee decided that it would be safer if opium tincture was added in the *Formulary* with appropriate restrictions on its use to prevent medication errors.

Opium tincture will be dispensed only after the approval of a pharmacy administrator. The pharmacy administrator on-call, working collaboratively with pharmacists, will verify the intended product from the prescriber. The following questions will be used since this product could be dangerous to the patient if the wrong drug is selected. "Are you sure you want tincture of opium instead of Paregoric®?" "Do you know that tincture of opium contains 25 times the opium content as Paregoric®?" "Has the patient failed Paregoric®?"

Tincture of opium will never be placed into a SureMed® cabinet without a pharmacy administrator on-call's approval and it will not be placed as an override medication in Sure-Med®. The nurse manager will be notified if a patient on the nursing unit is on tincture of opium. Once a patient is discharged from the hospital, pharmacy personnel will be responsible for removal of the drug from the SureMed® cabinet. Bright orange warning labels will be placed on all tincture of opium oral syringes that warn that the syringe contains "highly concentrated morphine."

Secretin was re-added in the *Formulary* when the FDA recently approved a synthetic secretin. Porcine secretin was deleted from the *Formulary* in August 2001 after the manufacturer stopped making it. Synthetic secretin has a labeled indication as a diagnostic aid in the location and cannulation of pancreatic ducts in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP).

Since secretin was deleted only because it was removed from the market, it is usually the standard that these agents be added back into the *Formulary*. Of course, if market conditions change (eg, other alternatives are now used), the need for re-addition will be evaluated.

Sildenafil is a phosphodiesterase inhibitor that was originally developed as a vasodilator for use in the treatment of hypertension and angina. Clinical trials did not show efficacy for these indications, but sildenafil was eventually approved for use in the treatment of erectile dysfunction. Sildenafil was evaluated for formulary addition based on its high nonformulary use to treat pulmonary hypertension.

There are small studies and case reports supporting the use of sildenafil for primary and secondary hypertension to decrease mean arterial pressures. There are limited safety data for this off-labeled use. There are also limited options for the treatment of pulmonary hypertension. Based on the severity of the disease and the few options available, sildenafil was added in the *Formulary* as another oral option in the management of pulmonary hypertension.

There is no established dosage for the use of sildenafil for the treatment of pulmonary hypertension. Dosages of 25 to 50 mg 2 or 3 times a day are usually used. The dosage is titrated to the desired effect. A dosage as high as 100 mg 5 times a day has been reported. Doses of 0.3 mg/kg have been reported in pediatric case reports.

Because of the potential for diversion, sildenafil will be handled like a controlled substance.

Urokinase, a thrombolytic used intravenously to dissolve arterial

thrombi and clear occluded catheters, was removed from the *Formulary* in August 2000 when it was no longer available from its manufacturer. In 1999, the FDA issued a warning concerning a possible risk of transmitting infectious agents because of the manufacturing process. It was subsequently removed from the market.

In October 2002, Abbott re-released urokinase with a labeled indication for the lysis of pulmonary emboli. Although urokinase was widely used for catheter clearance before it was removed from the market, alteplase has replaced urokinase for this use. Alteplase is now more cost effective for catheter clearance.

Because urokinase was removed from the *Formulary* only because of lack of availability, it was re-added. There is considerable literature in the area of the lysis of arterial thrombi. Urokinase was designated nonformulary and not available for catheter clearance.

Ziprasidone is an atypical antipsychotic. Like other atypical antipsychotics, ziprasidone is supposed to have increased effectiveness against the negative symptoms of schizophrenia and decrease the risk of extrapyramidal adverse effects. Ziprasidone's low H1-receptor affinity is the theory for the decreased weight gain for ziprasidone compared with other atypical antipsychotics.

There are still no good head-to-head trials that compare oral ziprasidone with other atypical antipsychotics. There are no new clinical data to support the use of ziprasidone over other atypical antipsychotics (eg, olanzapine, risperidone). Therefore, oral ziprasidone remains nonformulary.

Intramuscular ziprasidone is the first injectable atypical antipsychotic. There are no published data on the intravenous use of ziprasidone. Also, there are no data on the use of ziprasidone for agitation in critical care or other medical settings besides acute agitation in schizophrenic patients.

There is 1 clinical trial that compares IM ziprasidone with IM haloperidol in the treatment of acute psychosis. This study found statistically improved agitation scales with IM ziprasidone compared with haloperidol. The results of this study are limited, however, by its open-label study design and subjective outcome variables. Ziprasidone caused less extrapyramidal adverse effects, but it caused more nausea.

IM ziprasidone costs 10 times more than injectable haloperidol.

Although the data are limited, injectable ziprasidone is currently the only injectable atypical antipsychotic. Therefore, injectable ziprasidone was added for a 12-month evaluation period (or less if new data become available) and restricted to use in the Psychiatric Unit or Emergency Department. Patients at risk for QT prolongation should not receive ziprasidone.

There is an important warning about the potential for medications errors with injectable ziprasidone. Although the label states that the concentration of a vial is 20 mg per mL after reconstitution with 1.2 mL of sterile water for injection, neither the label nor the package insert mentions that this creates a total volume of 1.5 mL (30 mg). It is important for staff to measure the dose based upon the 20-mg/mL concentration, and not to draw up the total contents of the vial for a 20-mg dose.

Liposomal daunorubicin was added in the *Formulary* in April 2002, but restricted to use only in an experimental protocol for acute myelocytic leukemia (ie, ECOG protocol 4999). This protocol has been closed. Therefore, liposomal daunorubicin was deleted from the *Formulary*.

Milk of magnesia with cascara was deleted after the FDA mandated the removal of cascara-containing laxatives from the market. This product was not used at Shands and its listing in the *Formulary* was a vestige of years gone by.

The FDA found that cascara is not generally recognized as safe and effective and is, therefore, misbranded. Milk of magnesia (MOM) with cascara was the only product listed in the *Formulary* containing cascara. Other stimulant laxatives are available.

Augmentin® XR is a combination of amoxicillin and clavulanic acid in a dosage form designed to allow for immediate release of amoxicillin and clavulanate and an extended release of amoxicillin. This dosage form was designed to prolong the time that bacteria are exposed to amoxicillin. Clavulanate protects amoxicillin from degradation by beta-lactamases. Augmentin® XR is given twice a day. The ultimate goal was to increase activity against *Streptococcus pneumoniae*.

Augmentin® tablets are listed in the *Formulary*. These tablets contain 875 mg of amoxicillin compared with 1000 mg in the XR-formulation. These differences could lead to confusion and medication errors.

Based on the currently available data and the possibility for confusion with multiple products, the Anti-Infective Subcommittee recommended that Augmentin® XR be designated nonformulary and not available.

Humalog mix is a mixture of insulin lispro and insulin lispro protamine suspension. This is a combination of a short-acting insulin with a rapid-onset (insulin lispro) and a longer-acting insulin product (insulin lispro protamine). Like any dosage form of insulin lispro, it is nonformulary and not available.

There have been incidences where a combination drug containing a nonformulary and not available product has been requested nonformulary. It was not clear whether these products were also "not available." The P&T Committee re-affirmed that these combination products should also be listed as "not available."

Prescribers are encouraged to re-assess their patients' insulin requirements if patients are hospitalized. Patients' diets frequently change. Changes in diabetic patients' caloric intake usually require modifications in their insulin dosing.

News, *from page 1*
also was marketed in 2002, although the FDA approved the first generic version of omeprazole in 2001. Patent litigation continues to delay the marketing of first-time generic ingredients making it difficult to predict when generics will be marketed after a brand name drug's patent has expired.

The marketing of generic loratadine was delayed when over-the-counter versions (eg, Alavert®) were approved in December. It is anticipated that OTC versions of other nonsedating antihistamines will eventually follow. Many patients' insurance plans have moved nonsedating antihistamines to the highest co-pays. Therefore, OTC loratadine is less expensive than the out-of-pocket cost for prescription nonsedating antihistamines and less expensive than the co-pays for nonsedating antihistamines for many insured patients.

Important generics that may be marketed in 2003 include ciprofloxacin (equivalent to Cipro®), a generic equivalent to the birth control pill Ortho Tri-Cyclen®, paroxetine (equivalent to Paxil®), gabapentin (equivalent to Neurontin®), mirtazapine (equivalent to Remeron®), and tamoxifen (equivalent to Nolvadex®). The unpredictability of the legal system makes these approvals uncertain, however.

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NEW DRUGS & SELECTED BIOLOGICS APPROVED BY FDA IN 2002

GENERIC NAME	TRADE NAME	INDICATION
Adefovir dipivoxil	Hepsera®	Chronic hepatitis B
Adalimumab‡	Humira®	Rheumatoid arthritis
Alpha-1 Proteinase Inhibitor‡	Aralast®	Alpha-1 proteinase deficiency & emphysema
Aripiprazole	Abilify®	Schizophrenia
Atomoxetine	Strattera®	Attention-deficit hyperactivity disorder
Diptheria, Tetanus Toxoid, Acellular Pertussis, Hepatitis B, & Inactivated Poliovirus Vaccine‡	Pediarix®	Combination vaccine
Eletriptan	Relpax®	Migraine (acute)
Eplerenone	Inspra®	Hypertension
Ezetimibe	Zetia®	Familial hypercholesterolemia and sitosterolemia
Fulvestrant	Faslodex®	Cancer: estrogen receptor-positive metastatic breast cancer
Icodextrin	Extraneal®	Peritoneal dialysis
Ibritumomab tiuxetan‡	Zevalin®	B-cell non-Hodgkin's lymphoma
Nitazoxanide	Alinia®	Diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia*
Nitisinone	Orfadin®	Hereditary tyrosinemia
Olmesartan medoxomil	Benicar®	Hypertension
Oxaliplatin	Eloxatin®	Cancer: recurrent or refractory metastatic carcinoma of the colon or rectum
Pegfilgrastim‡	Neulasta®	Neutropenia
Peginterferon alfa-2a‡	PEGASYS®	Chronic hepatitis C
Perflexane lipid microspheres	Imagent®	Diagnostic: suboptimal echocardiograms
Rasburicase†‡	Elitek®	Tumor lysis syndrome
Secretin†‡	SecreFlo®	Diagnostic: pancreatic dysfunction & gastrinoma
Sodium oxybate	Xyrem®	Cataplexy associated with narcolepsy
Tegaserod	Zelnorm®	Short-term treatment of women with constipation-predominant irritable bowel syndrome
Treprostinil	Remodulin®	Pulmonary hypertension
Voriconazole†	Vfend®	Antifungal
Ziprasidone Mesylate†	Geodon® IM	Acute agitation in schizophrenia

†Listed in the Shands UF *Formulary*
‡Biological