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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met January 16, 2007. 1 drug was added in the *Formulary*, and 5 drugs were deleted. 3 drugs were designated nonformulary and not available. 3 interchanges were approved.

◆ ADDED

Morphine Extended-release (generic version of MS-Contin®)*

**Automatic interchange for Oramorph® at same dosage*

◆ DELETED

Amprenavir (Agenerase® by GlaxoSmithKline)†

Benzylpenicilloyl-Polylysine Skin Test (Pre-Pen® by Hollister Stier)†

Histamine Skin Tests (compounded)

Immune Globulin, Intravenous (Gammagard® S/D by Baxter)‡

Morphine Extended-release (Oramorph® by Xanodyne Pharmaceutical)*

†No longer manufactured; nonformulary and not available

‡High-priority Nonformulary Drug; Available only via a limited distribution program

**Nonformulary and not available; generic version of MS-Contin® automatically interchanged*

◆ INTERCHANGES

Levetiracetam Oral (Keppra®) for **Levetiracetam IV** (Keppra® IV)§

Lisinopril (generic) for **Benazepril** (generic)**

MS Contin® (generic) for **Oramorph®** (Xanodyne Pharmaceutical)**

§IV to PO switch approved

***Same milligram dosage*

(continued on next page)

NEWS

New drugs approved in 2006

Again in 2006, the number of new drugs approved by FDA was very low. Only 18 new drugs (ie, new molecular entities or NMEs) were approved in 2006 *(see table on page 4)*. The most new drugs approved in 1 year occurred 10 years ago in 1996 when 53 new drugs were approved. The 18 new drugs approved this year is consistent with a downward trend since the 1996 peak. Several new biological "drugs" were approved. For completeness, the table includes selected new biologicals, new combination drugs (Atripla®), and dosage forms (Vivitrol®).

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Experts predict the number of new drugs approved each year will remain low over the next few years. The decrease is attributed to the relative poor success of the research "pipelines" of pharmaceutical companies. For example, the recent failures of drugs in the late stages of development (eg, torceptrapib, the drug intended to increase HDL cholesterol) contribute to the relative low numbers of new drug approvals. It is interesting that the number of approvals has decreased dramatically since drug safety concerns increased after the rofecoxib (Vioxx®) withdrawal from the market.

New drugs used to treat or prevent cancer led approvals with 5 new products. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), the major brand name pharmaceutical trade organization, there are more drugs in the pipeline for cancer than any other indication. There were no other obvious trends noticed and many different indications were approved for the small number of drugs approved. Several of the drugs approved were for very rare diseases that occur in small numbers of patients (eg, Pompe Disease and Hunter Syndrome).

However, 2006 was another big year for first-time generic approvals. Generic versions of brand name drugs continue for be marketed as patents expire. Many third-party payers, including Medicare Part D plans, encourage the use of generics by assessing much lower co-pays for patients.

Important first-time generic version of brand name drugs were approved in 2006, including generic versions of Flonase® (fluticasone propionate nasal spray), Glucophage® XL (metformin ER), Luvox® (fluvoxamine), Mavik® (trandolapril), Mobic® (meloxicam), Novantrone® (mitoxantrone), Omnicef® (cefdinir), Paraplatin® (carboplatin), Pravachol® (pravastatin), Zocor® (simvastatin), Zofran® (ondansetron), and Zoloft® (sertraline).

The growing arsenal of generics makes it easier to find a less expensive option in many therapeutic categories. In general, patients pay less for generics. After generics have been on the market for several months, the cost to health systems can drop by as much as 70% or more.

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INSIDE THIS ISSUE

Formulary update, *from page 1*

Oral morphine extended-release products are commonly used for the treatment of chronic moderate to severe pain. **MS Contin®** and **Oramorph®** have been interchanged at Shands at UF for more than 10 years. Although the pharmacokinetics of these products are not identical, they are close enough that they provide the same pain-relief effects.

Oramorph® has been the product listed in the *Formulary* and has been automatically interchanged for MS Contin®. Because MS Contin® is now available as generic versions, it is now less expensive. Thus, a generic version of MS Contin®, made by Mallinckrodt, will now be dispensed for orders for Oramorph® or MS Contin®.

Amprenavir is a protease inhibitor that has been used to treat patients infected with human immunodeficiency virus (HIV). The manufacturers of Agenerase® will no longer be making this product due to decreased demand.

Fosamprenavir (Lexiva®), the calcium phosphate ester prodrug of amprenavir, has made amprenavir obsolete. Fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir and inorganic phosphate by cellular phosphatases in the gut epithelium as it is absorbed. This agent is more soluble in water than amprenavir, allowing patients to take fewer dosage forms per day and still achieving the same results as with amprenavir. Fosamprenavir is available as a 700-mg tablet and, therefore, reduces the "pill" burden to, at most, 2 tablets twice daily. Since this agent is converted in the body to amprenavir, the adverse effect profile is no different than the parent compound. Fosamprenavir was added in the *Formulary* in May 2004.

Pre-Pen® was a **benzylpenicilloyl-polylysine skin test** used in the diagnosis of penicillin allergy. It is no longer commercially available, presumably because of insufficient demand. It was deleted from the *Formulary* and designated not available because all commercial supplies have been exhausted.

A manufacturer (ie, AllerQuest) has acquired the rights to produce benzylpenicilloyl-polylysine skin tests and it could be re-marketed as soon as the second quarter of 2007. It would likely be re-added in the *Formulary,* if it is re-marketed.

Penicillin allergy skin testing can still be performed; however, a penicillin skin test solution must be compounded. Please consult the Allergy and Immunology Service for additional information.

Histamine skin tests have been used as controls to document that patients can mount reactions to skin tests, like penicillin. These products are no longer being used in the inpatient setting and were deleted from the *Formulary.*

Gammagard® S/D is the brand of **intravenous immune globulin** (IVIG) that is known for having the lowest concentration of IgA contaminant. This is important because some patients, particularly those who must take repeated doses of IVIG to get IgG (eg, patients with primary immunodeficiency disease), develop sensitivity to IgA. In order to minimize the risk of reaction to IgA, these patients receive the product with the lowest amount of IgA (ie, Gammagard® S/D).

Baxter, the manufacturer of Gammagard® S/D, has placed it in a limited distribution program (http://www.immunedisease.com/US/therapies/gammagard/index.html) in order to reserve the limited supply of product for those patients who have a documented sensitivity to IgA (eg, IgA level less than or equal to 5 mg/dL, laboratory result indicating the presence of anti-IgA antibody, or history of anaphylactic shock or anaphylactoid reaction to IVIG with higher IgA content). Since Gammagard® S/D cannot be stocked, it cannot be listed in the *Formulary.* Thus, it was deleted from the *Formulary,* but designated a high-priority nonformulary drug so that a pharmacist will contact the prescriber immediately to facilitate inpatient use of drug from the limited-distribution system—assuming the patient qualifies to receive product.

In order to qualify patients for the limited supply of Gammagard® S/D, prescribers will have to submit patient-specific information to Baxter. Forms are available on the Internet at: http://www.immunedisease.com/US/pdfs/Low_IgAQA_and_Application_FINAL102006.pdf.

Levetiracetam is a novel anticonvulsant that is chemically unrelated to other drugs. It has a labeled indication as adjunctive therapy in the treatment of patients with partial onset seizures; however, it has been used for various other off-labeled uses. The published data on the off-labeled use of levetiracetam are limited. Levetiracetam may offer an alternative for patients with seizure disorders who have not responded to other therapies.

Because levetiracetam is not metabolized by the cytochrome P450 (CYP) system, drug interactions are not anticipated to be as critical as with other anticonvulsants. Like with other anticonvulsants, CNS adverse effects (eg, somnolence, fatigue, coordination difficulties, and behavioral abnormalities) should be expected.

Levetiracetam injection was added in the *Formulary* in September 2005 as a line-item extension for oral levetiracetam. The injectable dosage form is used when oral administration is temporarily not feasible. Since there is little evidence to support off-labeled uses of injectable levetiracetam, the off-labeled use of levetiracetam injection was monitored.

Since the use of injectable levetiracetam has been extensive, a plan has been approved to automatically convert intravenous (IV) levetiracetam to oral or enteral (PO) levetiracetam based on its 100% bioavailability and the availability of an oral liquid. The criterion for switching follows our current criteria for IV to PO conversions.

Some experts feel that intravenous antiepileptic drugs have been shown to be superior to oral administration in the treatment of convulsive and nonconvulsive status epilepticus/seizure clusters. There are also theoretical concerns that actively seizing patients may have alterations of gastrointestinal absorption, which could result in lower-than-anticipated levels. There currently is no published evidence to support these concerns.

The majority of IV levetiracetam use is off-labeled for patients who are not actively seizing (eg, prophylaxis), and the logistics of IV to PO conversion will not likely affect patients who are actively seizing. However, concerned prescribers can order IV levetiracetam with the stipulation "do not convert to oral administration" and these patients will not be converted by the IV-to-PO policy.

Benazepril and **lisinopril** are angiotensin-converting enzyme (ACE) inhibitors that have both been on the market for many years. Both are available as generics.

In August 2003, lisinopril was designated the preferred once-daily ACE inhibitor listed in the *Formulary* and several other ACE inhibitors (ie, benazepril, fosinopril, moexepril, perindopril, quinapril, and trandolapril) were designated nonformulary and not available. This required pharmacists to contact the prescriber to get a new order for lisinopril to replace the ACE inhibitor that the patient was admitted taking.

The P&T Committee approved an automatic interchange that will switch patients receiving benazepril to lisinopril. The dose and dosage interval are the same. This interchange will be documented in the Orders and Progress Notes sections of the chart. There will be notification of the interchange in the Medication Administration Record (MAR) and on the Medication Reconciliation Report. Prescribers should consider re-prescribing the benazepril upon discharge to prevent therapeutic duplication when the patient resumes their home medications after discharge.

POLICIES AND PROCEDURES

Therapeutic interchange — 2007

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 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 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.

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 overruled. 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. Often 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."

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.

There is concern that patients getting switched to a different drug during their hospitalization will be discharged on the new drug, then resume their old medication, resulting in therapeutic duplication and possible adverse effects. Prescribers must take this into consideration during the medication reconciliation process. When an interchange occurs, it is noted on the Medication Reconciliation Report and the medication administration record (MAR). Often, it is best to switch patients back to the medication they were admitted on, which may be preferred by the patient's third-party payor.

SHORTAGES

Albumin and IVIG shortages expected in 2007

Shortages of pharmaceuticals have, unfortunately, become a way of life for institutional practitioners. The reasons for shortages are multifactorial, which makes solving these shortages a challenge.

Albumin and intravenous immune globulins (IVIGs) are expected to have major shortages in 2007. When this will occur is difficult to project. We do expect that a shortage of albumin will happen first, and an IVIG shortage is likely. There will most likely be times when we will not be able to supply either product to patients who should reasonably receive these therapies. This will occur near the end of the month based on the way these products are being rationed.

Both albumin and IVIGs are on allocations. At the beginning of each month Shands at UF receives a supply of albumin and IVIG. As the month progresses the supplies dwindle. If indiscriminant use occurs early in the month, chances are that "needier" patients will not receive treatment later in the month. The rationing of pharmaceuticals is never popular; however, it is more acceptable when it is based on perceived need and limited supply.

Both albumin and IVIGs are products of blood donations. Blood products come from both voluntary and paid donors. After red blood cells are harvested, the remaining plasma is used to create several products with albumin and IVIGs being 2 of the most commonly used products.

Because of financial incentives, manufacturers have become more efficient at harvesting IVIGs from donated blood. This results in less albumin per unit of donated blood. This cuts the albumin supply.

Because the price of albumin has been low over the last few years, many companies and their donation centers have gotten out of the albumin business. This has now created a severe albumin shortage nationwide. As the shortage gets more severe, the price of albumin is expected to increase. However, it is easier to get out of the business than to get into the business; therefore, the shortage is not anticipated to be resolved soon.

The only short-term solution for the albumin shortage is to ration its use to the most critical indications. This is always controversial and always difficult to do. However, prescribers must make these difficult choices. More crystalloid will need to be tried. Alternative colloids (eg, hetastarch in lactated ringers [Hextend®]) will need to be used. There will be a concerted effort to try to facilitate rational albumin use.

A similar effort will be initiated for IVIG use. In addition to decreasing supply, demand for labeled and off-labeled uses of IVIGs continues to increase. IVIG is a shortage that is being driven by increasing demand and decreasing supply. Again, rationing IVIGs may also be needed in 2007.

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NEW DRUGS & SELECTED BIOLOGICALS APPROVED BY THE FDA IN 2006

GENERIC NAME	TRADE NAME	INDICATION
Alglucosidase alfa†‡	Myozyme®	Pompe Disease
Anidulafungin	Eraxis®	Antifungal
Avobenzone; **Ecamsule; Octocrylene**	Anthelios® SX	Sunburn prevention
Biskalcitrate; Metronidazole; Tetracycline hydrochloride	Pylera®	*Helicobacter pylori* infection
Ciclesonide nasal spray	Omnaris®	Seasonal Allergic Rhinitis
Darunavir‡	Prezista®	HIV Infection
Dasatinib*‡	Sprycel®	Cancer: Chronic Myeloid Leukemia
Decitabine	Dacogen®	Myelodysplastic Syndrome
Efavirenz; Emtricitabine; Tenofovir disoproxil fumarate§	Atripla®	HIV infection
Herpes Zoster Virus Vaccine†	Zostavax®	Prevention of Shingles
Idursulfase†‡	Elaprase®	Hunter Syndrome
Kunecatechins	Veregen®	Genital and Perianal Warts
Lubiprostone	Amitiza®	Chronic idiopathic constipation
Naltrexone injection§	Vivitrol®	Alcohol Dependence
Paliperidone	Invega®	Schizophrenia
Panitumumab†‡	Vectibix®	Cancer: Colorectal Cancer
Papillomavirus Vaccine†	Gardasil®	Cancer: Prevention of Cervical Cancer
Posaconazole*‡	Noxafil®	Antifungal
Ranibizumab†‡	Lucentis®	Macular Degeneration
Ranolazine	Ranexa®	Chronic Angina
Rasagiline mesylate	Azilect®	Parkinson's Disease
Rotavirus Vaccine†	Rotateq®	Prevention of gastroenteritis
Sitagliptin phosphate	Januvia®	Diabetes Mellitus
Sunitinib malate‡	Sutent®	Cancer: Gastrointestinal stromal tumor
Telbivudine	Tyzeka®	Chronic Hepatitis B
Varenicline*‡	Chantix®	Smoking cessation
Vorinostat‡	Zolinza®	Cancer: Cutaneous T-Cell Lymphoma

18 New Molecular Entities (NMEs) shown in bold
*Listed in the Shands at UF *Formulary*
†Biological
‡Priority Review
§New dosage form or combination of previously approved drugs