

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met January 17, 2006. 3 products were added in the *Formulary* and 3 were deleted. 4 products were designated nonformulary and not available, and 1 was evaluated, but not added in the *Formulary*.

◆ ADDED

Buprenorphine Sublingual
(Subutex[®] by Reckitt Benckiser)*

Iloprost (Ventavis[®] by CoTherix)**

Lopinavir + Ritonavir Tablets
(Kaletra[®] Tablets by Abbott)

*Restricted to Shands Vista

**Restricted to patients approved for the limited distribution program.

◆ DELETED

Dextran-1 (Promit[®] by Akorn)

Lopinavir + Ritonavir Capsules
(Kaletra[®] Capsules by Abbott)***

Thiabendazole
(Mintezol[®] by Merck)

***Nonformulary and Not Available

◆ NONFORMULARY AND NOT AVAILABLE

Buprenorphine Injection
(Buprenex[®] by Reckitt Benckiser)

Buprenorphine + Naloxone Sublingual
(Suboxone[®] by Reckitt Benckiser)

Ketorolac Tablets (generic)

◆ EVALUATED, BUT NOT ADDED

Paricalcitol Capsules
(Zemiplar[®] Capsules by Abbott)

Buprenorphine sublingual tablets were added in the *Formulary*, but restricted to use at Shands Vista for the treatment of opioid detoxification, opioid maintenance, and for the off-labeled treatment of chronic pain in patients who are opioid-

(continued on next page)

POLICIES AND PROCEDURES

Standardized fentanyl concentrations

Intravenous fentanyl infusions will now be available in only 2 concentrations for adult patients. The standard fentanyl concentration will be 10 mcg/mL, which will be used for most patients. A more concentrated solution of 50 mcg/mL will also be available for patients who are fluid-restricted or who required very large opioid dosages. No other concentrations will be dispensed, unless the request has been reviewed

and approved by a clinical pharmacy specialist. This puts additional safeguards in place.

The move towards standardized concentrations of drugs is to promote medication safety. This is particularly important in drugs with a high risk of dose-dependent toxicities. The use of standardized concentrations decreases the risk of prescribing and dispensing errors.

NEWS

New drugs in 2005

In 2005, the number of new drugs approved was lower than usual. Only 18 new drugs (ie, called new molecular entities or NMEs) were approved in 2005 (see table on page 4). The most new drugs approved in 1 year occurred less than 10 years ago in 1996 when 53 new drugs were approved. The 18 new drugs approved this year is consistent with a general downward trend since the 1996 peak. Only 3 unique biological “drugs” (ie, abatacept, galsulfase, and Vaccinia Immune Globulin [IV-VIG]) were approved, which is also a decrease compared with previous years.

Experts predict the number of new drugs approved each year to remain low over the next few years. However, there is disagreement as to whether we have reached the nadir or if the number of drugs approved will increase significantly any time soon. The current decrease cannot be attributed to the Food and Drug Administration’s bureaucracy. Late-stage failures of drugs in development and the relative poor success of the research “pipeline” are blamed. For example, muraglitazar (Pargluva[®]), an investigational alpha/gamma peroxisome proliferator-activated receptor (PPAR) activator diabetes drug, was being touted for its ability to target both glucose and lipid control. After an FDA advisory committee rec-

ommended muraglitazar’s approval in September 2005, information published in *JAMA* in October suggested a higher risk of death, heart attack, and stroke. This at least delayed and possibly prevented the release of this drug.

The decrease in new drug approvals is occurring despite record expenditures on research and development by industry, government, and academia. Last year drug companies spent \$38 billion on research. Annual drug research expenditures are estimated to be over \$100 billion when government and academic support is included. The approval of few marketable drugs, despite this large investment, has been equated with poor research “productivity” and may be an indication that research breakthroughs are not being developed for general use.

New drugs used to treat diabetes led approvals with 3 NMEs. There were no other obvious trends noticed and many

(continued on page 3)

INSIDE THIS ISSUE

- ◆ Charity Care additions
- ◆ Nonformulary preprinted orders

Formulary update, from page 1 dependent. Before the availability of sublingual buprenorphine, the only options for opioid maintenance were methadone and levomethadyl (LAAM), which could be prescribed only in specialty clinics. Sublingual buprenorphine offers a new option for the treatment of opioid dependency.

Opioid dependence includes the abuse of illicit drugs (eg, heroin) and abuse of prescription pain relievers for nonmedical uses. The abuse of prescription pain relievers has been increasing. There are also some patients who become dependent on opioids after being treated for chronic pain.

A sublingual tablet containing both **buprenorphine and naloxone** is available for outpatient use, but will not be available for inpatient use at Shands. The naloxone is present to prevent the grinding and injection of the tablets for abuse purposes. **Buprenorphine injection**, which was deleted from the *Formulary* in 1991 because of lack of use and reports of central nervous system adverse effects (eg, hallucinations), was also designated nonformulary and not available.

Buprenorphine is a partial agonist at the μ -opioid receptor and an antagonist at the κ -opioid receptor. If buprenorphine is given with opioids, it initiates withdrawal symptoms. Thus, patients admitted under the influence of opioids should not begin sublingual buprenorphine until they begin to exhibit symptoms of withdrawal.

Sublingual buprenorphine is administered as a single-daily 12- to 16-mg dose for opioid maintenance. Oral buprenorphine has poor bioavailability because of a high first-pass effect. Thus, each dose must be administered sublingually.

Clinical trials show that sublingual buprenorphine is effective for opioid maintenance. Most studies assessed the effectiveness of buprenorphine therapy in combination with psychosocial counseling and as part of a comprehensive addiction treatment program, which included supervised medication administration rather than take-home medication. These studies show that buprenorphine is equal to or slightly less effective than methadone. A Cochrane review concluded that buprenorphine appeared to be less effective than methadone in retaining patients in opioid dependency treatment (RR= 0.82; 95% CI: 0.69-0.96).

There are limited published data on the use of sublingual buprenorphine for use in chronic pain; however, buprenorphine has been used for moderate to severe pain for many years in its injectable form. Use for chronic pain in patients who are also dependent on opioids may be an acceptable off-label

use of sublingual buprenorphine.

Adverse effects of buprenorphine are as expected for a partial opioid agonist. It can cause central nervous system effects and respiratory depression.

Based on the labeled dose for sublingual buprenorphine, the cost ranges from \$8 to \$13 per day. The dosages used for chronic pain can cost \$15 per day.

Sublingual buprenorphine can be prescribed for opioid maintenance and detoxification only by physicians who have specific credentials and who have received a special DEA number. More information on these restrictions can be found at www.suboxone.com.

Iloprost inhalation solution is a prostacyclin analogue with a labeled indication for the treatment of pulmonary arterial hypertension (PAH), (WHO group 1) in patients with New York Heart Association class III or IV symptoms. Its primary mechanism of action is through selective vasodilation of pulmonary vasculature. Pulmonary vascular vasodilation is more predominant than systemic vasodilation when iloprost is administered via inhalation. Other mechanisms, such as antiplatelet and antiproliferative activity, may also contribute to its mechanism of action in PAH.

There are currently several other medications in the *Formulary* for PAH: continuous intravenous epoprostenol [Flolan[®]], continuous infusion subcutaneous treprostinil [Remodulin[®]], oral sildenafil [Revatio[®]], and oral bosentan [Tracleer[®]]. These medications are usually administered in addition to anticoagulant therapy with or without digoxin. Currently, no comparative trials define superior therapies or treatment algorithms for PAH.

Continuous infusion epoprostenol, oral bosentan, and high-dose calcium-channel blockers (in few select patients), have demonstrated survival benefits for patients with PAH. However, relative contraindications and complications exist for these therapies. Epoprostenol is associated with repeated catheter-related infections and patient inability to care for vascular access devices. High-dose calcium-channel blockers cause hypotension, and bosentan is associated with elevated hepatic transaminases. Therefore, given patient-specific considerations, alternatives for PAH treatments are needed for patients who fail or who do not tolerate initial treatment with these agents. In addition, most patients require combination therapy with 2 agents due to eventual disease progression.

Although multiple small, noncomparative trials of inhaled iloprost exist, there is only 1 large randomized placebo-controlled trial examining the safety and efficacy of inhaled iloprost for pulmonary artery hypertension. The primary endpoint was an increase of at least 10% in

the distance walked in 6 minutes and an improvement in NYHA class in the absence of any clinical deterioration or death within 12 weeks. This large randomized trial showed improvement in hemodynamic parameters, NYHA classification, 6-minute walk test, and quality of life.

Inhaled iloprost is administered 6 to 9 times daily while the patient is awake. Adverse effects of inhaled iloprost are similar to other PAH therapies. The most common adverse effects are flushing, cough, and headache. Inhaled iloprost does not require special laboratory monitoring, and no dosage changes are recommended for patients with renal or hepatic impairment.

Inhaled iloprost is available for ambulatory use only through a limited distribution system. Hospitalized patients must be enrolled in this program before iloprost will be dispensed. To determine whether a patient is enrolled in this program or to obtain information how to enroll a patient, call 877-483-8628 and select option #2.

Due to high cost (\$220 per day for drug and \$5000 per inhalation device) and lack of data showing superiority of this agent, inhaled iloprost will be reserved for patients who have failed therapy with other agents, who are poor candidates for continuous IV therapy, or who have experienced intolerable adverse effects of the other available therapies.

Kaletra[®] tablets have replaced **Kaletra[®] capsules** in the *Formulary*. Abbott is phasing out Kaletra[®] capsules (lopinavir 133 mg/ritonavir 33.3 mg) in favor of the new tablet formulation (lopinavir 200 mg/ritonavir 50 mg). The tablet formulation decreases the number of tablets needed per day (ie, "pill burden"). Also, the tablets do not require refrigeration like the capsules.

The capsules were designated nonformulary and not available to prevent 2 different strengths of Kaletra[®] being listed in the *Formulary*, which could lead to medication errors.

Dextran-1 is no longer being marketed and, therefore, was deleted from the *Formulary*. Dextran-1 was given before dextran-40 or dextran-70 in order to minimize the risk of anaphylactoid reactions. Dextran-40 and dextran-70 have been on the US market for more than 40 years. They have been used as volume expanders in the treatment of hypovolemic shock, to prime cardiopulmonary bypass machines, and for postoperative thromboembolic prophylaxis. Because they reduce platelet aggregation and promote blood flow in the microcirculation, dextran solutions are used in patients undergoing plastic reconstructive skin flaps and by vascular surgeons in patients undergoing carotid endarterectomies.

(continued on next page)

Formulary update, from page 2

Anaphylactoid reactions associated with dextran solutions vary in severity. Serious reactions are initiated by cross-linking of dextran-specific IgG with dextran molecules; binding of IgG complexes to receptors located on the membrane surface of mast cells and basophils triggers them to release potent vasoactive mediators that cause circulatory collapse and severe bronchoconstriction. Dextran-1 is a hapten (low molecular weight dextran) that blocks the cross-linking of dextran-40 or dextran-70 with IgG. This has been shown in clinical trials to decrease the incidence of severe adverse reactions.

There is a national effort to find a manufacturer to re-release dextran-1 in the US. If dextran-1 is re-marketed, it will be re-added in the *Formulary*.

Thiabendazole is a broad spectrum anthelmintic structurally related to mebendazole. Thiabendazole liquid was discontinued by its manufacturer in September 2004, which necessitates its deletion from the *Formulary*. Based on purchasing records, the use of thiabendazole chewable tablets has been very low. Mebendazole is an alternative listed in the *Formulary*.

Ketorolac tablets were designated nonformulary and not available because they offer no therapeutic advantage over other oral traditional non-steroidal anti-inflammatory drugs (NSAIDs) listed in the *Formulary*.

Injectable ketorolac remains in the *Formulary* because it is the only injectable NSAID commonly used for pain management.

Ketorolac has been associated with a relatively high incidence of gastrointestinal and renal toxicity. Ketorolac treatment is limited to a maximum of 5 days of use. Although oral ketorolac is rarely requested through the nonformulary process, the not-available designation was made to prevent possible adverse effects associated with prolonged use.

Paricalcitol capsules were evaluated for addition in the *Formulary* for the labeled indication (ie, treatment of patients with secondary hyperparathyroidism and Stage 3 or 4 chronic kidney disease [CKD]), but there is currently insufficient published evidence to support addition. Paricalcitol capsules will be available via a nonformulary request. Paricalcitol injection remains in the *Formulary*.

Paricalcitol is a synthetic vitamin D analog that mimics the actions of endogenous activated vitamin D (calcitriol). Vitamin D reduces elevated parathyroid hormone (PTH) levels that occur in CKD. This decreases bone turnover and the consequences of calcium and phosphate resorption from bone. Animal data suggest that paricalcitol stimulates less osteoclastic activity than calcitriol and induces similar inhibition of osteoblast maturation. Vitamin D receptors in the gastrointestinal tract increase the absorption of calcium and phosphorus from the diet, which exacerbates the prob-

lems of serum calcium and phosphorus control in patients with CKD. Animal data suggests that paricalcitol stimulates less intestinal calcium uptake than calcitriol. Abnormally high serum calcium and/or phosphorus level (and the calcium-phosphorus product) are linked to tissue and vessel calcification, which is thought to be the mechanism for the associated organ problems, including cardiovascular disease.

There are no published studies on the efficacy of oral paricalcitol in Stage 3 or 4 CKD. The only available information is the official labeling and abstracts, which compare paricalcitol to placebo. There are no data comparing oral paricalcitol with calcitriol or any other available vitamin D analog. There are published observational data for injectable paricalcitol in Stage 5 CKD associating its use with lower morbidity and hospitalizations compared with calcitriol.

Current American Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines for Stages 3 and 4 CKD do not currently include oral paricalcitol. The guidelines do recommend therapy with an active oral vitamin D sterol when serum levels of 25(OH)-vitamin D are greater than 30 ng/mL and plasma levels of intact PTH are above the target range.

Paricalcitol capsules are approximately 7 times more expensive than calcitriol tablets.

OUTPATIENT PHARMACY

Charity Care Formulary additions

New drugs were added in the *Charity Care Formulary* to offer options for the treatment of hypertension, depression, and pain. **Extended-release felodipine, citalopram, and tramadol** are now available as inexpensive alternatives to brand name products.

Extended-release felodipine [eg, Plendil®] is a dihydropyridine calcium-channel blocker used for the treatment of hypertension and angina. Felodipine ER costs the institution \$10.35 for a month's supply based on a dosage of 5 mg per day.

Citalopram [eg, Celexa®] is a selective serotonin reuptake inhibitor (SSRI) similar to the brand name products of escitalopram [Lexapro®] and sertraline [Zoloft®]. There are other generic SSRIs available (eg, fluoxetine). Citalopram costs the institution \$0.65 to \$5.11 per month based on common dosages.

Tramadol [eg, Ultram®] is a synthetic analog of codeine that has lower affinity for opioid receptors. It has less potential for abuse and respiratory depression. Tramadol is used for moderate pain. While tramadol does not perform well

in head-to-head studies with acetaminophen-codeine or acetaminophen-hydrocodone, it appeals to prescribers because it is not a controlled substance. Tramadol is listed in some osteoarthritis and rheumatoid arthritis treatment guidelines and is listed in the WHO

guidelines for cancer pain management. Tramadol costs the institution approximately \$1.15 to \$4.60 per day.

Prescribers are reminded that Medicare patients are no longer eligible for the *Charity Care Formulary*. The complete list of therapeutic options can be found on the intranet at <http://intranet>.

News, from page 1

different indications were approved for the small number of drugs approved. Several of the drugs approved were for very narrow indications in small patient populations.

However, 2005 was another big year for first-time generic approvals. Generic versions of drugs continue to 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 versions of azithromycin [Zithromax®], ceftriaxone [Rocephin®], fexofenadine [Allegra®], glimepiride [Amaryl®], leflunomide [Arava®], octreotide

[Sandostatin®], ramipril [Altace®], transdermal fentanyl [Duragesic®], and zidovudine [Retrovir®] were approved in 2005. Some generics were approved by FDA, but have been held up by challenges in court (eg, amlodipine [Norvasc®]). This demonstrates the difficulty in predicting when drugs will become commercially available as generics when patients "expire."

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

Volume 20, No. 2 February 2006
 This publication is produced by the Drug Information and Pharmacy Resource Center under the direction of the Department of Pharmacy Services and the Pharmacy and Therapeutics Committee.

**EDITOR,
 DRUGS & THERAPY BULLETIN**

Randy C. Hatton, PharmD

**DIRECTOR,
 PHARMACY SERVICES**

Alan Knudsen, MS, RPh

**CHAIRMAN,
 PHARMACY & THERAPEUTICS
 COMMITTEE**

Ricardo Gonzalez-Rothi, MD

EDITING, DESIGN, & PRODUCTION

Shands HealthCare's Publication Svcs.
 © Copyright 2006. All rights reserved.
 No portion of the *Drugs & Therapy Bulletin* may be reproduced without the written consent of its editor.

**FOR MORE INFORMATION,
 VISIT US ONLINE**

<http://shands.org/professional/drugs/bulletin.htm>

SHANDS
Shands at the University of Florida
DRUG INFORMATION SERVICE
 PO Box 100316
 Gainesville, FL 32610-0316

NON-PROFIT ORG.
 U.S. POSTAGE
 PAID
 GAINESVILLE, FL
 PERMIT NO. 94

**NEW DRUGS & SELECTED BIOLOGICALS
 APPROVED BY THE FDA IN 2005**

GENERIC NAME	TRADE NAME	INDICATION
Abatacept†	Orencia®	Rheumatoid Arthritis
Conivaptan	Vaprisol®	Euvolemic Hyponatremia
Deferasirox	Exjade®	Iron Toxicity
Entecavir	Baraclude®	Hepatitis B
Exenatide	Byetta®	Diabetes Mellitus
Galsulfase†	Naglazyme®	Mucopolysaccharidosis VI (MPS VI)
Hyaluronidase (bovine)†	Hydase®	Drug Absorption & Dispersion
Hyaluronidase (human)	Hylenex®	Drug Absorption & Dispersion
Insulin Detemir	Levemir®	Diabetes Mellitus
Lenalidomide	Revlimid®	Myelodysplastic Syndrome
Mecasermin	Increlex®	Insulin-like Growth Factor Deficiency
Mecasermin Rinfabate	iPlex®	Insulin-like Growth Factor Deficiency
Micafungin	Mycamine®	Antifungal (Intravenous)
Nelarabine	Arranon®	Leukemia and Lymphoma
Nepafenac	Nevanac®	Ocular Pain & Post-Operative Inflammation
Pramlintide	Symlin®	Diabetes Mellitus
Ramelteon	Rozerem®	Insomnia
Sorafenib	Nexavar®	Advanced Renal Cell Carcinoma
Tigecycline	Tyggacil®	Antibiotic
Tipranavir	Aptivus®	HIV Infection
Vaccinia Immune Globulin†	IV-VIG	Vaccinia Virus Infections

†Listed in the Shands at UF *Formulary*
 ‡Biological

POLICIES AND PROCEDURES

**Nonformulary drugs
 are not permitted on
 preprinted orders**

Drugs that are readily available for use at Shands at UF are listed in the *Formulary*. Shands has a liberal policy that allows the use of most nonformulary drugs, except those that have been explicitly evaluated and designated nonformulary and not available.

Preprinted order forms cannot contain nonformulary drugs. In order for these agents to be included in preprinted orders, the drug must be evaluated by the P&T Committee and added in the *Formulary*.

The P&T Committee uses an evidence-based approach when evaluating drugs for inclusion in the *Formulary*. Safety, comparable efficacy, and cost are considered when drugs are evaluated. In order to be listed in the *Formulary*, a drug must be available to stock in the hospital pharmacy. Drugs available only via limited distribution programs cannot be listed in the *Formulary* because they are not "readily available."

If you have any questions about what is listed in the *Formulary*, please contact a pharmacist in your area or check the online *Formulary* at <http://intranet.shands.org/pharm/drugs.htm>.