Volume 16, Number 2

SHANDS at the University of Florida

February 2002

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met January 15, 2002. 3 drugs were added in the *Formulary* and 2 drugs were deleted. 2 drugs were designated not available. 1 drug was evaluated, but not added.

◆ ADDED

Metaraminol (Aramine® by Merck)

Valsartan (Diovan® by Aventis)

Zoledronic acid (Zometa® by Novartis)

◆ DELETED

Antivenin Micrurus Fulvius (Coral Snake Antivenin by Wyeth-ESI Lederle)

Antivenin Polyvalent (Antivenin Polyvalent by Wyeth-ESI Lederle)

◆ NONFORMULARY, NOT AVAILABLE

Saquinavir (Invirase® by Roche)

Cisatracurium (Nimbex® by Glaxo Wellcome)

◆ EVALUATED, BUT NOT ADDED

Buprenorphine (Buprenex® by Reckitt Benckiser)

Metaraminol is a sympathomimetic amine that acts by a direct effect predominantly on alpha-adrenergic receptors and constricts both capacitance and resistance blood vessels. Metaraminol also directly stimulates beta-adrenergic receptors of the heart, but not those of the bronchi or peripheral blood vessels. Metaraminol increases both systolic and diastolic blood pressure, but does not usually increase heart rate.

(continued on next page)

NEWS

New drugs in 2001

Another year has passed, and there are over 30 new drugs or biologicals that were approved for marketing in the United States in 2001. 7 of these "drugs" are biologicals and reflect the increasing number of biological agents that are approved each year. Alemtuzumab, drotrecogin, and nesiritide are biologicals approved in 2001 that are already listed in the Shands at UF *Formulary*.

Several new generics were approved in 2001, which should offer treatment options for patients who have difficulty paying for their medications.

The nonbiologicals that were approved in 2001 are often referred to as *new molecular entities* or NMEs. 4 of these 24 NMEs are already listed in the Shands at UF *Formulary*, despite the fact that 11 of these drugs were approved in the 4th quarter of the year.

When the FDA reviews NMEs, they are classified as standard or priority. About 30% of the NMEs approved in 2001 were priority drugs (ie, bimatoprost, caspofungin, fondaparinux, imatinib, tenofovir, travaprost, and zoledronic acid).

Caspofungin, which was added in the *Formulary* in April 2001, is the 1st antifungal approved in the US in the category of echinocandins. There are limited published data on caspofungin, and 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). Caspofungin can only be used after the approval of the ID Service or in the Bone Marrow Transplant Unit.

Imatinib was added in the *Formulary* in August 2001. It was approved with a labeled indication for the treatment of the 3 stages of chronic myeloid leukemia (CML): blast crisis, accelerated phase, and chronic phase after interferon failure.

Zoledronic acid was added in the *Formulary* in January 2002. A more complete discussion of this new agent can be found in the Formulary Update in this issue of the *Bulletin*.

Several important new generics were approved in 2001, which should offer treatment options for patients who have difficulty paying for their medications. These new generics include buspirone (equivalent to Buspar® for anxiety), calcitriol (activated vitamin D equivalent to Rocaltrol®), famotidine (H2-blocker equivalent to Pepcid®), fluoxetine (equivalent to Prozac® for depression), and lovastatin (equivalent to Mevacor® for hypercholesterolemia).

Several "blockbuster" generics are anticipated in 2002: loratidine (equivalent to Claritin® for rhinitis); lisinopril (ACE inhibitor equivalent to Prinivil® or Zestril®); metformin (equivalent to Glucophage® for diabetes); and, omeprazole (proton-pump inhibitor equivalent to Prilosec®). These 4 products accounted for $10 billion in sales in 2001 in the United States. In 1994, the US Congressional Budget Office estimated that generic drugs saved patients $8 to $10 billion, which shows what a huge impact these 4 drugs could have in 2002 and beyond.

See the chart on page 4 for the complete list of new drugs and selected biologicals approved by the FDA in 2001.

INSIDE THIS ISSUE

Formulary, *from page 1*

In March 2000, metaraminol was deleted from the *Formulary* because of lack of use. It was re-evaluated as an alternative to ephedrine (and other vasopressors like phenylephrine) for hypotension associated with spinal or epidural anesthesia. There are at least 2 trials that compare ephedrine and metaraminol. These studies suggest that metaraminol may have a role in addition to ephedrine.

Aramine® is the only available metaraminol product. It is currently on an allocation of up to 6 vials per patient per week. The manufacturer would not provide any reason for the allocation, or even whether there is a shortage of the product.

Although it is difficult to estimate the relative costs, it is estimated that metaraminol is nearly 35-times more expensive than ephedrine and 6-times more expensive than phenylephrine. However, the absolute cost of metaraminol is not high and the overall impact on pharmaceutical expenditures should be small.

Although the data are limited, there was sufficient evidence to support potential differences in the effectiveness of ephedrine and metaraminol for the management of hypotension associated with spinal or epidural anesthesia. As long as Aramine® is available, metaraminol will be re-listed in the *Formulary*.

Valsartan is an angiotensin-receptor blocker (ARB). It was evaluated for formulary addition as part of a review of the class of ARBs that was done in response to the high nonformulary use of valsartan. Before the review, only losartan was listed in the *Formulary*. Losartan was listed in the *Formulary* because of frequent use and not clinical superiority.

Currently, there are 6 ARBs on the US market. According to the Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 6), ARBs are 1st-line agents in selected patients. ARBs are used in the treatment of hypertension in patients who have a good treatment response to an angiotensin-converting enzyme (ACE) inhibitor, but who experience an adverse effect, (eg, cough).

All ARBs are effective in lowering blood pressure, either alone on in combination with other antihypertensives, especially diuretics. ARBs are as effective as ACE inhibitors. There does not appear to be a significant difference among the ARBs in the treatment of hypertension, except losartan may have to be given twice a day and the other ARBs are given once daily.

There is less agreement on the equivalency among the ARBs for the off-label uses of heart failure and renal-sparing effects (eg, in diabetic nephropathy). The val-HeFT trial compared valsartan to placebo in over 5000 patients with NYHA II-IV heart failure. This study showed that valsartan was superior to placebo based on the composite endpoint of hospitalization/all-cause mortality/sudden death/need for IV inotropes or vasodilators. The main driver in this finding was the difference in the need for hospitalization. The ELITE II trial studied over 3000 patients (NYHA II-IV) and compared losartan and captopril. There was no difference in the primary endpoint of all-cause mortality, but the secondary endpoint of sudden death/cardiac arrest favored captopril. There are studies pending (CHARM, OPTIMAAL, VALIANT) that will better describe whether there is a difference between ACE inhibitors and ARBs in heart failure, whether a combination of an ACE inhibitor and ARB is favorable, and whether adding an ARB to a beta blocker is advisable.

There are 2 studies that suggest that losartan (RENAAL) and irbesartan (IDNT) have effects similar to ACE inhibitors in the prevention of the progression of renal damage in patients with diabetes. Reportedly, there are unpublished studies that show that valsartan also prevents renal damage. Thus, the renal-sparing effects of ARBs appear to be a class effect.

Currently, there is no cost advantage among the ARBs. Selecting among these agents is difficult for the off-labeled indications because of the limited available data at this time. Valsartan was added in the *Formulary*. It was specified that the class be re-reviewed once additional data become available.

Zoledronic acid is a more potent bisphosphonate than pamidronate. Clinical trial data suggest that zoledronic acid is at least as effective as pamidronate. The main advantage of zoledronic acid is a shorter infusion time compared with pamidronate. The 15- to 30-minute infusion time is an advantage compared with the 2 to 4 hours needed for a pamidronate infusion. In the clinic setting (eg, Outpatient Bone Marrow Transplant Clinic), the shorter infusion time could increase patient turnover.

Zoledronic acid is used off-label in low doses to prevent osteoporosis in bone marrow patients and in higher doses to treat metastatic bone disease. For the labeled indication of hypercalcemia, zoledronic acid does not appear to offer an advantage over pamidronate. Pamidronate remains in the *Formulary* and is the drug of choice for inpatient use

There has been a question about the potential for increased renal toxicity with zoledronic acid. When zoledronic acid is given over 5 minutes in clinical trials, there was a higher rate of renal toxicity. The labeling recommends that zoledronic acid be given over 15 to 30 minutes. It is important that the slightly longer infusion time be followed.

Because pamidronate is now generic, it is less expensive than zoledronic acid and the difference in cost should be considered. In the clinic setting, the increased cost of zoledronic acid is offset by increased turnover. However, there is currently no outpatient reimbursement code for zoledronic acid and all use will be unreimbursed until this code is established (estimated to be April 2002).

Antivenin Micrurus Fulvius, or coral snake antivenin, has been discontinued by the manufacturer. It was used for the neutralization of snake venom from the North American coral snake and certain related snakes. These envenomations must now be managed by symptomatic support. Because coral snake venom is a neurotoxin, patients may require ventilatory support.

Antivenin Polyvalent was derived from the serum of horses that had been immunized against the venoms of the Western Diamondback rattlesnake, the Eastern Diamondback rattlesnake, Cascabel (a tropical rattlesnake), and Bothrops atrox (a tropical snake that contain the basic antigens in the venoms of all members of the family Crotalidae). Antivenin polyvalent was discontinued after the manufacturer had quality control problems at the manufacturing plant.

CroFab® remains in the *Formulary* as an alternative for the treatment of bites from rattlesnakes and water moccasins. CroFab® is ovine polyvalent crotalide immune fab. The fab fragments of immunoglobulins derived from sheep exposed to the venoms of Western, Mojave, and Eastern Diamondback rattlesnakes and the Water Moccasin are included in CroFab®. CroFab® is used within 6 hours of envenomations to prevent clinical deterioration and systemic coagulation abnormalities.

Cisatracurium is a nondepolarizing neuromuscular blocker that is similar to atracurium. It is considered

(continued on next page)

Formulary, *from page 2*
intermediate in onset and duration of action relative to other neuromuscular blockers. Cisatracurium is 1 of several isomers of atracurium and is 3 times as potent as atracurium. Atracurium is listed in the *Formulary* and cisatracurium is not listed.

The Institute for Safe Medication Practices (ISMP) has identified a medication safety issue with the labeling of the 2 strengths of cisatracurium. The vials are the same size (10 mL) with the same colored labeling, but the vials have a 10-fold difference in concentration. For this reason, cisatracurium was designated not-available in order to prevent possible medication errors with nonformulary use.

Invirase® was the first commercial form of saquinavir when it was marketed in 1995. It is a hard gel capsule with poor bioavailability. In 1997, Fortovase®, a soft-gelatin capsule form of saquinavir, was marketed. At that time, many clinicians were using Invirase® in combination with ritonavir to increase its activity in patients being treated for HIV infections.

The current Department of Health and Human Services Guidelines for the Treatment of HIV Infection recommend that Invirase® only be used in combination with ritonavir. However, there is now enough data to support the use of Fortovase® in combination with ritonavir. Therefore, there is no longer a need for Invirase®. Further, having 2 different formulations of saquinavir with differing bioavailabilities could cause confusion and inappropriate substitution of Invirase® for saquinavir. The P&T Committee designated Invirase® nonformulary and not available based on the recommendation of the Anti-Infective Subcommittee.

Buprenorphine is an opioid agonist-antagonist that can be given IM or IV for moderate to severe pain. This controlled substance was deleted from the *Formulary* more than 10 years ago because of low usage. Also, several patients experienced severe central nervous system adverse effects from buprenorphine.

It was requested that buprenorphine injection be re-listed in the *Formulary* for use in combination with local anesthetics in nerve blocks. Several adjuvants have been used in combination with local anesthetics to prolong or improve pain control (eg, clonidine, neostigmine, epinephrine, and bicarbonate). Buprenorphine and several other opioids have also been studied.

There are 3 trials that compare buprenorphine with other adjunct opioids and/or local anesthetic alone. These studies suggest that buprenorphine prolongs the action of the local anesthetic. However, recent systematic reviews have questioned the methodologies used in the comparative studies of opioid adjuvants and the clinical relevance of these data.

It is also unclear how buprenorphine compares with other opioid adjuvants. 2 out of 3 comparative studies suggest that buprenorphine had a longer duration of pain relief compared with morphine. However, 1 study suggested that buprenorphine was similar to morphine and alfentanil. Long-acting local anesthetics appear to minimize differences among opioid adjuvants. More importantly, these studies appear to be flawed because they do not give systemic therapy to the control groups. When patients take oral opioids, differences among adjuvants and local anesthetics alone are less clinically relevant. Comparisons between buprenorphine and an opioid with lipophilic properties similar to buprenorphine (eg, fentanyl) have not been done. Like buprenorphine, data suggest that local anesthetics plus fentanyl are superior to local anesthetics alone.

Since low dosages of buprenorphine are used for nerve blocks, the incidence of adverse effects should be lower than with systemic buprenorphine. Nausea, vomiting, and pruritus were reported in the clinical trials; however, infrequently. No central nervous system adverse effects were reported in the clinical trials, but the number of patients in these studies is small. No local effects were noted.

Buprenorphine is 4-times more expensive than morphine and 10-times more expensive than fentanyl, while sufentanil is 3.5-times more expensive than buprenorphine. Although more expensive than morphine and fentanyl, adding buprenorphine in the *Formulary* would have a minor impact on pharmaceutical expenditures

Based on the limited information available on the use of buprenorphine as an adjuvant with local anesthetics in nerve blocks and based on the questionable clinical relevance of buprenorphine compared with other agents, it was not added in the *Formulary*.

POLICIES AND PROCEDURES

Patients' own ophthalmic meds

The P&T Committee recently revised the hospital policy about patients bringing in their home medications for use in the hospital. Occasionally, patients want to or need to take their medication that they have brought from home. Patient safety must be our most important consideration when this occurs. The following problems may result when patients take their own medications.

- The drug may not be listed in the patient's medication profile. Drugs must be listed in the patient's medication profile to avert drug interactions or some adverse effects.
- Patients' own medications may be out of date or cannot be identified.
- Patients may combine medications in the same prescription bottle.
- Parenteral or liquid medications may contain ingredients or amounts not accurately listed on the label. Liquid medications also may be contaminated.
- Patients may run out of nonformulary medication before it is reordered, resulting in an interruption in therapy.

The policy is designed so that patients at Shands at UF will not be exposed to unnecessary risks.

However, the policy also has to recognize patients' need to use some of their medications while they are hospitalized. This occurs in some special patient populations, like patients who have received a transplant. This exception is now being extended to allow patients to use their own ophthalmic medications.

Because of the wide array and combinations of ophthalmic medications that are used chronically, it is not possible to have all of these drugs listed in the *Formulary*. Further, a delay in some types of ophthalmic medications could result in significant patient harm (eg, ophthalmic antibiotics, glaucoma medications). By allowing patients to use their own medications, potential harm could be avoided. Also, the risk of a commercially available medication in the original container having integrity problems was deemed to be less than the risk of a delay in therapy.

All drugs used for patient care, including patient's own medications, will be verified by the Pharmacy Department before they can be used

(continued on next page)

Drugs & Therapy
B · U · L · L · E · T · I · N

Volume 16, No. 2 February 2002

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.

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 BIOLOGICS APPROVED BY FDA IN 2001

GENERIC NAME	TRADE NAME	INDICATION
Alemtuzumab†‡	Campath®	Cancer: refractory B-cell CLL
Almotriptan	Axert®	Migraines: acute attacks
Anakinra‡	Kineret®	Rheumatoid arthritis
Azeleic acid cream	Finevin®	Acne
Bimatoprost	Lumigan®	Open-angle glaucoma
Bosentan	Tracleer®	Pulmonary arterial hypertension
Caspofungin†	Cancidas®	Antifungal: refractory aspergillosis
Cefditoren pivoxil	Spectracef®	Antibiotic
Darbepoetin‡	Aranesp®	Anemia: chronic renal failure
Desloratidine	Clarinex®	Antihistamine: seasonal allergic rhinitis
Digoxin immune Fab (ovine)‡	DigiFab®	Digoxin overdose
Drospirenone/Ethinyl estradiol	Yasmin®	Contraceptive
Drotrecogin†‡	Xigris®	Sepsis
Dutasteride	Not assigned	BPH
Ertapenem	Invanz®	Antibiotic
Esomeprazole	Nexium®	GERD
Etonogestrel/Ethinyl estradiol	NuvaRing®	Contraceptive
Fondaparinux	Arixtra®	DVT prophylaxis: hip & knee surgery
Formoterol	Foradil®	Asthma: long-acting beta agonist
Frovatriptan	Frovan®	Migraines: acute attack
Galantamine	Reminyl®	Alzheimer's Disease
Imatinib†	Gleevec®	Cancer: CML
Nesiritide†‡	Natrecor®	CHF: acute decompensated
Norelgestromin/Ethinyl estradiol	Ortho Evra®	Contraceptive
Peginterferon alfa-2b‡	PEG-Intron®	Chronic hepatitis C
Perflutren lipid microsphere	Definity®	Diagnostic
Pimecrolimus cream	Elidel®	Atopic dermatitis
Tenofovir	Viread®	Antiviral: HIV
Travaprost	Travatan®	Open-angle glaucoma
Valdecoxib	Bextra®	Arthritis: Rheumatoid & Osteo
Valganciclovir†	Valcyte®	Antiviral: CMV retinitis
Ziprasidone	Geodon®	Schizophrenia
Zoledronic acid†	Zometa®	Hypercalcemia of malignancy

†Listed in the Shands UF *Formulary*
‡Biological

Policies and procedures, *from page 3*
in the hospital. This procedure is important. There have been numerous incidences nationally, and some locally, where the medication brought into the hospital was mislabeled. The potential for these errors to continue during an admission exists unless each home medication is verified before it is used.

The prescriber must write a specific order for each of a patient's *own meds* that will be used, including dose and schedule. Nonspecific orders, like *patients may take own meds,* cannot be honored. After the specific order is written, a pharmacist will identify the medication and verify the proper labeling and storage conditions have been followed.

The medication must be in the original container. If these conditions are not met, the *home med* cannot be used during their hospitalization. Verified medications will have a label showing that they have been approved. Compounded medications cannot be used. If a patient's *own meds* are used up while the patient is hospitalized, the pharmacy should be notified in advance to make sure their supply is not interrupted.