

Drugs & Therapy

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FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met August 21, 2001. 5 drugs or dosage forms were added in the *Formulary*. 2 drugs were deleted. 1 drug combination and 2 drugs were designated not available. 1 drug was evaluated but not added.

◆ ADDED

Amphotericin B liposomal
(AmBisome® by Fugisawa)

Ceftazidime
(Ceptaz®, Fortaz®, and Tazidime®)

Imatinib
(Gleevec® by Novartis)

Piperacillin + Tazobactam
(Zosyn® by Lederle)

Valganciclovir
(Valcyte® by Roche)

◆ DELETED

Mitotane
(Lysodren® by Bristol-Myers Squibb)

Secretin, Porcine
(Secretin by Ferring)

◆ NONFORMULARY & NOT AVAILABLE

Fenoldopam
(Carlopam® by Abbott)

Hydrocodone + Acetaminophen
(eg, Lorcet®, Lortab®, Norco®, Vicodin®)

Papain-Urea-Chlorophyllin Complex
(Panafil® by Health Point)

◆ EVALUATED BUT NOT ADDED

Ziprasidone
(Geodon® by Pfizer)

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NEWS

Is Synthroid® being removed from the market?

Synthroid® remains on the US market...and should continue to be on the market...at least for a year. However, the manufacturer is under an order from the FDA to scale back its production, pending the approval of a New Drug Application (NDA) that proves that Synthroid® is safe and effective.

In 1997, the FDA mandated that the maker of Synthroid® and other manufacturers of levothyroxine submit NDAs in order to continue marketing these products. The deadline for these NDAs was August 14, 2001.

Even though the FDA has mandated a general scale back in the production of Synthroid®, a shortage is not anticipated.

Levothyroxine sold after this date without either an approved or filed application are subject to regulatory action.

Unithroid® and Levoxyl® have already applied for and received approval from the FDA to continue marketing their products. Unithroid® was the 1st levothyroxine approved by an NDA and is now the "innovator product." Synthroid® was perceived as the innovator before this change.

Synthroid® did not previously have an NDA because it is a very old product. Synthroid® was marketed before the 1962 Kefauver-Harris Act was passed. The Kefauver-Harris Act was landmark legislation that requires drug companies to prove their products are both safe and effective by submitting an

NDA. Synthroid® previously fell into a class of "not new drugs," which are generally recognized as safe (GRAS) and generally recognized as effective (GRASE).

In the mid-1990s, the FDA compiled data on problems with manufacturing and on adverse events related to the use of Synthroid®'s and other levothyroxine products that were on the market. This review stimulated the FDA to require all levothyroxine manufacturers to submit NDAs.

Originally, Synthroid® chose not to submit an NDA, but sued the government to be able remain on the market based on its GRASE designation. When the maker of Synthroid® (ie, Abbott) lost this legal battle, they raced to submit their NDA before the deadline so it could remain on the market. Abbott filed their NDA approximately 2 weeks before the deadline.

Even though the FDA has mandated a general scale back in the production of Synthroid®, a shortage is not anticipated. Abbott stockpiled enough supplies to avoid a shortage during the next year while the NDA is being reviewed.

Even though there are no AB-rated generic equivalent levothyroxine products, practitioners should be aware of objective data that suggest that there are no clinically relevant differences among the available products.¹

REFERENCES

1. Dong BJ, Hauck WW, Gambertoglio JG, et al. Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. *JAMA* 1997;277:1205-13.

INSIDE THIS ISSUE

- ◆ Patient allergy information

Formulary update, from page 1

Liposomal amphotericin B is a "lipid-based" amphotericin B. Lipid-based amphotericin B products were designed to provide the antifungal activity of conventional amphotericin B, yet decrease the potential to cause nephrotoxicity.

In October 1999, amphotericin B lipid complex (ie, ABLC or Abelcet®) and liposomal amphotericin B were deemed therapeutically equivalent. In March 2000, Abelcet® was designated the formulary agent. At that time AmBisome® was designated nonformulary and not available, which is what usually occurs with therapeutic equivalent designations. When rare instances were identified in which AmBisome® was preferable to Abelcet®, the status of AmBisome® was changed to nonformulary restricted in November 2000.

In order to make products available, even when the need is rare, the P&T Committee is recommending that nonformulary-restricted agents be changed to formulary-restricted agents. The product is stocked and can be easily acquired, but the restriction process prevents unnecessary use. Therefore, AmBisome® was added in the *Formulary*, but it can be used only with Infectious Diseases' approval (or by the approval of Dr. Wingard in the Bone Marrow Transplant Unit).

Ceftazidime is a parenteral 3rd-generation cephalosporin. When cefepime was added in the *Formulary* in April 1998, ceftazidime was "deleted." However, due to the limited information about the use of cefepime in children, ceftazidime has been available for this use.

It is still reasonable to use ceftazidime in children less than 2 months of age, instead of cefepime. Ceftazidime has also been used in patients infected with *Pseudomonas aeruginosa*, when the laboratory results have erroneously reported that it is sensitive to ceftazidime, but resistant to cefepime. This difference is not an accurate laboratory finding. By restricting this agent, prescribers can be educated on the appropriate indications for using ceftazidime instead of cefepime. Ceftazidime was added in the *Formulary*, but it can be used only with Infectious Diseases' approval.

Imatinib (also known as STI571) is an oral agent used in chronic myelogenous leukemia (CML) when patients have failed interferon therapy. There are good studies that are summarized in the package insert and preliminary data published in the *New England Journal of Medicine* that document the efficacy of imatinib. It is used in ALL when patients are Philadelphia-chromosome

positive.

The Philadelphia chromosomal abnormality in CML results in the fusion of Bcr-Abl protein, which is a constitutively activated tyrosine kinase. Imatinib is a potent and selective inhibitor of Bcr-Abl tyrosine kinase. It arrests growth and causes cell death in hematopoietic cells that express Bcr-Abl with little effect on normal cells.

The recommended dosage for imatinib is 400 mg per day for chronic CML and 600 mg per day for patients in accelerated phase or blast crisis. Patients who tolerate therapy and who do not demonstrate a hematologic response may have their dosages increased to 600 mg per day and 800 mg per day, respectively. A month's supply of imatinib at 600 mg per day will cost nearly \$3000.

The most frequently reported adverse effects with imatinib are nausea, vomiting, edema, and muscle cramps. Since imatinib is metabolized by CYP3A4, drug interactions are a consideration. Inhibitors (eg, ketoconazole) may increase a patient's exposure to imatinib. Inducers (eg, phenytoin) may decrease a patient's exposure. Imatinib may increase the effect of other agents metabolized by CYP3A4 (eg, simvastatin).

Imatinib will be used primarily in outpatients; however, some inpatients will receive it. Therefore, it was added in the *Formulary*. It was not added in the *Charity Care Formulary*. Indigent patients will have to rely on the manufacturer's prescription benefit program.

Piperacillin and tazobactam are combined to improve the spectrum of piperacillin alone. Piperacillin is an extended-spectrum penicillin with bactericidal activity against gram-negative and anaerobic bacteria. Piperacillin is susceptible to beta-lactamases produced by many gram-positive and gram-negative bacteria. Tazobactam is an irreversible beta-lactamase inhibitor that prevents beta-lactamase destruction of piperacillin.

Early in 2000, Timentin® (a combination of ticarcillin and clavulanate) and Zosyn® were deemed therapeutically equivalent by the P&T Committee. Timentin® was selected as the representative in this class. Zosyn® then became nonformulary and not-available. After it was identified that there are rare patients in whom Zosyn® would be an appropriate choice, this designation was changed to nonformulary-restricted. Although Zosyn® was added in the *Formulary*, it can be used only with Infectious Diseases' approval.

Valganciclovir is a prodrug of ganciclovir, which is currently listed in the *Formulary*. Ganciclovir is a synthetic, purine nucleoside analog used in the treatment and prevention of cytomegalovirus (CMV) infections.

Because of the poor bioavailability of oral ganciclovir (ie, <10%), it has not been used in the treatment of CMV disease. Oral valganciclovir is an alternative to oral ganciclovir and, in some cases, injectable ganciclovir. In patients with active CMV retinitis, the dosage of valganciclovir is 900 mg twice a day for 21 days with food. The dosage is decreased in patients with renal dysfunction.

The 900-mg twice a day dosage of valganciclovir costs approximately \$100 per day. Although valganciclovir is more expensive than oral ganciclovir, its increased utility appears to warrant the increased expense.

Valganciclovir is recommended for the treatment of CMV retinitis in patients with AIDS, the prevention of CMV in patients undergoing solid organ and bone marrow transplants, and the treatment of CMV antigenemia in solid organ and hematopoietic stem cell transplant patients.

Whether oral ganciclovir could be deleted was considered. Because it is still used in pediatrics, it was decided that it would be premature to delete it at this time.

Mitotane is an adrenocortical anti-neoplastic agent used almost exclusively for adrenocortical carcinoma. Adrenocortical cancer is very rare and the Oncology Division supports its deletion. It has not been used in the last 20 months. It costs approximately \$250 per 100 tablets. It can be obtained nonformulary if it is needed.

Porcine secretin was made for many years by Ferring AB, a Swedish pharmaceutical company. It was used for in vivo diagnostic use in pancreatic dysfunction. The market demand was low for this product and Ferring anticipated the introduction of a synthetic secretin on the market. The company created enough of the hormone to supply the market for several years and then discontinued its secretin production. This limited quantity was quickly depleted by off-label use secretin—primarily for autism. There currently is no commercial alternative. Human recombinant secretin is still investigational.

Fenoldopam is a selective D1-dopamine agonist with a labeled indication for the short-term management of severe hypertension. Fenoldopam was 1st evaluated in 1998 for use in patients undergoing thoraco-abdominal aneurysm (TAA) repairs to help prevent renal dysfunction. There was evidence that fenoldopam increases urine output, and there was an abstract published in a small number of patients that suggested that it might be beneficial for this indication.

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Formulary update, from page 2

An ad hoc expert committee was formed to consider whether fenoldopam should be listed in the *Formulary*, when it should be used if added, and whether any limitations needed to be put on its use. The ad hoc committee concluded that there was insufficient evidence to conclude that fenoldopam was better than the available antihypertensive agents were. It was more than 100-times more expensive than the alternatives (eg, nitroprusside).

The ad hoc committee recommended that fenoldopam be allowed to be used nonformulary for use in TAA repairs. The data on effectiveness was then compared with historical controls to determine whether there was any measurable renal-sparing benefit.

These data were collected for 50 patients in each group. The analysis of these data did not show any measurable renal-sparing effects for fenoldopam. The trend was that the fenoldopam-treated patients had worse renal function compared with the controls. Therefore, fenoldopam was designated nonformulary and not available.

Although studies using historical controls are not optimal, the internal data are better than any currently available published data. Should new published data become available, the formulary status of fenoldopam can be re-evaluated.

Hydrocodone-acetaminophen combinations have frequently been requested for nonformulary use by patients who are taking this combination on admission for pain. All hydrocodone-acetaminophen combinations (co-hycodAPAP) were deemed nonformulary and not available. There is no obvious reason to start a patient on a co-hycodAPAP in the hospital. Patients admitted on hydrocodone-acetaminophen can be switched to oxycodone plus acetaminophen or oxycodone alone. Hydrocodone and oxycodone are equipotent on a milligram-per-milligram basis.

Co-hycodAPAP combinations are often used to manage moderate to moderately severe pain in a variety of patients. The use of acetaminophen with hydrocodone allows a lower dose of each agent to be used than if either agent were used alone. However, by using a fixed-dose combination, it limits the prescriber's ability to raise dosages beyond the maximum daily dose of acetaminophen.

Hydrocodone is a semi-synthetic opioid similar to codeine. It is only available in combination with other drugs. It is most commonly used in combination with acetaminophen for

pain control. Hydrocodone does not have any therapeutic advantages compared with other opioids, like oxycodone. However, co-hycodAPAP is a Schedule III controlled substance, while co-oxycodAPAP is a Schedule II controlled substance. This quirk in the law allows for more convenient outpatient prescribing of hydrocodone combinations. A Schedule II controlled substance prescription must be written new each time (ie, no refills) and it cannot be telephoned into a pharmacy. Since co-hycodAPAP combinations can be refilled and telephone into a pharmacy, they are popular. This "advantage" does not apply to the inpatient setting.

As tolerance develops with chronic use, the dosage of hycodAPAP has to be increased to get the same therapeutic benefit. This argues against fixed combinations of hydrocodone with acetaminophen for chronic pain.

Acetaminophen is a widely used for its analgesic and antipyretic effects. When used in appropriate doses, it has a very safe adverse effect profile. In large acute or chronic dosages, acetaminophen can be hepatotoxic. Current guidelines recommend that the daily ingestion of acetaminophen be limited to 4 grams per day when used for a short duration (ie, 10 days or less). If used for longer than 10 days, the total daily dose of acetaminophen is recommended to be 2.6 grams per day or less. Further, it is recommended that patients avoid the use of alcohol if taking more than an occasional 1 or 2 doses of acetaminophen. This recommendation comes from the increased risk of liver toxicity, especially in alcoholics, with high doses or prolonged use.

Shands' policy does not allow patients to use their own supply of controlled substances. Patients who bring in their own supply of drugs like Vicodin®, Lortab®, or Lorcet® will have their prescriptions sent home with their families or stored securely with their other valuables until their discharge.

Papain-Urea-Chlorophyllin Complex sodium ointment is used to "promote the healing" of acute and chronic wounds. Papain is in the ointment for its proteolytic effects (ie, debridement). When used alone, papain is an ineffective debriding agent. Papain requires the presence of activators to exert its digestive function. Urea is in the ointment to expose, by solvent action, the papain activators and to denature nonviable protein matter in lesions to make it more susceptible to enzymatic digestion. Chlorophyllin copper complex sodium is purported to add wound-healing properties to the combination by promoting healthy

granulation, controlling local inflammation, and reducing wound odors.

There are no randomized controlled trials supporting the effectiveness of Panafil®. Presumably, Panafil® is on the market based on anecdotal data from the 1940s and 1950s. Because of the lack of objective evidence of effectiveness, the P&T Committee did not add Panafil® in the *Formulary*.

Ziprasidone is the 5th atypical antipsychotic marketed in the US. It is most similar to risperidone, olanzapine, and quetiapine, all of which are in the *Formulary*. Clozapine is not listed in the *Formulary* because of its limited distribution system. Because of the risk of agranulocytosis, a limited supply of clozapine is released once the distributor has evidence of an adequate white blood cell count. Clozapine remains an important therapeutic option—even though it is not listed in the *Formulary*, because of its efficacy in the treatment of patients with resistant schizophrenia.

The therapeutic choice among the atypical antipsychotics is generally based on the adverse drug effect profile, with the most common adverse effects influencing product selection. Ziprasidone appears to be an attractive agent because it does not cause the significant weight gain associated with olanzapine and, to a lesser extent, risperidone and quetiapine. It may also have less of an effect on serum lipids and other metabolic effects (eg, less effect on prolactin and blood glucose).

However, there are limited comparative data published on the efficacy and safety of ziprasidone compared with other atypical agents. The limited data that are available are poor quality. The weight gain effects of ziprasidone appear to be similar to haloperidol. It also appears as effective as haloperidol. A superior effect on negative symptoms compared with haloperidol has not been shown in published trials.

The potential for cardiac toxicity is an issue with ziprasidone. Ziprasidone's labeling states that when deciding among the alternative treatments for schizophrenia, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT-interval compared with several other antipsychotic drugs.

Certain circumstances may increase the risk of torsade de pointes and sudden death in association with the use of drugs that prolong the QT-interval, including bradycardia,

(continued on next page)

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ADVERSE DRUG REACTION PROGRAM

Information on patients' allergies

Where do you find up to date information on your patient's allergies? You ask the patient...right? What if they cannot tell you because of their age, present condition or absence of a knowledgeable care giver?

Next, you would probably look the hospital computer system (ie, HIS). Have you ever thought about how this information gets there?

When a patient is admitted to the hospital, several people ask about allergies including physicians, admitting staff, and the patients' nurses. Thanks to the admission and nursing staffs, we have a good system in place

to compare a patient's verbal reports and admitting orders with HIS. This information is also transmitted to the Pharmacy Department, where another check on allergies takes place when a medication order is processed. So why bring this topic up?

The Medication Safety Committee has been investigating problems associated with the reporting and documentation of allergies. Although everything seems to work well on admission to the hospital, there are several potential "holes" that need to be patched to prevent our patients from getting drugs or food to which

they are allergic. We are asking the housestaff to make a habit out of writing an order in the medical record to add a newly discovered allergy to HIS or to correct an allergy that was incorrectly recorded in HIS. Although documentation of new allergies is usually made in the progress notes, this information is not always read by people who need to know. The nursing staff and pharmacy staff will be happy, upon notification, to make sure that HIS and the notices on the back of the charts are updated.

by Kathleen Reilly, PharmD

Formulary update, from page 3 hypokalemia or hypomagnesemia, concomitant use of other drugs that prolong the QT-interval and the presence of congenital prolongation of the QT-interval. Ziprasidone should be avoided in patients with conditions or concomitant drugs that prolong the QT-interval. In patients at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium

levels done. Patients on diuretics and with diarrhea may be at risk and electrolytes should be periodically monitored. Ziprasidone should be avoided in patients with histories of significant cardiovascular illness (ie, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or arrhythmia). Patients taking ziprasidone who experience symptoms that could indicate torsade de pointes like dizziness, palpitations, or syncope

should be evaluated further (eg, Holter monitoring).

The P&T Committee concluded that there is currently insufficient published evidence to support the addition of ziprasidone in the *Formulary*. As additional information on the efficacy and safety of ziprasidone become available, the P&T Committee will reconsider the formulary status of ziprasidone.