

Drugs & Therapy

B U L L E T I N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met May 17, 2005. 8 drugs or dosage forms were added in the *Formulary* and 2 dosage forms were deleted. 1 dosage form was evaluated and designated non-formulary and not available.

◆ ADDED

Acamprosate
(Campral® by Forest Pharmaceuticals)

Bevacizumab
(Avastin® by Genentech)*

*Restricted to oncology prescribers AND pharmacy administration approval.

Bosentan
(Tracleer® by Actelion... distributed by Accredo)**

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

Cefdinir Suspension
(Omnicef® by Abbott Laboratories)

Fenofibrate Tablets
(Tricor® by Abbott Laboratories)***

***Only the 48-mg and 145-mg tablets are available.

Irbesartan
(Avapro® by Bristol Myers Squibb)

Naltrexone (generic)

Oxycodone-Acetaminophen
(eg, Percocet)****

****A "Percocet" generic will be automatically dispensed for orders for "Tylox." Effective 7/1/05.

◆ DELETED

Fenofibrate (old Tricor®)***

Oxycodone-Acetaminophen
(eg, Tylox)****

◆ NONFORMULARY & NOT AVAILABLE

Cefdinir Capsules
(Omnicef® by Abbott Laboratories)

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PRESCRIBING

Hepatic dysfunction & drug dosing: The ABCs of the Child-Pugh Score

Child and Turcotte published their empirical criteria for the prognosis of hepatocellular functional reserve in 1964. It was proposed as a tool for determining whether a patient should undergo surgery for the complications of portal hypertension. There have been modifications to the original criteria, and the Child-Pugh score represents the version used today in clinical practice. The Child-Pugh score predicts the probability of death; it also quantitatively estimates liver function and the capacity to tolerate invasive procedures, such as surgery.¹

The Child-Pugh score estimates liver function with a "score" based on selected variables, which helps determine what kind of adjustments need to be made in drug dosages. The 5 components of the Child-Pugh score are serum bilirubin, serum albumin, ascites, neurological disorder (encephalopathy), and prothrombin time.³ A patient is graded as either A, B, or C, with C associated with the worst prognosis. It is generally, but not universally, accepted that patients with a score between 5 to 8 are grade A, between 9 to 11 are grade B, and with a score between 12 to 15 are grade C.³

THE CHILD-PUGH SCORE²

Points	1	2	3
Encephalopathy	None	Minimal	Advanced (coma)
Ascites	Absent	Controlled	Refractory
Total Bilirubin	Less than 2	2-3	Greater than 3 (mg/dL)
Albumin (g/dL)	Greater than 3.5	2.8-3.5	Less than 2.8
Prothrombin Time Prolongation (sec)	Less than 4	4-6	Greater than 6

In addition to being a prognostic indicator, the Child-Pugh score is used for adjusting drug doses based on hepatic function, similar to how the Cockcroft-Gault equation is used to adjust doses based on renal function. The liver is critical for metabolism and clearance of some drugs and their metabolites. With hepatic impairment, drug accumulation or failure to form active metabolites can lead to toxicity or lack of efficacy. Liver disease can further lead to kidney impairment, which can also contribute to drug accumulation, even when the liver is not primarily responsible for the metabolism of the drug.²

In 2003, the FDA published guidelines for industry for pharmacokinetics in patients with impaired hepatic function.¹ The purpose was to propose recommendations for study design and dosing of drugs. The FDA recommended that pharmacokinetic and pharmacodynamic studies be conducted in
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- ◆ Non-formulary presentations

Formulary update, from page 1

Acamprosate is 1 of 3 commonly used drugs used for the promotion of abstinence in alcohol dependence. The other drugs are **naltrexone** (ReVia® and generics), and **disulfiram** (Antabuse®). These agents were reviewed for potential use at Shands at Vista's substance abuse treatment program.

The agents used for alcohol abstinence all work by different proposed mechanisms. Disulfiram discourages alcohol consumption by inhibiting metabolism. This results in the accumulation of acetaldehyde and produces nausea (and other adverse symptoms). Disulfiram is rarely used today and remains nonformulary. Both naltrexone and acamprosate are thought to inhibit alcohol craving via different mechanisms. Because these agents have different mechanisms of action, combination therapy has been used to try to decrease relapse rates.

Although the exact mechanism of acamprosate is unknown, it is a synthetic taurine derivative with a structural resemblance to gamma-aminobutyric acid (GABA). It is thought to have GABA agonist activity and glutamate inhibitory activity. It presumably restores the balance between neuronal inhibition and excitation that is altered with chronic alcohol use.

Naltrexone is thought to work by the inhibition of natural opioids (ie, endorphins) that are associated with the positive rewards of alcohol abuse. Since naltrexone is an opioid antagonist, it cannot be used in patients requiring opioids.

Published evidence shows acamprosate has modest efficacy compared with placebo when both are used with psychosocial support. Acamprosate has similar efficacy to naltrexone when both agents are used alone. Efficacy improves when these agents are used in combination. Therefore, acamprosate and naltrexone were added in the *Formulary*. Acamprosate alone may be useful when naltrexone cannot be used (ie, patients with severe liver disease or receiving opioids).

Acamprosate is often taken with food because this helps patients comply with the difficult, 3-times-a-day dosage. Acamprosate's half-life is prolonged in renal dysfunction and the dosage is halved with a creatinine clearance between 30-50 mL/min, and it is not recommended when the creatinine clearance is less than 30 mL/min. It is unclear why a drug with a long half-life (20-33 hrs) must be given 3 times a day.

Most patients appear to tolerate acamprosate; common adverse

effects are not serious. Suicidality, renal failure, and toxic epidermal necrolysis are potential serious adverse effects.

Acamprosate is more expensive than naltrexone in the inpatient setting; however, it is similarly priced in the outpatient setting (ie, ~\$125/month).

Bevacizumab is a recombinant, humanized monoclonal antibody that inhibits vascular endothelial growth factor, thus inhibiting angiogenesis. By inhibiting blood vessel development, bevacizumab disrupts and limits tumor growth, invasion, and metastases. Its lack of cytotoxicity requires that bevacizumab be used in combination with other cytotoxic agents to produce synergism.

Bevacizumab has a labeled indication for use in combination with intravenous fluorouracil-based chemotherapy as a treatment for patients with first-line or previously untreated metastatic cancer of the colon or rectum. This indication is based on the results of a randomized, phase III study that compared irinotecan, fluorouracil, and leucovorin (IFL) with placebo to IFL plus bevacizumab in patients with histologically confirmed metastatic colorectal carcinoma that was previously untreated. The median duration of survival was 4.7 months longer in the group who received IFL plus bevacizumab. The median duration of progression-free survival was 4.4 months longer. In the safety analysis, there was a 10% higher incidence of any grade 3 or 4 adverse events in the bevacizumab group, which mainly included grade 3 hypertension (controlled with anti-hypertensive medications) and a small incidence in grade 4 leukopenia and diarrhea. Gastrointestinal perforation occurred in 6 patients (1.5%) receiving IFL plus bevacizumab. This finding led the manufacturer of bevacizumab to include a black-box warning on the labeling of the product for gastrointestinal perforations.

Currently, the standard of care for metastatic colon cancer at Shands at UF is FOLFOX4 (oxaliplatin, fluorouracil, and leucovorin) plus bevacizumab. Since FOLFOX4 plus bevacizumab is first-line therapy, these patients are treated on admission with this regimen.

Also, there is a subset of patients who are too unstable to receive their chemotherapy regimens as outpatients due to their poor health status and who are intolerant of chemotherapy-induced adverse reactions (eg, severe nausea). These patients require more frequent monitoring and must receive their chemotherapy in the hospital.

Bevacizumab will be restricted to chemotherapy prescribers and to pharmacy administrative approval. Most patients should receive bevacizumab as

outpatients. Administrative approval will prevent shifting to inpatient administration to avoid expensive co-pays. It will also avoid unnecessary use of inpatient beds, which are in short supply.

Bosentan is an endothelin antagonist that is an oral alternative to intravenous epoprostenol (Flolan®) for the treatment of pulmonary hypertension. Bosentan was initially listed in the *Formulary*; however, 2 years ago it was deleted because it could no longer be stocked in the hospital.

The FDA mandated a limited distribution program for bosentan because of its potential to cause serious liver injury. Dosage adjustments are critical with elevated liver function tests. Bosentan can cause major birth defects; therefore, documentation that a patient is not pregnant was also deemed critical. Only a limited distribution network can dispense bosentan in the outpatient setting. These specialty pharmacies verify liver function tests and pregnancy tests before the supply of bosentan is dispensed.

In a recent reversal of policy, the distributors of bosentan (Accredo) notified Shands at UF that bosentan could be stocked for use in "approved patients only." This presents operational issues (ie, determining who is an "approved patient" when bosentan is ordered). However, Accredo will not provide bosentan to patients when they are hospitalized. It is impossible for patients to use their own supply if they need a refill during their hospitalization. This requires that bosentan be re-added in the *Formulary*.

Bosentan is restricted to approved patients (ie, those patients accepted into the limited distribution program). Pharmacists will screen for approval by contacting Accredo at the toll-free number, which is available 24 hours a day, 7 days a week.

Cefdinir suspension is an oral third-generation cephalosporin with good in vitro activity against many of the pathogens that commonly cause community-acquired infections. It was evaluated proactively because of interest by pediatric practitioners.

Cefdinir suspension is convenient (ie, given once or twice a day), is well tolerated (ie, few common adverse effects), tastes good, may be less expensive that similar liquid antibiotics (eg, Augmentin® and cefuroxime), and is equally effective in clinical trials. For these reasons, the Anti-Infective Subcommittee recommended the addition of cefdinir suspension in the *Formulary*. **Cefdinir**
(continued on next page)

Formulary update, from page 2 capsules were not recommended for approval, because they are more expensive than alternatives.

Cefdinir is active against *Staphylococcus aureus*, methicillin-sensitive *Staphylococcus epidermidis*, penicillin-sensitive *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, Viridans-group streptococci, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Citrobacter diversus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. It does not have activity against *Pseudomonas aeruginosa*. Cefdinir has a labeled indication for mild to moderate infections caused by susceptible organisms. The labeled pediatric indications include pharyngitis/tonsillitis, uncomplicated skin and skin structure infections, and acute bacterial otitis media. Cefdinir is useful for a variety of mild to moderate respiratory and skin infections.

Typical adverse reactions associated with cefdinir are similar to those found with other antibiotics and include diarrhea, nausea, abdominal pain, rash, and headache. As with most antibiotics, pseudomembranous colitis has been reported.

The oral suspension used in children is roughly the same cost as amoxicillin-clavulanate. It is, however, less expensive than cefuroxime

suspension. In adults, the capsules are more than twice the cost of generic amoxicillin-clavulanate tablets and 3 times the cost of cefuroxime tablets.

Taste tests of cefdinir suspension in children show good palatability. Cefuroxime suspension is rarely used because its taste is unpleasant.

Fenofibrate is a fibric acid derivative used to treat dyslipidemias. The strength of tablets listed in the *Formulary* needed to change because of product availability. The patent recently expired for the most commonly used dosage form of fenofibrate. Although the FDA has approved generic versions of the old formulation of Tricor® (ie, the 54-mg and 160-mg tablets), these generic products have not yet been marketed.

Tricor® has been reformulated to be more bioavailable, and the new 48-mg and 145-mg tablets are equivalent to the old 54-mg and 160-mg tablets. This appears to be a patent extension move, but we have no choice except to switch to these tablets since the old strengths are no longer available. Both the old and new strengths of Tricor® tablets are equivalent to the older 67- and 200-mg capsules. The P&T Committee previously approved therapeutic interchange of the tablets for the capsules.

The 48-mg and 145-mg Tricor® tablets will be the only dosage forms listed in the *Formulary*. Orders for old strengths will now have to be clarified in order to

avoid medication errors (ie, patients receiving a double dose of the old and new strengths after discharge).

Irbesartan is 1 of 6 angiotensin receptor blockers (ARBs) on the market. 2 ARBs (ie, losartan and valsartan) have been listed in the *Formulary*, but irbesartan has been the most commonly prescribed nonformulary drug. Irbesartan was added in the *Formulary* for convenience, not based on therapeutic superiority.

A generic version of **Percocet**® will be the oxycodone-acetaminophen combination listed in the *Formulary* effective July 1, 2005. Orders for **Tylox** will be interchanged to oxycodone 5 mg + acetaminophen 325 mg.

It is a goal to lower patients' daily exposure to acetaminophen from various sources to promote medication safety. Percocet generics have less acetaminophen per dose (ie, 325 mg per tablet versus 500 mg per capsule in Tylox generics).

A Cochrane review of oxycodone-acetaminophen combinations concluded that the dose of acetaminophen has not been shown to make a difference in efficacy between 325 mg, 500 mg, and 1 gram of acetaminophen. The combination is, however, more effective than oxycodone alone.

Prescribers who wish to use a higher dose of acetaminophen with oxycodone can prescribe each ingredient individually.

Prescribing, from page 1

patients with impaired hepatic function if hepatic metabolism and/or excretion accounts for a portion (greater than 20% of the absorbed drug) of the elimination of the parent drug or the active metabolite. They also recommended conducting studies in patients with hepatic impairment if the drug or metabolite is eliminated to a lesser extent (less than 20%), if it has a narrow therapeutic range.

Package inserts contain information regarding the Child-Pugh score and dosage adjustments that need to be done based on the score. For example, the package insert for caspofungin (Cancidas®) states that there is no dosage adjustment needed in patients with mild hepatic insufficiency (Child-Pugh score 5-6). However, in patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), following the 70-mg loading dose, a dose reduction to 35 mg/day is recommended. It further states that there is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score greater than 9).⁴

In order to develop specific dosing guidelines in patients with hepatic impairment, a study needs to be con-

ducted in patients in all 3 categories of the Child-Pugh score. Between 1995 and 1998, the FDA conducted a survey of 57 pharmacokinetic studies in patients with hepatic impairment. They discovered that 55% of the studies used the Child-Pugh score in order to determine hepatic impairment. 19 of the 57 studies assessed oral drug clearance in patients with and without hepatic impairment. Of the 19 studies, 17 demonstrated a negative correlation between oral drug clearance and hepatic impairment. 16 studies showed impaired hepatic metabolism in patients with Child-Pugh grade B hepatic dysfunction. Based on these findings, the FDA recommended that the Child-Pugh score be used to categorize the degree of hepatic impairment in patients.²

The lack of knowledge and utilization of the Child-Pugh score can be attributed to the several limitations of this scoring system.³ The first limitation is that the 5 components of the Child-Pugh score have been selected empirically, rather than based on objective evidence (ie, a multivariate analysis). Another limitation is the selection of cut-off values for the variables. There is no evidence to support that the cut-off levels chosen are the ideal values for

defining significant changes in mortality. In addition, there is no evidence to indicate that the risk of mortality increases linearly across Child's grades A, B, and C.

A third limitation is that each variable holds as much weight as the next variable. This results in overestimating or underestimating the true influence of each variable. When discrete variables (eg, encephalopathy and ascites) are graded using arbitrary categories (eg, none, minimal, or advanced), measurement bias can affect the results. Despite its limitations, the Child-Pugh score is the only widely used estimate for the adjustment of drugs in patients with hepatic impairment. Unfortunately, it is not as well understood as such measurements for renal dysfunction (eg, the Cockcroft-Gault equation), but it does give guidance for drug therapy adjustments.

by *Jamie Shapiro, PharmD*

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POLICIES AND PROCEDURES

Nonformulary drug presentations prohibited

Drug manufacturers' sales representatives must abide by established rules in order to be permitted into Shands at UF. Access to the hospital is a privilege, and following the guidelines for drug manufacturers' sales representatives is required in order to have this access.

These rules are reviewed with all sales representatives, and they must adhere to these policies or face disciplinary actions. After the first infraction, the Director of Pharmacy or his designee will meet with the sales representative to review the policy. The second infraction will result in a meeting with the sales representative and their supervisor. The third infraction will result in a 3-month suspension. The most serious listed consequence of not following the established rules would be the manufacturer (not just the sales representative) not being allowed to have representatives in the hospital for 6 months.

The policy does allow for more severe consequences if additional disciplinary actions are necessary. Fortunately, violations of this policy are very rare, and action is usually limited to a meeting to review the rules with the

sales representative or their immediate supervisor. With each infraction, the drug manufacturers' sales representative and their immediate supervisor receive a written report stating their infraction and the disciplinary action taken.

The P&T Committee recently approved revisions in this policy to strengthen the rules regarding presentations about nonformulary drugs on the hospital's premises. Nonformulary presentations to housestaff (ie, interns, residents, and fellows) are prohibited. Nonformulary drug presentations should be limited to attending physicians. This prohibition is based on limiting discussions to those who can request that a drug be considered for formulary addition. It is the role of the attending physician to evaluate the information presented.

The prohibition of presentations about nonformulary drugs is now also extended to Shands at UF staff who cannot request drugs for formulary addition. Currently, the only hospital staff who can request the evaluation of a drug for formulary addition are pharmacists.

The purpose of limiting drug manufacturers' sale representatives from presenting nonformulary drugs is to avoid demand for drugs that are not readily available. By definition, drugs not listed in the *Formulary* are not readily available. Sales pressures may stimulate the use of products that are not available.

This prohibition does not apply to presentations outside of the hospital.

Other important limitations on drug manufacturers' sales representative activities are included in this policy. For example, all representatives must register at Hospital Purchasing before meeting with anyone in the hospital. They may not be in any patient care areas (eg, nursing wards, ICUs, the OR). Representatives must have a definite scheduled appointment for each meeting. Pens, pads, calendars, and other "gifts" with drug product information cannot be left in hospital areas.

If drug manufacturers' sales representatives are observed violating any of these policies, please contact the Department of Pharmacy Services at 265-0404.