

Drugs & Therapy

B ♦ U ♦ L ♦ L ♦ E ♦ T ♦ I ♦ N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met December 17, 2003 and January 20, 2004. 2 drugs were added in the *Formulary*. 1 drug was deleted and designated non-formulary and not available, while several brands of a nonformulary drug were designated not available. New restrictions were placed on 1 drug.

◆ ADDED

Oxaliplatin (Eloxatin® by Sanofi)*

*Restricted to credentialed chemotherapy prescribers

Somatropin (Saizen® by Serono)

◆ DELETED

Theophylline liquid (generic)**

**Designated nonformulary and not available

◆ NONFORMULARY AND NOT AVAILABLE

Somatrem
(Protoprin® by Genentech)

Somatropin
(Genotropin® by Pharmacia)

Somatropin (Humatrope® by Eli Lilly and Company)

Somatropin
(Norditropin® by Novo Nordisk)

Somatropin (Nutropin® & Nutropin AQ by Genentech)

Somatropin (Serostim by Serono)

Somatropin Depot
(Nutropin® Depot by Genentech)

Theophylline elixir (generic)

◆ CRITERIA FOR USE CHANGES

Nesiritide (Natrecor® by Scios)***

***Restricted to its labeled indication & "bridge to transplant"

(continued on next page)

PRESCRIBING

Treatment options for alcohol withdrawal

Alcoholic beverages (beer, whiskey, and wine) were deleted from the Shands at UF *Formulary* in March 2003. The role of oral alcohol for the prevention of alcohol withdrawal is suspect, and "dispensing" alcoholic beverages without a liquor license is questionable. Therefore, how should alcoholic patients be managed during their hospitalization?

Benzodiazepines are the drugs of choice for prevention of acute alcohol withdrawal.

Alcoholism is common, affecting up to 10% of the American population at some point during their lives.¹ With the high prevalence of the disease, healthcare professionals will frequently encounter patients experiencing alcohol dependence and alcohol withdrawal. Medications have been proven to successfully control symptoms of alcohol withdrawal.

Symptoms of alcohol withdrawal include anxiety, agitation, nausea/vomiting, tachycardia, hypertension, insomnia, diaphoresis, hallucinations, delirium tremens, and seizures.² A goal of managing alcohol withdrawal is to prevent these adverse effects. However, it is particularly important to prevent the more serious effects such as delirium tremens and seizures.

Benzodiazepines are the drugs of choice for prevention of acute alcohol withdrawal. Benzodiazepines reduce the risk of seizures and delirium. In a meta-analysis of studies for the pharmacological management of alcohol withdrawal, 6 prospective, placebo-controlled trials evaluating the effects of benzodiazepines on alcohol

withdrawal symptoms showed significant overall risk reductions in seizures (reduction of 7.7 seizures per 100 patients treated) and delirium (reduction of 4.9 cases per 100 patients treated). Trials done to compare efficacy of different benzodiazepines in alcohol withdrawal have shown that there is no difference among agents in reducing symptoms.

However, available data suggest that longer-acting benzodiazepines, such as chlordiazepoxide and diazepam, may be more effective in preventing seizures. The duration of action provided by these agents provides less opportunity for breakthrough symptom activity than short-acting agents. Shorter-acting agents, such as lorazepam and alprazolam, provide less risk of excess sedation. This may be particularly important in certain populations, such as the elderly.³

Other medications with anticonvulsant activity, including barbiturates and carbamazepine, have been used for their effects in alleviating symptoms of alcohol withdrawal. Only 1 controlled trial compares a barbiturate to diazepam. This study showed no difference between these agents in time to effect or clinical condition. It is important to remember that barbiturates may cause respiratory depression, particularly when combined with alcohol, and they have a lower safety profile overall when compared to benzodiazepines. Carbamazepine lacks sufficient evidence in humans

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Oxaliplatin is a third-generation platinum analog with antitumor activity in various types of solid tumors, particularly gastrointestinal cancers. It has a labeled indication for the treatment of patients with meta-static colon cancer whose disease has progressed or recurred within 6 months of completing first-line therapy with 5-fluorouracil (5-FU) and leucovorin. Oxaliplatin is used in combination with 5-FU and leucovorin for metastatic colon cancer.

Clinical studies have shown that oxaliplatin produces good response rates in metastatic colon cancer. It has also been used alone or in combination for other gastrointestinal (ie, pancreatic and gastric), ovarian, lung, head & neck, prostate, and breast cancers in Phase I and Phase II trials.

The adverse effects of oxaliplatin are distinct from other platinum analogs. Cold-related dysesthesia and dose-limiting cumulative peripheral sensory neuropathy are the most concern. Other common adverse effects include neutropenia, diarrhea, nausea, vomiting, and mucositis.

Colorectal cancer is usually treated as an outpatient. However, some patients who are newly diagnosed may require hospitalization followed by immediate treatment with oxaliplatin. Therefore, oxaliplatin was added for these infrequent patients. Like all cytotoxic cancer chemotherapy, oxaliplatin prescribing is limited to credentialed prescribers.

The Saizen® brand of **somatropin** was added in the *Formulary* for use in patients prescribed growth hormone during their hospitalization. Occasionally patients on chronic growth hormone therapy are admitted to Shands at UF. It can be problematic when these products are requested through the nonformulary process. Although all somatropin growth hormone products are the same chemical entity, they come in different dosage forms.

When the P&T Committee reviewed growth hormone products, the focus was on whether there is sufficient evidence to support the inpatient use of these products and whether there is any evidence to support differences in tolerability among the products. It was determined that there is ample evidence to support the use of growth hormone for use in the inpatient setting. This is supported by meta-analyses and published guidelines. However, there are no data to support differences in tolerability among the products.

There are published surveys that show patients do prefer 1 brand of

growth hormone to another. Further, a national survey of pediatric endocrinologists shows that practitioners do not support the interchange of these products. However, these surveys apply to the outpatient setting. Pediatric endocrinologists at UF supported the selection of 1 product for *inpatient* use.

The Saizen® brand was selected because it can be purchased as single vials, does not need to be refrigerated, is low cost (compared with the other brands), and is versatile enough to provide a broad range of doses. All other brands of somatropin (Genotropin®, Humatrope®, Norditropin®, Nutropin®, Serostim®, and Protropin®) were designated not available. Somatropin will be handled in a controlled manner because of its potential for diversion, even though it is not a controlled substance.

Somatrem, a form of growth hormone with an additional amino acid (ie, methionine) compared to native human growth hormone (ie, somatropin), was designated nonformulary and not available. Also, the **depot** form of **somatropin** was designated nonformulary and not available. The depot form is associated with a high rate of injection site reactions and inpatient reimbursement schemes do not cover this dosage form.

Theophylline liquid is a drug that has been used for decades to treat respiratory problems. It is used infrequently today to treat asthma and neonatal apnea.

The only manufacturer of an alcohol-free theophylline oral liquid (18 mg/mL) has stopped making this dosage form. Theophylline liquid is now only available as an 80-mg/15-mL elixir. This less-concentrated, alcohol-containing liquid cannot be used in neonates to treat apnea. Therefore, **theophylline elixir** has not been listed in the *Formulary*. Its availability could have resulted in medication errors.

Neonates with apnea should be treated with caffeine liquid, which is listed in the *Formulary*. The lack of a liquid theophylline dosage form should not be a problem in this population.

Whether theophylline liquid is needed in adults is debatable. Therefore, all liquid forms of theophylline were designated nonformulary and not available. Oral extended-release tablets and bead-filled capsules are also listed in the *Formulary*. The bead-filled capsules could be used instead of theophylline liquid in children and adults, if needed.

Nesiritide is a recombinant form of human brain natriuretic peptide. It was added in the *Formulary* in the fall of 2001 for use in the treatment of acute decompensated heart failure, which is the labeled indication.

There has been considerable use of nesiritide for off-label indications at Shands at UF. The projected expenditures of nesiritide led to an evaluation of whether the use of nesiritide at Shands at UF is justified.

Interested parties, who were identified as major off-label users of nesiritide, were invited to submit science supporting their use of nesiritide. In order to evaluate the quality of the available evidence, an ad hoc committee of the P&T Committee was formed. This ad hoc committee was composed of 7 faculty staff physicians with varying backgrounds (eg, cardiology and nephrology) including expertise in evidence-based medicine. There was 1 pharmacist on the committee and 1 ex-officio pharmacist. The ex-officio pharmacist was a non-voting member who did the search of the literature and summary of the available evidence. The Nesiritide Ad Hoc Committee was provided with a summary of the data and copies of the available literature. All information submitted by the interested parties was also provided.

The P&T Committee evaluated 5 questions.

- Is there sufficient scientific evidence to support the off-labeled use of nesiritide in patients who are awaiting heart transplantation (ie, bridge to transplantation)?
- Is there sufficient scientific evidence to support the off-labeled use of nesiritide in post-cardiothoracic surgery patients to prevent renal injury?
- Is there sufficient scientific evidence to support the off-labeled use of nesiritide in patients undergoing mitral valve surgery?
- Is there sufficient scientific evidence to support the off-labeled use of nesiritide in patients that have diuretic-resistant fluid retention after atrial ablative procedures?
- Is there sufficient scientific evidence to support the off-labeled use of nesiritide in patients with pre-existing renal dysfunction who require procedures necessitating cardiopulmonary bypass?

The P&T Committee, using the input of the Nesiritide Ad Hoc Committee, concluded that there was only sufficient evidence to support the “bridge to transplant” indication. All other off-labeled uses were deemed inappropriate.

A Nesiritide Order Form will be used for an ongoing medication use evaluation to assure that the approved criteria for use are followed. Nesiritide can only be used for acute decompensated congestive heart failure or bridge to cardiac transplantation.

New drugs in 2003

Similar to last year, there were fewer new drugs approved in 2003 compared with historical standards. The 21 new molecular entities (NMEs) approved in 2003 (see Table on page 4) were higher than the 17 approved last year, which was the lowest total since 1983 when only 14 NMEs were approved.

A decrease in NMEs over the last 2 years is attributed to a lower number of submissions by pharmaceutical companies. FDA rejections or deferrals do not explain the decrease. This trend

is expected to continue in 2004. Only 25 NME submissions were submitted to the FDA in 2003. This suggests that a similar number of approvals will occur in 2004.

Several important new biologicals (ie, biological license applications or BLAs) were approved in 2003. This continues the trend of increasing biological approvals. The table includes some of the significant new biologicals that were approved in 2003.

Several new oncological agents are expected next year. Often these drugs

are given priority review, which increases their likelihood of being approved this year. The agents most likely to be approved this year include cetuximab, pemetrexed, and bevacizumab. As indicated by their names, 2 of these agents are monoclonal antibodies ("mab").

There were several important generics approved in 2003. Again, this trend is expected to continue in 2004. However, because the first generic to market receives exclusivity, the price breaks on generics usually take more than 6 month (eg, paroxetine).

Prescribing, from page 1

regarding its effectiveness in preventing seizures or delirium during withdrawal.⁴

Sympatholytics are another group of medications that have been postulated to alleviate symptoms of alcohol withdrawal. Antagonism of the increased sympathetic outflow present in withdrawal theoretically could assist in reducing symptoms. Beta-blockers and clonidine have been shown to normalize heart rate and blood pressure; however, these agents have not been shown to have any effect on preventing seizures or delirium. Also, correction of these vital signs may produce a false sense of security in patients who may be progressing to more serious symptoms within the withdrawal phase.⁴

Neuroleptic agents, which include phenothiazines and butyrophenones, may reduce some symptoms of withdrawal. These agents have not been proven to reduce delirium and they may actually increase the likelihood of seizures. Their use is recommended only in conjunction with benzodiazepines for patients with agitation.³

Ethyl alcohol is another agent that has been used in the past to treat withdrawal. Evidence demonstrating efficacy and safety compared to placebo and benzodiazepines is lacking. Also, alcohol has toxicities such as pancreatitis, bone marrow suppression, and hepatitis.⁴

The efficacy of medications used for alcohol withdrawal is of highest importance; however, the manner in which the medications are used to treat the patient is of equal relevance. Withdrawal symptoms can vary greatly; therefore, each pharmacological regimen for withdrawal must be individualized for each patient.

Guidelines suggest a structured assessment scale before starting treatment. The Clinical Institute Withdrawal Assessment Scale for Alcohol, Revised (CIWA-Ar), can be used to evaluate patients (<http://addiction-medicine.org/files/15doc.html>). This scale consists of several symptoms of alcohol withdrawal that the healthcare professional ranks according to severity. Ranked symptoms include visual, tactile, and auditory disturbances; nausea and vomiting; paroxysmal sweats; agitation; headache or fullness in the head; anxiety; tremor; and, degree of orientation. A total score composed of each symptom is formulated (maximum CIWA-Ar score = 67) and used to determine the level of treatment the patient should receive.²

Recommendations state that patients should be monitored by using this assessment every 4–8 hours until the cumulative score is < 8–10 for 24 hours. Patients with mild scores (< 8–10) may benefit from non-pharmacological supportive care only. In those with moderate scores (8–15), pharmacological therapy may lower the possibility of major complications and should be initiated. Patients who have scores \geq 15 should receive pharmacological management because they have considerable risk of developing complications. In patients with a history of withdrawal seizures and in those with significant concomitant diseases, medications should be considered regardless of the symptom score.³

Once the decision to initiate treatment has been made, medications may be given according to different treatment regimens. Fixed-schedule therapy provides doses of medication

at fixed intervals. Benzodiazepines given according to this treatment regimen are the gold standard for the treatment of alcohol withdrawal. An example of a fixed-schedule regimen is diazepam 10 mg intravenously every 6 hours for 8 doses, then 5 mg intravenously every 6 hours for 8 doses.³

Symptom-triggered therapy is another approach. This approach only uses medications when patients are symptomatic.

Medication is given aggressively until symptoms resolve, then they are stopped. For example, chlordiazepoxide 10–100 mg or diazepam 10–20 mg are given orally every hour when the CIWA-Ar score is = 8–10.⁴ The regimen is stopped when symptoms resolve or when the patient is sedated.

A front-loading regimen can also be used. This approach uses aggressive doses early in treatment when the patient is symptomatic (eg, diazepam 20 mg orally every 2 hours). The dosage is decreased when symptoms resolve. Most patients respond to 3 doses or less.⁴

Regardless of the approach used, benzodiazepine dosing should allow for variation in regimens and dosages depending on the patient's symptoms. Benzodiazepines currently listed in the *Formulary* that are commonly used in the treatment of alcohol withdrawal include diazepam, chlordiazepoxide, and lorazepam.

by Julie Whitehurst, PharmD

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NEW DRUGS & SELECTED BIOLOGICS APPROVED BY FDA IN 2003

GENERIC NAME

Abarelix
Agalsidase beta†
Alefacept†
Alfuzosin
Aprepitant†
Atazanavir†
Bortezomib
Botulism Immune Globulin‡
Daptomycin†
Efalizumab‡
Emtricitabine†
Enfuvirtide†
Epinastine
Gefitinib
Gemifloxacin
Ibandronate
Influenza Virus Vaccine, Live Intranasal‡
Laronidase‡
Memantine
Miglustat
Omalizumab††
Palonosetron
Pegvisomant
Prussian Blue
Rosuvastatin
Sertaconazole
Tadalafil
Tositumomab and Iodine I-131 Tositumomab‡
Vardenafil

TRADE NAME

Plenaxis®
Fabrazyme®
Amevive®
UroXatral®
Emend®
Reyataz®
Velcade®
BabyBIG®
Cubicin®
Raptiva®
Emtriva®
Fuzeon®
Elestat®
Iressa®
Factive®
Boniva®
FluMist®
Aldurazyme®
Namenda®
Zavesca®
Xolair®
Aloxi®
Somavert®
Radiogardase®
Crestor®
Ertaczo®
Cialis®
Bexxar®
Levitra®

INDICATION

Advanced, symptomatic prostate cancer
Fabry's disease
Severe chronic plaque psoriasis
Benign prostatic hyperplasia (BPH)
Chemotherapy-induced nausea and vomiting
HIV
Multiple myeloma
Botulism in infants
Antibiotic: gram-positive infections
Severe plaque psoriasis
HIV
HIV
Allergic conjunctivitis
Lung cancer
Fluoroquinolone antibiotic
Osteoporosis
Prevention of influenza
Mucopolysaccharidosis I
Alzheimer's disease
Gaucher's disease
Asthma
Chemotherapy-induced nausea and vomiting
Acromegaly
Treatment of radioactivity exposure
Hypercholesterolemia
Tinea pedis
Erectile dysfunction
Non-Hodgkin's Lymphoma
Erectile dysfunction

†Listed in the Shands UF *Formulary*

‡Biological