

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met March 17, 2009. 3 drugs were added in the *Formulary* with restrictions, while none were deleted. 2 drugs were designated nonformulary and not available and will be interchanged to formulary alternatives. Restriction criteria were changed for 2 drugs, and 1 "contraindicated" drug-drug combination was approved under specific conditions.

◆ ADDED

Desflurane (Suprane® by Baxter)*

*Restricted to the Florida Surgical Center

Loxapine

(Generics and Loxitane® by Watson)†

Thiothixene

(Generics and Navane® by Roerig)†

†Restricted to Shands Vista

◆ DELETED

None

◆ NONFORMULARY AND NOT AVAILABLE

Dexlansoprazole

(Kapidex® by Takeda Pharmaceuticals)‡

Megace® ES

(Megestrol Acetate Suspension)†
‡Interchanged

◆ INTERCHANGES

Lansoprazole (Prevacid®)
for **Dexlansoprazole**

Megestrol Suspension (Generic)
for **Megace® ES**

(continued on next page)

NEWS

Unapproved drugs: What do you mean "My colchicine is unapproved?!"

You might recall that only 3 months ago, papain-urea (Accuzyme®) ointment was removed from the *Formulary*. The reason for this was that Accuzyme® was an unapproved product and the Food and Drug Administration (FDA) had ordered manufacturers to stop

markets only a single ingredient from this product. For example, the combination of oral colchicine and probenacid is an FDA-approved drug. However, oral colchicine, as a single active ingredient, is an unapproved drug.

The opposite of this is when 2 ingredients are FDA-approved separately but are being marketed in combination as an unapproved drug.

There are also unapproved drugs whose makers claim have been "grandfathered" in, but they do not meet the requirements for this category. Under the 1962 Grandfather Clause, the Federal Food, Drug, and Cosmetics Act exempts a drug from effectiveness requirements if its composition and labeling have not changed since 1962. However, the FDA believes that genuinely "grandfathered" drugs represent only a few of all unapproved drugs currently marketed. Any change in formulation (eg, a sustained-release product) or labeling (eg, new adverse reactions listed) overrides the grandfather designation and makes the product unapproved.

What is the FDA doing to remove these unapproved drugs from the market? In June 2006, the FDA submitted its Compliance Policy Guide (CPG) on Marketed Unapproved Drugs. In this guide, the FDA outlined a risk-based approach to enforcement to concentrate its resources on those products that pose the highest threat to public health. The CPG gives highest priority to drugs that pose potential safety or health fraud risks, lack evidence of

(continued on page 5)

How many drugs on the market are unapproved, and how can unapproved drugs be readily available? What is the FDA doing to remove these unapproved drugs from the market? How can healthcare practitioners determine if a drug is FDA-approved?

making it. This story, while not unique, raises some interesting questions. How many drugs on the market are unapproved, and how can unapproved drugs be readily available? What is the FDA doing to remove these unapproved drugs from the market? How can healthcare practitioners determine if a drug is FDA-approved?

All drugs must be FDA-approved or comply with an OTC monograph unless they fall into 1 of the following categories: Drug Efficacy Study Implementation (DESI) review, OTC monograph pending, generally recognized as safe and effective (GRASE), or grandfathered.

The FDA estimates that about 2% of currently marketed drugs are unapproved. There are a number of reasons this happens. Sometimes only 1 company has approval to market a drug, but other companies illegally market their own version without approval.

This could also happen when a combination ingredient product has been approved by the FDA but a manufacturer

INSIDE THIS ISSUE

- ◆ Paying for prescriptions
- ◆ Burns from patches

◆ **CRITERIA-FOR-USE CHANGES**

Methadone (Generic)§

§Physicians certified in Pain or Substance Abuse may initiate and adjust dosage

Potassium Chloride Extended-Release

(K-DUR® by Key Pharmaceuticals)¶

¶Given with at least 100 mL of fluid and bed elevated greater than 45 degrees for at least 10 minutes

Tetanus Toxoid, Reduced Diphtheria Toxoid, & Acellular Pertussis Vaccine [Tdap]

(Adacel® by Sanofi Pasteur)**

**Restricted: Routine postpartum use prohibited

Last fall, **desflurane** was added in the *Formulary* for a 4-month evaluation. It was restricted to the Shands Florida Surgical Center (FSC). If overall use of inhaled anesthetics and propofol decreased at FSC during the evaluation period, then desflurane would be added permanently in the *Formulary* (but remain restricted to FSC).

Desflurane is an inhaled anesthetic gas that is vaporized to a gas and used for general anesthesia in combination with other gases and intravenous (IV) anesthetic agents (eg, propofol). Because the post-operative recovery of these agents is more rapid than with isoflurane, they may be preferred for outpatient surgeries.

A meta-analysis of articles published through 2003 comparing desflurane and sevoflurane found minor differences. No significant differences were detected in PACU recovery times.

The adverse effects associated with desflurane are the same as those associated with isoflurane and sevoflurane. Like all inhaled anesthetic gases, desflurane is associated with more post-operative nausea and vomiting (PONV) than propofol; however, the incidence of PONV is similar between desflurane and sevoflurane. Desflurane is the most pungent agent, with respiratory irritation seen above 1 minimum alveolar concentration (MAC). Therefore, desflurane is not used for mask induction.

Independent assessments of cost suggest that desflurane is generally more expensive than sevoflurane. Desflurane is available only from a single vendor and requires a special vaporizer for administration, which can add to expenses. However, the per-MAC-hour cost at a lower flow rate for desflurane (ie, 1 mL/hr) can be compared with a higher

flow rate for sevoflurane (ie, 3 mL/hr). Using a lower flow rate with desflurane requires extra effort to maintain adequate anesthesia.

Comparing purchase data (ie, of desflurane, sevoflurane, and propofol) from May 2008 through August 2008 with data from October 2008 through January 2009 shows overall cost of anesthetics decreased by 16% at the FSC. Therefore, desflurane remains in the *Formulary* and continues to be restricted to the FSC. There will continue to be periodic evaluations of anesthetic costs to assure continued use of low flow rates of desflurane.

Loxapine and **thiothixene** are conventional antipsychotic agents that were added in the *Formulary* as inexpensive generic options for patients who do not respond to, cannot tolerate, or who cannot afford atypical antipsychotic agents. Since most atypical antipsychotics are brand name drugs, they can be very expensive in patients who have difficulty paying for their prescriptions (ie, cannot afford the total cost or even their co-pay). Risperidone is the only generic option among the atypical antipsychotics.

Inexpensive generic conventional antipsychotics offer options for some patients with schizophrenia. The conventional antipsychotic with the best evidence of efficacy is perphenazine. In the National Institutes of Mental Health sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), perphenazine was found to be as effective as atypical agents were. As expected with conventional antipsychotics, more patients discontinued therapy because of extrapyramidal adverse effects (EPS). EPS is also a possible adverse effect for loxapine and thiothixene. Perphenazine was already listed in the *Formulary*.

Loxapine and thiothixene are also alternatives to thioridazine (Mellaril®). Thioridazine causes QT-prolongation and has been associated with torsade de pointes and sudden death. The thioridazine labeling states that it should be reserved for patients who do not tolerate or who do not respond to other agents. Thiothixene and thioridazine are sound-alike agents and care must be taken not to confuse these medications. Thioridazine remains in the *Formulary* because there may be patients who have been receiving it for many

years and switching these patients to another agent cannot be justified.

The evidence to support the effectiveness of thiothixene is limited, probably because it was approved by the FDA in 1967 when the standards for evidence were not as rigorous. Loxapine was approved by the FDA in 1975. There is better evidence published supporting the efficacy of loxapine, including a Cochrane review.

Dexlansoprazole is the R-enantiomer of lansoprazole, which is a racemic mixture of the R- and S-enantiomers of lansoprazole. Dexlansoprazole was FDA-approved January 20, 2009, with labeled indications for erosive and non-erosive gastrointestinal reflux disease (GERD). Studies described in the labeling show that dexlansoprazole 60 mg produces similar effects compared to lansoprazole 30 mg. Large noninferiority trials should be able to show superiority of dexlansoprazole, if it existed. Since racemic lansoprazole is a combination of R- and S-isomers, it is striking that no difference in efficacy could be shown considering that the dexlansoprazole dose was effectively 4-times the amount of R-lansoprazole. You would have to give 120 mg of lansoprazole to expose the patient to 60 mg of dexlansoprazole (from the racemic mixture).

Dexlansoprazole was designated nonformulary and not available and will be automatically interchanged to lansoprazole based on 30 mg lansoprazole equals 60 mg dexlansoprazole (and 15 mg lansoprazole equals 30 mg dexlansoprazole).

Megestrol acetate is a synthetic derivative of progesterone. **Megace® ES** (megestrol acetate) **Oral Suspension** has labeled indications for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS). **Megace® Oral Suspension** has the same labeled indications.

The recommended adult initial dosage of Megace® ES (megestrol acetate) oral suspension is 625 mg/day (5 mL/day or one teaspoon daily). The table below is provided in the labeling to guide correct dosing and administration. Care must be taken to prevent dosage errors when converting these products.

(continued on next page)

MEGESTROL PRODUCT DIFFERENCES

	Megace® ES Oral Suspension	Megace® Suspension
Concentration	125 mg/mL	40 mg/mL
Recommended Daily Dose	625 mg	800 mg
Daily Volume Intake	5 mL (one teaspoonful)	20 mL (one dosing cup)
Formulation	Concentrated Formula	Regular Formula

Formulary update, from page 2

The dosage of Megace® ES is lower because this dosage form is more concentrated (ES = Extra Strength) and is more bioavailable. In clinical trials, daily doses of 400 and 800 mg/day of megestrol acetate oral suspension were found to be clinically effective.

The interchange of Megace® ES oral suspension to Megace® Suspension was approved based on 800 mg equals 625 mg (ie, 20 mL for 5 mL). This allows stocking of fewer dosage forms of this rarely used product. The original or “regular formula” of Megace® Suspension is available as a generic.

Methadone is a potent synthetic opioid with complicated pharmacokinetic properties and pharmacodynamic effects that make it difficult to use. Since methadone is a “long-acting” opioid, it can be used for the treatment of pain, which is regulated like all other Schedule II controlled substances. Methadone has a black box warning in the official labeling that states methadone treatment for acute or chronic pain management should be initiated only if the potential benefits outweigh the risks.

Methadone use is difficult because there is wide patient-to-patient variation in its pharmacokinetics. Duration of effect becomes longer with prolonged use, and initial effects do not reflect the full effect of repeated doses. There are no reliable dosage conversions to methadone from other opioids. These properties make initiation and adjusting therapy or converting from another opioid to methadone difficult.

Based on recommendations from the Pain Committee and the Medication Safety Committee, methadone use was restricted in December 2008 to ongoing treatment of opioid addiction, treatment of pediatric and adult opioid withdrawal symptoms, ongoing treatment of chronic and cancer pain, and initiation or adjustment of chronic pain treatment by the Pain Service. A patient’s methadone dose for chronic pain or methadone maintenance could not be changed, unless it is done by the Pain Service. Methadone cannot be used for acute pain. It cannot be included in any pre-printed orders (unless it meets the above criteria). All orders for methadone must include the indication for use.

After difficulties implementing these restrictions were identified at Shands Vista (SV) and the Rehab (SRH) hospitals, methadone’s restriction was modified to authorize “qualified” SRH/SV medical staff members to initiate and adjust methadone for SRH/SV inpatients. “Qualified” is determined by certification in Chronic

Pain or Substance Abuse. Prescribers who provide proof of certifications by either the American Board of Anesthesiology’s Subspecialty certification in Pain Medicine or the American Society of Addiction Medicine are permitted to initiate and adjust methadone.

Further, any prescriber at SUF, SV, or SRH can decrease the dose of methadone, if needed. However, to increase a dose (even after it has been reduced), the above restrictions apply.

K-Dur® is an oral extended-release tablet form of potassium chloride. There are several generic versions of K-Dur®; all products easily disperse in a small amount of fluid. The labeling for K-Dur® states that all solid oral dosage forms of potassium chloride are contraindicated in any patient in whom there is pharmacologic cause (use of anticholinergic agents or other agents with anticholinergic properties at sufficient doses to exert anticholinergic effects) for arrest or delay in tablet passage through the gastrointestinal tract.

One possible method of avoiding the contraindication of using anticholinergic drugs with an oral solid potassium product is to use K-Dur® as a slurry. Unfortunately, the procedure is time-consuming and requires appropriate technique to deliver the entire dose. K-Dur® slurries must be used immediately or discarded and cannot be prepared ahead of time.

Despite a specific contraindication in the labeling, conflicting evidence exists regarding the clinical significance of this drug-drug interaction. However, several cases in the literature report extended-release potassium chloride formulations causing severe esophageal damage and even death.

The list of all anticholinergic drugs that trigger alerts for this contraindicated drug-drug combination is extensive. These alerts are frequent at Shands at UF. Suggestions of how to avoid a problem include using oral liquid potassium products. To avoid esophageal damage from K-Dur® (even without concomitant anticholinergic drugs), patients should take their dose with at least 100 mL of water and remain upright for 5 to 10 minutes. Oral solid dosage forms of potassium chloride are associated with esophagitis if not taken with sufficient fluid while sitting up. Additional steps, like eating a small amount of food after a dose, can help with esophageal transit.

Since K-Dur® dissolves easily in a small amount of fluid, a restriction was approved that requires that all patients receiving K-Dur® must take their dose with at least 100 mL of fluid and that the bed must be elevated at least 45 degrees for 10 minutes. This minimizes the possible adverse effects of con-

comitant use of anticholinergics and prevents the need to convert to an oral liquid potassium product (which is unpalatable for some patients) or discontinue the anticholinergic medication (which is often impractical). K-Dur® slurries require too much nursing time and could lead to incomplete doses (eg, not rinsing the container). K-Dur® dissolves so rapidly, lower gastrointestinal toxicity is not a concern. A Medication Administration Record (MAR) note will instruct nurses to follow this restriction. Considering this change in procedure, the contraindicated use of K-Dur® with anticholinergic drugs is deemed acceptable by the P&T Committee.

Tdap is an acronym for the **tetanus toxoid, reduced diphtheria, and acellular pertussis vaccine**. Tetanus is listed first and with a capital “T” because it is the main constituent and is a full-strength vaccine. The abbreviation of diphtheria uses a lower-case “d” because the diphtheria is a reduced dose intended for adult patients. The “ap” (lower-case) represents “acellular,” reduced-dose pertussis vaccine intended for adults.

CDC guidelines state that postpartum women should receive a Tdap vaccine “as soon as feasible” after delivery. In 2006, the Advisory Committee on Immunization Practices recommended routine administration of Tdap for postpartum women who were not vaccinated previously with Tdap to provide personal protection and reduce the risk for transmitting pertussis to their infants. Standing orders for postpartum Tdap vaccination before discharge have successfully raised vaccination rates to more than 80% of eligible women. Inpatient vaccination has been recommended.

Unfortunately, current fixed reimbursements do not cover this additional expense (unlike pneumococcal and influenza vaccinations). Routine vaccination in this population would result in an increase of \$100,000 in uncompensated pharmaceutical expenditures. Reimbursement, although modest, does occur in the outpatient setting. Therefore, routine postpartum administration of Tdap will be prohibited until reimbursements are adjusted to cover this expense.

A preconception dose of Tdap is best. This prevents pertussis, reduces morbidity associated with pertussis, and might prevent exposing persons at increased risk for pertussis and its complications, including infants. The risk for pertussis death and severe pertussis is highest among infants in the first months of life and remains elevated until an infant has received 1-2 doses of pediatric DTaP.

"Do you have any difficulties paying for your meds?"

Prescribers should know how their patients pay for their prescriptions. Patients should be asked if they have difficulties paying for their medications. More patients than ever have limited or no prescription coverage or have difficulty paying their co-pays. By asking patients if they have any difficulties paying for their medications, modifications in their prescriptions can be made **before** the patient is at the pharmacy counter and cannot afford to pay. Asking this question also helps you avoid telephone calls and pages to get a patient's prescriptions changed.

A recent *Consumer Reports* poll, released March 17, 2009, in conjunction with *Best Drugs for Less* magazine, showed that only 4% of patients have a conversation with their prescriber about the cost of a medication. The poll also found that 28% of patients took "dangerous" actions

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A recent *Consumer Reports* poll found that 28% of patients took "dangerous" actions to save money on their prescriptions.

to save money on their prescriptions. Patients skipped doses on purpose (16%), cut tablets in half without guidance (10%), or did not fill prescriptions (16%). Just to emphasize this finding, 1 in 6 patients reported not filling a prescription because of its cost. Also, patients reported intentionally taking expired medications (11%) and sharing prescriptions (4%). Generic drugs work just as well as brand name products. Sometimes generics work better; the brand name medication will not work if the dosage is below recommended (from skipping or splitting doses) or if the patient does not take the drug at all (because they never filled the prescription). Maybe that expensive angiotensin-receptor blocker (ARB) is not working to lower the patient's blood pressure simply because the patient is not taking it. Can a generic angiotensin-converting enzyme (ACE) inhibitor be used instead?

When the giant retailer Wal-Mart started offering hundreds of generic drugs for \$4 for a 1-month supply over 2 years ago, other pharmacy chains quickly followed their lead. Now a 3-month supply of many generics is available for \$10. Patients can often afford this out-of-pocket expense. It may be less than their prescription co-pay, in some instances. Some generic antibiotic prescriptions (eg, cotrimoxazole) are available at no cost at some pharmacies (eg, Publix).

In 2007 (the most recent data), the average cost of a generic drug prescription was \$34.34 versus \$119.51 for a brand name prescription. For chronic medications, this projected cost difference is over a thousand dollars per year (ie, \$85.17 per prescription per month times 12 months).

Although patients under 65 years of age with no insurance have the most difficulty paying for their medications, even patients with insurance (including Medicare Part D prescription coverage) can have difficulty paying their co-pays for the most expensive products. Please consider this information as you write discharge prescriptions and see patients in the clinics.

News, from page 1

effectiveness, present direct challenges to the NDA and OTC monograph systems, or that are reformulated to evade FDA enforcement action.

A good example of this risk-based approach is FDA's removal of injectable colchicine from the market. There are currently no approved products that contain *only* colchicine as an active ingredient. In February 2008, the FDA ordered companies to stop making and shipping drug products that contain colchicine in injectable form. However, the FDA did not taking any oral colchicine products off the market, approved or not. This is because colchicine toxicity is more likely when administered intravenously. When dosed orally for acute gout, colchicine is usually titrated over time until symptoms resolve or dose-limiting adverse effects occur. This emergence of adverse effects provides a "margin of safety." With intravenous colchicine, adverse effects may not be experienced until the patient has received potentially fatal amounts. The FDA is aware of 50 adverse events reports associated with intravenous colchicine, 23 of which included patient's deaths. Because of the significant risk it poses to the public's health, the FDA is focusing its time and efforts on removal of this dosage form.

How can healthcare providers determine if a drug is FDA-approved? There are 3 ways. The first is to visit the FDA's online *Orange Book* (www.fda.gov/cder/ob/), which identifies drugs that have been approved based on both safety and effectiveness (ie, have an approved new drug application [NDA]). Drugs can be searched by proprietary name or active ingredient. If approved, a list will provide approved products by dosage form, route, and name of applicant. Keep in mind that DESI review drugs and pre-1938 drugs (eg, phenobarbital) are not included in the *Orange Book*, yet they are approved drugs.

The second way is to search the *National Drug Code (NDC) Directory* (www.fda.gov/cder/ndc/database/). Search results from the directory contain a column marked "Application Number." If a drug product is approved by the FDA, an NDA or ANDA number will be listed in that column. The word "other" indicates that the product is not approved or that the manufacturer did not provide the number. The manufacturer can clarify this issue by providing the drug's application number to the FDA so the database can be updated. Keep in mind that the *NDC Directory* is limited to prescription drugs and insulin products only.

The third way is to search Drugs@FDA (www.accessdata.fda.gov/scripts/cder/drugsatfda), which contains *most*, but not all, of the drug products approved since 1939.

These search strategies can aid professionals trying to determine the approval status of a drug. It is important to remember that due to limitations, there are cases where a drug can appear to be unapproved even though it is approved (eg, pre-1938 drugs). The only way to be 100% sure is to contact the FDA. Unfortunately, there is no list of unapproved drugs.

The FDA has serious concerns that drugs marketed without approval may not meet standards of safety, effectiveness, quality, and labeling. The Agency is taking a risk-based approach to enforcement of its drug safety initiative. The ultimate goal is to remove all unapproved drugs from the market, but this will take time. Therefore, removing the most risky products is their immediate priority. Even though Accuzyme® is now nonformulary and not-available, collagenase (Santyl®), its formulary replacement is FDA-approved – and provides a reasonable alternative for most patients.

By Jennifer Ashton, PharmD

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2. Marketed Unapproved Drugs-Compliance Policy Guide. Available at <http://www.fda.gov/cder/guidance/6911fnl.pdf>
3. Alonso-Zaldivar R. Govt pays for risk unapproved drugs. AP Press 2008 Nov 24.

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**EDITOR,
 DRUGS & THERAPY BULLETIN**

Randy C. Hatton, PharmD

**DIRECTOR,
 PHARMACY SERVICES**

Alan Knudsen, MS, RPh

**CHAIRMAN,
 PHARMACY & THERAPEUTICS
 COMMITTEE**

Ricardo Gonzalez-Rothi, MD

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MEDICATION SAFETY

Don't get burned prescribing transdermal drugs

On March 5, 2009, the FDA issued a Public Health Advisory regarding the risk of burns from transdermal patches with metallic (ie, aluminum or other metal) backing that are not removed prior to an MRI.¹ Not all patches contain metal, but it is sometimes difficult to tell which products do. In the future, product labels will be updated to include this information. In the meantime, at right is a list of products that contain metal in the patch. Do not assume that this list is complete. Non-formulary drugs are included in the list, since patients may come in on these medications and may require an MRI.

FDA recommends that healthcare professionals referring patients to have an MRI scan identify those patients who are wearing a patch before the patients have the MRI scan. The healthcare professional should advise these patients about the procedures for removing and disposing of the patch before the MRI scan, and replacing the patch after the MRI scan.

REFERENCE

1. FDA Public Health Advisory: Risk of burn during MRI scans from transdermal drug patches with metallic backings. Available online at <http://www.fda.gov/cder/drug/advisory/transdermalpatch.htm>.

BRAND NAME	GENERIC/ESTABLISHED NAME
Androderm®	Testosterone patch
Catapres® TTS	Clonidine patch
Duragesic®/Generic Fentanyl	Fentanyl patch
Habitrol®	Nicotine patch
Lidopel®	Lidocaine and Epinephrine patch
Neupro®	Rotigotine patch
Nicotrol® TD	Nicotine patch
Prostep®	Nicotine patch
Salonpas®	Methyl Salicylate and Menthol patch
Synera®	Lidocaine and Tetracaine patch
Transderm-Scop®	Scopolamine patch