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B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met October 20, 2009. 4 products were added in the *Formulary,* and none were deleted. 3 products were designated nonformulary and not available with 1 interchange approved. Restrictions were added for 2 drugs.

◆ ADDED

Antithrombin III, Human (Thrombate III® by Talecris Biotherapeutics)

Carbamazepine Extended-Release (Carbatrol® by Shire)

Nicotine Gum (Nicorette® by GlaxoSmithKline Consumer Healthcare)*

**Fruit Chill Flavor; Restricted to Nicotine Withdrawal Order Form*

Prasugrel (Effient® by Eli Lilly and Company)

◆ DELETED

None

◆ NONFORMULARY AND NOT AVAILABLE

Antithrombin, Recombinant Human (ATryn®)

Canakinumab (Ilaris®)

Pitavastatin (Livalo®)

◆ INTERCHANGES

Pitavastatin (Livalo®) **to Simvastatin** (Generic)†

†1 mg = 10 mg

◆ CRITERIA-FOR-USE CHANGES

Fentanyl Transdermal Patch (Generic)‡

‡Fentanyl Patch Order Form required

Nicotine Transdermal Patch (Generic)§

§Must be ordered on the Nicotine Withdrawal Order Form

(continued on next page)

POLICIES AND PROCEDURES

P&T Policy Update: Changing criteria for use & sterile compounds from nonsterile ingredients

The P&T Committee approved a comprehensive update of all P&T Committee policies at the October meeting. All P&T Committee polices are available on the Shands at UF Portal.*

The following policies were updated and posted to the Portal: *Pharmacy and Therapeutics (P&T) Committee*, *Formulary Subcommittee*, *Anti-Infective Subcommittee*, *Pharmacy and Therapeutics Committee Policies*, *Conducting P&T Committee Business*, *Pharmacy and Therapeutics Committee Membership*, *P&T Committee Disclosure and Conflict of Interest*, *The Medication Formulary*, and *Requesting a Drug for Possible Addition in the Formulary*.

New members appointed to the P&T Committee receive a copy of all policies, and all P&T members receive copies of all policies once a year. Any changes to these policies or new policies must be approved by the P&T Committee.

Two new policies were also approved at the October P&T Committee meeting: *Request for Change of Criteria for Use* and *Formulary Status of Sterile Products Compounded from Nonsterile Ingredients.*

There have been several requests to change the criteria for use for a product listed in the *Formulary*. Often these requests are to lift or alter restrictions on products. A policy was developed that parallels the *Request for Formulary Addition* policy. Similar to the *Requesting a Drug for Possible Addition in the Formulary* policy, the *Request for Criteria for Use Change* policy requires new evidence or a new perspective and P&T approval for criteria to be modified within 12 months. If there is no new science or unique perspective that has not been previously considered by the P&T Committee, a review of the current evidence and P&T consideration will not be done (until 12 months has passed).

After a discussion about compounded cyclosporine ophthalmic solution in August, it was determined that a policy was needed describing the formulary status of sterile products from nonsterile ingredients. These compounded products are ineligible for addition in the *Formulary* (ie, because they cannot be stocked), and must be ordered on a patient-specific basis from an outside compounding pharmacy. Shands does not currently have the type of clean room necessary to prepare these products. The compounding pharmacy can meet USP standards for type of clean room and end-product testing. These products are considered a high risk for microbiological contamination.

These sterile products can be designated "high-priority nonformulary drugs" with computer entries that provide instructions on how to obtain them. This designation can occur only after an informed consent has been approved by the Legal Department and the evidence for efficacy and safety has been reviewed by the P&T Committee. Without an informed consent document, the P&T Committee will not review the evidence regarding efficacy and safety. Examples of informed consent documents that have been approved by the Legal Department are available as models.

LINKS

*https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Pharmacy/UF/Admin_Staff/Policies/99-Pharmacy%20and%20Therapeutics.

INSIDE THIS ISSUE

Formulary update, *from page 1*

Antithrombin is a protein in plasma necessary for heparin to exert its anticoagulant effect. Patients may have a hereditary or acquired antithrombin deficiency. These patients are at increased risk of thrombosis during surgery and when giving birth. Often, these conditions are not identified prior to a thrombotic event.

Antithrombin deficiency can be also identified when a patient undergoes cardiopulmonary surgery because the patient does not respond to typical doses of heparin used for bypass. Traditionally, these patients have been managed by being given more heparin and fresh frozen plasma (FFP). Two units of FFP contain approximately 500 units of antithrombin. If the patient does not respond to FFP and increased heparin doses, the patient could receive additional FFP or antithrombin as an off-labeled use.

There are 2 forms of antithrombin currently on the US market: human antithrombin from pooled plasma **(Thrombate III®)** and recombinant human antithrombin harvested from the milk from genetically altered goats **(ATryn®)**. The labeled indications for these products are similar, but not identical. Both are used peri-operatively or peri-partum in patients with hereditary antithrombin III deficiency. Thrombate III®'s labeling lists treatment of antithrombin deficiency, while ATryn®'s specifies prevention of thrombosis. Hereditary antithrombin deficiency, which is estimated to occur in 3000 to 5000 patients in the US, is diagnosed based usually on family history or antithrombin levels.

Use of antithrombin in heparin-resistant patients undergoing cardiopulmonary bypass surgery is an off-labeled use for both products. The diagnosis of antithrombin deficiency in this setting is based on inadequate response to heparin (as measured by the activated clotting time [ACT]) and does not differentiate between hereditary or acquired antithrombin deficiency.

The protocol for use of Thrombate III® endorsed by the Division of Hematology of the Department of Medicine only uses antithrombin after two 500-unit doses of FFP and increased heparin have failed to adequately increase ACT during cardiopulmonary bypass. It is expected that the use of Thrombate III® with this protocol would be relatively rare. This is reasonable based on efficacy and potential risks of antithrombin.

Thrombate III® is derived from pooled donor plasma. There are safety concerns as with all plasma-derived products (ie, risk of virus and prion transmission). However, ethanol fractionation and other processes used in production reduce these risks and, in over 15 years on the market, there has not been a documented case of infectious transmission. These warning are, however, listed in the labeling and provide incentive to reserve use of Thrombate III® to those patients where it is necessary. Common adverse effects include dizziness, lightheadedness, chest tightness, nausea, and a foul taste in the mouth. Because of its mechanism of action, appropriate titration of heparin is needed to avoid bleeding.

ATryn® is the first FDA-approved transgenic biologic. ATryn® is derived from the milk of genetically engineered goats. It is harvested literally on a farm and then purified and converted to a finished dosage form in a laboratory. The risks associated with this method of production are unknown, but are expected to be also very low. For example, the transgenic goats that produce antithrombin in their milk have to be certified free of scrapie.

The labeled units and dosages for Thrombate III® and ATryn® are not interchangeable. Availability of both antithrombin products could contribute to medication errors. Further, Thrombate III® is considerably less expensive than ATryn®.

Several studies have evaluated the use of plasma-derived antithrombin in heparin-resistant patients undergoing cardiopulmonary bypass. These studies showed success in most patients. Based on these studies, a dose of 500 units, followed by a second 500-unit dose, if needed, is recommended after FFP failure.

Carbatrol® is a twice-daily, extended-release, bead-filled capsule form of the anti-epileptic drug carbamazepine. It was reviewed for possible addition in the *Formulary* based on high volume nonformulary use (ie, 3 patients a month or more). This dosage form was added primarily because the capsule can be opened and the beads sprinkled on food for administration and the other dosage forms listed in the formulary (ie, carbamazepine immediate-release tablets and carbamazepine extended-release tablets) cannot be given this way.

Nicotine gum was added in the *Formulary* as an alternative for the treatment of nicotine withdrawal in patients who cannot tolerate nicotine transdermal patches. Both nicotine gum and **nicotine transdermal patches** must now be ordered using the *Adult Nicotine Dependence Treatment Order Form.*

The Health Science Center is now tobacco-free. A *Nicotine Dependence Treatment Order Form* was developed to facilitate the management of nicotine withdrawal for patients. Patients will no longer have an area in which to smoke.

An informational article on this topic was published in the July-August issue of the *Drugs & Therapy Bulletin.* This review of the evidence, along with benchmarking of orders from other tobacco-free hospitals, led to the *Nicotine Dependence Treatment Order Form.* This form provides treatment options, doses, and monitoring parameters for both nicotine withdrawal symptoms and possible adverse effects of the treatment options.

Prasugrel is a thienopyridine similar to clopidogrel but demonstrates faster onset of action and greater (10-fold higher compared to clopidogrel) and more consistent inhibition of platelet aggregation. Onset of the inhibition of platelet aggregation is 15 to 30 minutes with prasugrel, while clopidogrel may take up to 6 hours to reach the desired antiplatelet effect. Duration of platelet aggregation inhibition is approximately 5 days with prasugrel, which is similar to clopidogrel.

Prasugrel has a labeled indication to reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with ACS who are to be managed with PCI. Prasugrel has the potential to be used off-label in patients not undergoing PCI for indications where clopidogrel is used. Prasugrel is given as a 60-mg oral loading dose and then continued at 10 mg orally once daily with or without food. In the TRITON-TIMI 38 trial, patients were continued on treatment for 6 to 15 months following PCI. Loading doses should be given after the coronary anatomy is visualized. Patients also take low-dose aspirin daily. Patients less than 60 kg may take a lower maintenance dose (5 mg). No dosage adjustment is needed for renal or hepatic impairment; however, there is limited experience in patients with end-stage renal disease and patients with severe hepatic impairment.

There is only 1 completed head-to-head clinical trial (TRITON-TIMI 38) that compares prasugrel to another antiplatelet agent (clopidogrel) and assesses clinical outcomes. The primary outcome was the composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. The primary outcome occurred in 9.9% of patients taking prasugrel and 12.1% patients taking clopidogrel (NNT = 46). The difference in the composite endpoint was primarily driven by the difference in nonfatal MIs between prasugrel and clopidogrel (7.3% vs. 9.5%, NNT = 46).

Prasugrel did have significantly higher bleeding rates, which is emphasized in a black box warning in the prasugrel labeling. This also stimulated a Risk Evaluation and

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Formulary update, *from page 2*
Mitigation Strategy (REMS) program. Patients with a higher risk of bleeding included those with a history of a transient ischemic attack (TIA) or stroke, those age 75 years and older, and those with a body weight less than 60 kg. Bleeding was also higher in patients taking prasugrel who needed to undergo urgent CABG; thus, the recommendation that prasugrel be given after the coronary anatomy is known.

The inpatient cost of prasugrel is similar to that of clopidogrel; however, prasugrel is approximately $50 more than clopidogrel for a 30-day outpatient supply. This cost disparity will increase once clopidogrel loses patent protection in November 2011. As more data become available and clopidogrel becomes available as a generic drug, criteria for use may need to be refined. If tests become available that measure clopidogrel's [lack of] effect on platelet aggregation [in some patients], prasugrel may be used in patients with an insufficient response to clopidogrel.

Canakinumab is an interleukin-1β blocker with a labeled indication for Cryopyrin-Associated Periodic Syndromes (CAPS). This is a very rare disorder. However, there appears to be no restrictions that would prevent this product from being purchased and stocked.

Canakinumab is the third option on the US market for the treatment of cryopyrin-associated syndromes (CAPS). None of the options are listed in the *Formulary*. Canakinumab and rilonacept [Arcalyst®] have labeled indications for CAPS, while anakinra [Kineret®] has been used off-label for this use. Canakinumab is labeled for patients greater than 4 years old, while rilonacept for patients greater than 12 years old.

CAPS are an array of genetic conditions that include familial cold autoinflammatory syndrome (FACS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystemic inflammatory disease (NOMID). FDA estimates that approximately 300 people in the US have these conditions. CAPS are orphan diseases and canakinumab is an orphan drug (as is rilonacept).

Because these are rare disorders, the evidence to support the use of canakinumab is limited (as is the evidence for the other options). There are no studies comparing active treatment options, and drugs used to treat this condition are compared to no therapy (if compared). The data do suggest that canakinumab is effective for treating symptom of CAPS, but the effects on the progression or course of the disease are unknown.

There is limited information on the safety of canakinumab. It is difficult to separate the common adverse effects from those associated with the disease, since the only available data do not have adequate controls. Canakinumab use may be associated with an increased risk of serious infections (eg, tuberculosis). Live virus vaccines should not be given with canakinumab. The formation of cytochrome P450 enzymes is suppressed by increased levels of cytokines (eg, IL-1) during chronic inflammation. Thus, it is expected that for a molecule that binds to IL-1, like canakinumab, the formation of CYP-450 enzymes could be normalized. This is clinically relevant for CYP-450 substrates with a narrow therapeutic index, where the dose is individually adjusted (eg, warfarin).

Rilonacept is only available via a restricted distribution program, so it was not eligible for addition in the *Formulary*. In June, the P&T Committee designated it a high-priority nonformulary drug, which allows patients to use their own supply (via the limited distribution system) while they are hospitalized.

Each dose of canakinumab, which is given every 8 weeks, would cost over $15,000. Because use should be rare and the acquisition cost is so high (even storage costs would be prohibitive), canakinumab was designated nonformulary and not available. All doses should be administered in the outpatient setting or patients should use their own supply from home.

Pitavastatin is an HMG-Co-A-reductase inhibitor or "statin" with a labeled indication to lower cholesterol levels. Currently, atorvastatin [Lipitor®], pravastatin [Pravachol®], and simvastatin [Zocor®] are listed in the *Formulary*. Nonformulary agents are interchanged to pravastatin or simvastatin based on their potency and/or potential to cause drug interactions.

Pitavastatin (1 mg, 2 mg, and 4 mg) has been compared to simvastatin (10 mg, 20 mg, and 40 mg) in a randomized, double-blind phase 3 trial in elderly patients with primary hyperlipidemia or mixed dyslipidemia. It was also compared (2 mg to 20 mg and 4 mg to 40 mg) in patients with primary hyperlipidemia or mixed dyslipidemia. Both studies showed noninferiority.

Therefore, a therapeutic interchange of pitavastatin to simvastatin was approved (ie, 10 mg simvastatin for each 1-mg dose of pitavastatin).

Transdermal fentanyl patches, like Duragesic®, deliver a constant amount of the powerful synthetic opioid fentanyl to patients with persistent moderate to severe chronic pain that requires continuous, around-the-clock opioid administration for an extended period. It should be used only when the patient's chronic pain cannot be managed by other options (eg, NSAIDs or oral opioids).

A recent audit of the use of fentanyl patches at Shands at UF showed potential for improvement. A *Fentanyl Patch Order Form* was approved by the P&T Committee to improve patient safety and provide additional guidance for prescribers and the nursing staff.

The use of fentanyl patches for acute pain is particularly problematic because it is contraindicated. The *Fentanyl Patch Order Form* will explicitly prohibit all contraindicated uses. The form lists which patients can receive the fentanyl patch and provides guidance for the definition of "opioid-tolerant." The definition was based on the Department of Veterans Affairs criteria and is defined as "patients taking more than or equal to 60 mg of oral morphine daily, 20 mg of oral methadone daily, 30 mg oral oxycodone daily, or an equianalgesic dose of another opioid for more than 1 week." The form provides instructions for converting other opioids to a fentanyl patch.

NEWS

Finding drug-specific order forms on the portal

This month, 2 new drug-specific order forms were approved. The *Fentanyl Transdermal Patch Order Form* and the *Adult Nicotine Withdrawal Order Form* (for nicotine gum and patches) are required to use these restricted products. One criticism of these restrictions has been the difficulty in locating these forms when you need them. However, these forms are quite easy to locate using the search engine on the UF Patient Care Forms Web site.*

This search is powered by a Google search engine. For drug-specific forms, the user simply enters the brand or generic name in the search field and hits enter. This search function can be used to find forms for dexmedetomidine

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DRUG INFORMATION FORUM

Resource for questions

The Drug Information and Pharmacy Resource Center is available to answer drug-related questions from Shands and UF healthcare professionals from 9 am to 4:30 pm Monday through Friday. This service is available to areas of UF&Shands not covered by an outpatient pharmacist, decentralized pharmacist, or clinical pharmacy specialist. Questions can be submitted by calling (352) 265-0408 or by registering and submitting questions via our website.* You can leave a voice mail message after hours, if you would like for us to contact you.

You can get to our Web site by going to the Shands Internet site (www.shands.org), select the For Healthcare Professionals link at the top of the page, then select the Drug Information Services link about halfway down the right side of the page.

The Center is staffed by Doctor of Pharmacy Students in the final year of their training. Each answer provided is, however, reviewed and approved by a faculty preceptor. Questions are thoroughly researched and answers fully referenced.

The Center is best used for questions that are not emergent. Call the pharmacist servicing your area with emergent questions. Since each Drug Information Service answer has to be reviewed before an answer is given, there may be a delay that is unacceptable for "stat" requests. Questions that require more thorough research of the available evidence on a topic are ideal to submit.

The following is a brief sample of recent questions the Drug Information Service has answered:

- Besides the abdomen, where can nicotine patches be placed on the body?
- How long can fosphenytoin vials be stored outside of a refrigerator?
- What are the specific risks of using oseltamivir [Tamiflu®] in each trimester for a pregnant woman?
- What is the recommended conversion from Armour Thyroid to levothyroxine?
- Is there evidence to support that lowering a patient's out-of-pocket expenses for chronic medications increases compliance?

LINKS

*http://www.shands.org/professionals/druglnfo/default.asp

News, *from page 3*

(Precedex), dofetilide (Tikosyn), drotrecogin (Xigris), methylnaltrexone (Relistor), and nesiritide (Natrecor). Forms for a drug-intensive protocol, like the Pediatric PCA order form, also are easy to locate.

Using the search engine makes it unnecessary to remember which tab has the form listed. Forms are listed only under 1 tab to make sure that when a form gets updated, the single version is updated (ie, there are not multiple versions posted).

Forms are not the ideal method to assure safe and effective use of drugs listed in the *Formulary*, but they are the best option available currently. These forms are being incorporated into the computerized order entry system (ie, EPIC) that will be launched in about a year-and-a-half. In the meantime, we will continue to try to refine the availability of existing forms.

LINKS

* https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Forms/UF

Inpatient use of Med Guides

Medication Guides are paper handouts that come with many new prescription medicines. These guides are also included in the drug's labeling (ie, the package insert). These guides address issues that are specific to particular drugs and drug classes, and they contain FDA-approved information that can help patients avoid serious adverse events.* FDA requires that Medication Guides be issued with certain prescribed drugs and biological products when it determines that certain information is necessary to prevent serious adverse effects, patient decision-making should be informed by information about a known serious adverse effect with a product, or patient adherence to directions for the use of a product is essential to its effectiveness.

Medication Guides are the most common component of FDA-mandated Risk Evaluation and Mitigation Strategies (REMS). In 2007, a new federal law (Food and Drug Administration Amendment Act) authorized the FDA to require manufacturers to establish REMS for new drugs or for previously approved drugs when safety issues are identified. The goal is to ensure that the benefits of a drug will outweigh its risks. Before REMS, FDA used similar strategies for new drugs, such as a RiskMAPS or Patient Package Inserts.

When prasugrel was approved by FDA in July of this year, a REMS was also approved to decrease the risk of serious bleeding that was associated with its use in clinical trials. The prasugrel REMS included a communications plan and a Medication Guide. The communications plan included a Dear Healthcare Provider Letter and a Prescriber Brochure. This strategy will be used for the first 2 years prasugrel is marketed. The communication plan emphasizes the risk of bleeding in patients at highest risk (ie, patients with a history of TIA or stroke, patients 75 years old or older, patients weighing less than 60 Kg, and patients undergoing a CABG). The 4-page Medication Guide is given to each patient by a pharmacist when they pick up their prescription.†

After doing benchmarking, it was determined that most hospitals are not distributing Mediation Guides in the inpatient setting. The federal law that discusses Medication Guides (Code of Federal Regulation, Title 21, Chapter I, Subchapter C, Part 208: Medication Guides for Prescription Drug Products, Subpart A: General Provisions, Section 208.1: Scope and Purpose) states, "[Medication Guides] apply primarily to human prescription drug products used on an **OUTPATIENT** [emphasis added] basis **without direct supervision by a health professiona**l." Thus, unless specified that the Medication Guide must be given in the inpatient setting, we will assume that guides do not have to be distributed. Prescribers may distribute them at their discretion.

Medication Guides differ from Consumer Medication Information (CMI). Compared to a Medication Guide, a Consumer Medication Information sheet offers broader information on how to use a medicine. CMI sheets are not developed or regulated by FDA. These information sheets are prepared by pharmacies and given out with prescription drugs. CMI sheets are not available on the FDA Web site. CMI sheets help consumers understand key information about their prescription medicine, including how to take it, how to store it, and how to monitor their treatment. The sheets also include information on precautions and warnings, as well as symptoms of serious or frequent adverse events and what to do if you experience one. Studies have shown a wide variation in the quality and contents of CMI sheets, but Medication Guides are always the same for a specific drug.

LINKS

*http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm

†http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022307s000MEDGUIDE.pdf

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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

EDITING, DESIGN, & PRODUCTION
Shands HealthCare's Publication Svcs.

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http://shands.org/professionals/druginfo/bulletin.asp

SHANDS
Shands at the University of Florida
DRUG INFORMATION SERVICE
PO Box 100316
Gainesville, FL 32610-0316

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