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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met February 17, 2009. 9 drugs were added in the *Formulary*, and 4 drugs were deleted from the *Formulary*. 7 drugs were designated nonformulary and not available, and 5 interchanges were approved. 1 drug was restricted, and 1 "contraindicated" drug-drug combination was approved under specific conditions.

◆ ADDED

Aminophylline (Generic)*

**Restricted to the Cath Lab for bradycardia*

Barium Sulfate
(several dosage forms)

Diatrizoate Meglumine-Sodium
(Sinografin® by Bracco Diagnostics)

Ethiodized Oil (Ethiodol® by Savage Laboratories)

Gadoexetate (Eovist® by Bayer)

Iothalamate Meglumine
(Cysto-Conray® by Mallinckrodt)

Ioxaglate
(Hexabrix® by Mallinckrodt)

Plerixafor
(Mozobil® by Genzyme)†

†Restricted to the Bone Marrow Transplant Service

Sodium Bicarbonate-Citric Acid-Simethicone (E-Z Gas® II by Bracco Diagnostics)

◆ DELETED

Iopromide (Ultravist® by Bayer)

Ipodate (Oragrafin® by Bracco Diagnostics)

Irbesartan (Avapro® by Bristol-Myers Squibb)‡

‡Nonformulary and not available. Interchanged to valsartan

(continued on next page)

SHORTAGES

Acyclovir shortage? What's the problem?

Prescribers are justifiably frustrated when critical drugs are not available. The recent shortage of injectable acyclovir is an example of why shortages occur and what can (and cannot) be done about them.

Shortages are caused by changes in production by a manufacturer, marketing decisions, or increased use patterns for drug products. Changes in production can be caused by a shortage of raw materials, damage to a production plant, or, most often, quality control problems that cause the FDA to halt production. Voluntary or mandatory recalls can cause havoc when there are few and/or less-desirable alternatives. An example of a marketing decision causing a shortage is when a manufacturer stops making a rarely used and unprofitable product. Increased use of a drug can cause a shortage when new information stimulates prescribing for a "new" indication. Production may not be able to meet this new demand.

When the word spreads that a critical drug is in short supply, matters worsen. The drug in short supply becomes harder to obtain than plywood when a hurricane is bearing down on Florida. Hoarding just exacerbates the problem.

The FDA only considers a drug shortage to exist when the drug is "medically necessary" and not when patient inconvenience alone exists. The FDA may take steps to help resolve a drug shortage. If the shortage was caused by a manufacturer's noncompliance with quality control standards, the FDA may weigh the risks of the "noncompliant" drug product with the risk of not having drug to treat a condition. They may also facilitate the importation of a foreign source of a drug product when they can assure the foreign manufacturer meets adequate quality control standards.

The FDA (and some manufacturers) have tried to address the effect that hoarding has on shortages. The FDA encourages the establishment of limited-access programs that release drugs based only on specified criteria. These criteria may be based on the amount that can be obtained at 1 time or based on the reason that the patient needs the drug. These patient-specific supplies can be used ONLY for that patient and cannot be shared with possible needy patients.

The current shortage of acyclovir injection started when 1 of the 2 manufacturers of injectable acyclovir experienced "manufacturing delays." Excess demand overwhelmed the only other supplier (ie, APP). FDA allowed the marketing of a Canadian-labeled product (made in the same plant to the same standards as the US product) to be used in the US to help alleviate the shortage. The manufacturer is rationing the limited supply in an attempt to get product to the most critical patients.

Only patient-specific supplies of IV acyclovir are being released by the manufacturer. Product must be requested from the manufacturer on a case-by-case basis. Documented or "highly suspected" (ie, not just part of a differential diagnoshis) herpes simplex virus (HSV) infections in adults and children are the mostly likely to get drug. Patients who can be switched to other options (eg, oral acyclovir, oral valacyclovir, oral and intravenous ganciclovir, or even foscarnet) are not good candidates for the limited supply of IV acyclovir. Even patients who are candidates for the rationing program may have to be started on ganciclovir (or another option) until the company approves its use and ships supply [only] for that patient. The American Academy of Pediatrics has provided recommendations for the use of IV acyclovir and its alternatives.[1] Getting an infectious diseases consult may help with the documentation process (eg, documented HSV PCR).

(continued on page 4)

Formulary update, *from page 1*

◆ **DELETED (cont.)**

Olmesartan (Benicar® by Daiichi Sankyo)‡

‡Nonformulary and not available. Interchanged to valsartan

◆ **NONFORMULARY AND NOT AVAILABLE**

Candesartan (Atacand® by AstraZeneca)‡

‡Interchanged to valsartan

Degarelix (No Tradename by Ferring Pharmaceuticals)

Eprosartan (Teveten® by Abbott)‡

‡Interchanged to valsartan

Telmisartan (Micardis® by Boehringer Ingelheim)‡

‡Interchanged to valsartan

Zolpidem Oral Spray (Zolpimist® by NovaDel Pharma)

◆ **INTERCHANGES**

Valsartan (Diovan® by Novartis) **for Candesartan**

Valsartan (Diovan® by Novartis) **for Eprosartan**

Valsartan (Diovan® by Novartis) **for Irbesartan**

Valsartan (Diovan® by Novartis) **for Olmesartan**

Valsartan (Diovan® by Novartis) **for Telmisartan**

◆ **CRITERIA-FOR-USE CHANGES**

Nitroglycerin, Intravenous (Generic)§

§Concomitant use with sildenafil permitted

Nitroglycerin, Sublingual (Generic)¶

¶Removed from the Override List

von Willebrand Factor Complex-Coagulation Factor VIII (Human) (Humate-P® by CSL Behring)**

***Restricted to use in von Willebrand Disease and must be ordered in von Willebrand factor units*

Aminophylline is the ethylene diamine salt of theophylline (contains 80% theophylline). The ethylene diamine salt was originally used to improve solubility. In addition to dosing errors caused by confusion between theophylline and aminophylline, there have been rare reports of adverse effects attributed to ethylene diamine (eg, exfoliative dermatitis).

This "more concentrated form of intravenous theophylline" was added in the *Formulary* and restricted to use in the Cardiac Catheterization Laboratory. Aminophylline will be used in this setting to reverse bradycardia that occurs during rotational atherectomies.

Aminophylline was originally deleted from the *Formulary* many years ago and designated nonformulary and not available. This action was taken to promote medication safety. Since the active ingredient of aminophylline is theophylline, products labeled with their theophylline content are usually preferred (and it prevents confusion). The premixed bag of theophylline (400 mg/500 mL) is too dilute for use in rotational atherectomies. It is difficult to give an adequate dose over a short period without delivering too much fluid.

Since there is no commercially available concentrated form of intravenous theophylline, aminophylline vials are the only viable option in this situation. Therefore, aminophylline vials are restricted to use in the Cardiac Catheterization Laboratory.

Several dosage forms of **barium sulfate** and other drugs used by the Department of Radiology (eg, **ethiodized oil**, **E-Z Gas® II**, **gadodiamide**, **gadoexetate**, **iothalamate meglumine**, **ioxaglate**, and **Sinografin®**) were added in the *Formulary* as part of a comprehensive review of radiologic agents. Most of these agents have been used for quite some time, and the formal addition by the P&T Committee will create listings in the online *Formulary*. **Iopromide** and **ipodate** were deleted from the *Formulary* because they are no longer used. Complete protocols using these agents are available on the Internet at http://xray.ufl.edu/patientcare/protocols/view-order-sheets.

Gadoexetate is the newest addition to this list. Gadoexetate injection is a gadolinium-based contrast agent with a labeled indication for intravenous use in T1-weighted magnetic resonance imaging (MRI) of the liver to detect and characterize lesions in adults with known or suspected focal liver disease. Like all gadolinium-based MRI contrasts, this agent must be used with caution in patients with impaired renal function (ie, a creatinine clearance less than 30 mL/minute or acute renal insufficiency). Patients with impaired renal function who receive gadolinium-based contrasts may develop nephrogenic systemic fibrosis (NSF). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs. All patients receiving gadoexetate should be screened for renal dysfunction by obtaining a history and/or laboratory tests.

Plerixafor is a novel therapeutic agent recently approved for the mobilization of hematopoietic stem cells to be collected for autologous hematopoietic stem cell transplantation (aHSCT). It was evaluated proactively because of nonformulary requests for use and its high cost. The Bone Marrow Transplant (BMT) Service participated in 2 of the pivotal Phase III trials for this agent, and several patients participated in a compassionate-use protocol that is no longer available.

Autologous hematopoietic stem cell transplantation has become the preferred method of treatment of a variety of hematologic malignancies. In order to perform aHSCT, stem cells must be collected from the peripheral blood through an outpatient apheresis procedure. Although a small amount of stem cells continuously circulates in the peripheral blood, it is necessary to "mobilize" large numbers of the cells from the bone marrow to the periphery for collection. The number of CD34 stem cells collected is a predictor of neutrophil and platelet engraftment (ie, transplanted cells "accepted" and begin to proliferate) after transplantation. Mobilization strategies have historically included the administration of colony stimulating factors (eg, filgrastim [G-CSF]), chemotherapy, or the combination. However, these strategies have limitations, such as high toxicity and low yield of CD34 cells. Chemotherapy mobilization is not used at Shands at UF.

Plerixafor is a reversible inhibitor of the CXCR4 chemokine receptor and prevents binding of the SDF-1α ligand. SDF-1α and CXCR4 play an important role in the retention of hematopoietic stem cells in the bone marrow. CXCR4 anchors the stem cells to the bone marrow matrix either directly through SDF-1α or by inducing other adhesion molecules.

Plerixafor has a labeled indication for use in combination with G-CSF to mobilize stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). It is usually administered as a subcutaneous injection in an outpatient setting after the patient has received G-CSF once daily for 4 days. Plerixafor is then administered the evening prior to (approximately 11 hours) initiation of apheresis for up to 4 consecutive days. G-CSF should be continued and given each morning before apheresis.

The results of numerous trials, including 2 large randomized controlled trials, demonstrate that plerixafor, when used in combination with G-CSF, is effective for the mobilization of hematopoietic stem cells for aHSCT. The proportion of patients achieving target CD34 cell collection and mean increases in circulating CD34 cells

(continued on next page)

Formulary update, *from page 2*
were significantly increased. In the randomized controlled trials, the median time to achieve successful mobilization was decreased, resulting in a significant decrease in the number of apheresis days required. A compassionate-use protocol showed that 75% of patients who previously failed to mobilize enough stem cells for transplantation were successfully transplanted. There are no data on the effect on survival.

The most frequently reported adverse effects of plerixafor (greater than 10% incidence when compared to placebo) are diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness, and vomiting. However, the ultimate safety profile of this agent is yet to be determined through post-marketing surveillance. A theoretical concern is the possibility of release of tumor cells from the bone marrow.

Although plerixafor is expensive ($6250 per single-use vial and up to $25,000 for a 4-dose cycle), it may provide outcome benefits in selected patients.

Plerixafor was added in the *Formulary* and restricted to use by the BMT specialty group according to criteria that should provide the most benefit, yet minimize excess use (see Table on next page).

After a comprehensive review of angiotensin receptor blockers (ARBs), **irbesartan** and **olmesartan** were deleted from the *Formulary* and were designated nonformulary and not available, while **candesartan**, **eprosartan**, and **telmisartan** were designated nonformulary and not available. Losartan remains in the *Formulary* because of its frequent use. Many patients are admitted taking this drug. **Valsartan** remains in the *Formulary* and will be the preferred ARB. All ARBs, except losartan, will be interchanged to valsartan using an approved interchange grid (see Table below).

Degarelix is a gonadotropin-releasing hormone (GnRH) with a labeled indication for the treatment of patients with advanced prostate cancer. Like other similar agents used to treat prostate cancer (eg, histrelin [Vantas® Implant] or leuprolide depot [Lupron® Depot]), degarelix suppresses testosterone production. It is administered subcutaneously every 28 days.

Also, like Lupron® Depot and Vantas® Implant, this intermittent outpatient drug was designated nonformulary and not available. The reimbursement for these expensive outpatient medications is poor in the inpatient setting.

Zolpimist® is an oral spray dosage form of the hypnotic drug zolpidem. It has a labeled indication for the short-term treatment of insomnia. Like oral dosage forms of zolpidem, Zolpimist® is a Schedule IV controlled substance.

Zolpimist® is promoted as having a faster onset without needing to take it with water (or some other liquid). Because there is no rational need for this dosage form in the *Formulary*, it was designated nonformulary and not available. Since it is a controlled substance, patients are unable to use their own supply from home during their hospitalization. Like all controlled substances, it will be sent home with family members or stored with the patient's valuables until discharge.

The use of **sildenafil** (Viagra® or Revatio®) and **nitroglycerin** are contraindicated in the official labeling because of the risk for severe hypotension. In February 2008, the P&T Committee endorsed a policy that prevents the use of contraindicated drug-drug combinations unless there is sufficient evidence to justify the continued use of these drugs… usually under specified conditions. The use of nitroglycerin and sildenafil fits this exception under the following specified condition.

There are data from a randomized, double-blind study where a nitroglycerin infusion and sildenafil were used together safely with a minimal effect on blood pressure. The P&T Committee approved the use of sildenafil with nitroglycerin infusion in units where patients' blood pressures are closely monitored.

Because the American Heart Association and the American College of Cardiology (AHA/ACC) do not recommend the use of sublingual nitroglycerin for 24 hours after sildenafil, the P&T Committee reiterated that this combination should not be used outside of a monitored unit. The AHA/ACC recommendations suggest the use of alternative agents, like morphine or beta-blockers, instead of sublingual nitroglycerin.

Sublingual nitroglycerin was removed from the list of override medications because it could not be screened for previous sildenafil use. Sublingual nitroglycerin is not considered life saving, and it is not needed emergently. Sublingual nitroglycerin should be ordered to be given STAT (ie, within 15 minutes). Orders processed by a pharmacist will be stopped if the patient is on sildenafil and the patient is on a general unit. The prescriber will be contacted and alternatives will be discussed (ie, use morphine or a beta-blocker or transfer the patient to a monitored unit).

Humate-P® is a combination of antihemophilic factor (factor VIII) and von Willebrand factor (vWF) complex. It is derived from pooled plasma and pasteurized to reduce the risk of viral transmission from the pooled donors to the patients being treated.

Humate-P® has labeled indications for the treatment and prevention of bleeding in adult patients with hemophilia A (classical hemophilia) and adult and pediatric patients with von Willebrand disease for treatment of spontaneous and trauma-induced bleeding episodes and prevention of excessive bleeding during and after surgery. However, there are better alternatives available for the treatment of hemophilia A (ie, recombinant factor VIII). Therefore, use of Humate-P® is now limited to patients with vWF deficiency.

Because of the labeled indications, each Humate-P® vial is labeled with factor VIII and vWF content. This leads to confusion about the appropriate dosage. With the support of both Adult and Pediatric Hematology, the P&T Committee restricted Humate-P® to use in patients with vWF deficiency. Dosages must be specified based on vWF units [only]. The formulary entry for Humate-P® has been modified to emphasize the vWF content (versus the factor VIII content).

ARB INTERCHANGE AT SHANDS AT UF

Valsartan* (Diovan®)	**Irbesartan‡** (Avapro®)	**Olmesartan‡** (Benicar®)	**Candesartan‡** (Atacand®)	**Telmisartan‡** (Micardis®)	**Eprosartan‡** (Teveten®)
20 mg		5 mg			
40 mg	75 mg	10 mg	4 mg	20 mg	400 mg
80 mg	150 mg	20 mg	8 mg	40 mg	600 mg
160 mg	300 mg	40 mg	16 mg	80 mg	800 mg
320 mg			32 mg		

*All ARBs (except losartan) will be interchanged to valsartan using these dose equivalencies.
‡Nonformulary and Not Available (NFNA)
Note: Combination products (eg, ARB + hydrochlorothiazide) will be interchanged to 2 agents.

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Formulary update, from page 3

CRITERIA FOR PLERIXAFOR (MOZOBIL®)

1. Use in patients who failed mobilization with standard doses of filgrastim (G-CSF) alone
2. Use in patients at high-risk for being poor mobilizers:
   a. The presence of the following may indicate an increased risk for poor mobilization:
      i. Prior lenalidomide therapy (4 or more months)
      ii. Prolonged prior chemotherapy:
         1. 3 or more prior treatment regimens
         2. 12 or more cycles of prior treatment
         3. 6 or more months of treatment with fludarabine
         4. 4 or more months of treatment with melphalan
      iii. Age > 65
      iv. Previous radiation therapy to the pelvis or spine
      v. Bone marrow involvement of disease of 30% or more. *Caution should be exercised in patients who have myeloma involving 30% or more of the bone marrow. These patients may be at risk for plerixafor-associated mobilization of myeloma cells.*
   b. These patients should begin filgrastim dosing on the Friday prior to beginning apheresis, with the first day of apheresis planned for the following Tuesday.
   c. Peripheral CD34+ concentrations should be assessed the Monday prior to apheresis. If peripheral CD34+ concentrations are < 5 cells/microL on day 4 of G-CSF mobilization, the patient may begin plerixafor that evening (prior to first day of apheresis).
3. If a patient receiving filgrastim-only mobilization fails to collect at least 50% of the target cell dose after 2 apheresis sessions, plerixafor therapy may be started the evening prior to the third day of apheresis.
4. If the total/targeted number of cells is collected on the first day of apheresis, the plerixafor dose should ***not*** be repeated that evening. Patients should continue on G-CSF and proceed to a half-run apheresis session the next day as per standard procedure.

***Shortages,** from page 1*

Prescribers are reminded that milligram-per-kilogram dosages should be based on ideal body weight. Dosing patients on total body weight consumes more acyclovir than necessary.

It is anticipated that the shortage of acyclovir should be resolved around the time that this article is published; however, it is not possible to predict accurately when a shortage will be resolved. Usually, the *Bulletin* is not timely enough to inform prescribers of shortages (and alternatives). If there are few typical prescribers, they are contacted individually. When the drug is used more broadly, mass communications like emails are usually more efficient at getting the message out quickly.

More detailed information about drug shortages and therapeutic alternatives can be found on the FDA's shortage website (www.fda.gov/cder/drug/shortages) and on the American Society of Health System Pharmacists' (ASHP) Drug Shortage Resource Center (http://www.ashp.com/shortage).

REFERENCES

1. Kimberlin DW. Ganciclovir may be used during the intravenous acyclovir shortage. AAP News 2009. Accessed online February 24, 2009 at http://aapnews.aappublications.org/cgi/content/full/aapnews.20090210-1v2.