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Shands at the University of Florida

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# Drugs & Therapy

## B • U • L • L • E • T • I • N

## FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met May 15, 2007. 1 dosage form was added in the *Formulary,* and 2 dosage forms were deleted and designated nonformulary and not available. 2 drugs were evaluated but not added in the *Formulary.* Criteria-for-use were changed for 1 drug.

### ◆ ADDED

**Aripiprazole Injection** (Abilify® Injection by Bristol-Myers Squibb)*

**Restricted to use by the Psychiatry Service, the ED, and Shands Vista.*

### ◆ DELETED

**Olanzapine Injection** (Zyprexa IntraMuscular® by Lilly)†

**Ziprasidone Injection** (Geodon® Injection by Pfizer)†

*†Nonformulary and not available.*

### ◆ EVALUATED BUT NOT ADDED

**Hyoscyamine** (Levsin® and generics)

**Iron Sucrose Injection** (Venofer® by American Regent)

### ◆ PRODUCT SELECTIONS

**Cyclosporine Modified** (Neoral® by Novartis)

**Cyclosporine Modified** (Gengraf® by Abbott)

### ◆ CRITERIA-FOR-USE CHANGES

**Potassium Chloride IV** (Generic)‡

*‡Maximum dosage of 1 mEq/kg/hr allowed for "special" circumstances.*

**Aripiprazole injection** for intramuscular use was added in the *Formulary* and restricted to use by the Psychiatry Service, in the Emergency Department, and at Shands Vista. Aripiprazole injection is the

*(continued on next page)*

MEDICATION SAFETY

# FDA warns that ESAs may increase thrombosis risk

The erythropoietin-stimulating agents (ie, darbepoetin and epoetin) have received considerable attention from the FDA Public Health Advisory issued March 9, 2007. Based on this warning, the P&T Committee approved automatically stopping darbepoetin or epoetin orders for hospitalized patients whose hemoglobin values are 12 g/dL or higher. If patients receiving these agents have hemoglobins approaching 12 g/dL, it is recommended that their dose be reduced or therapy with an ESA should be stopped, depending on the reason for ESA use. In patients who will receive ESAs chronically, like patients with chronic renal failure, it would be reasonable to decrease the dose by 25% (or less) or reduce the frequency of administering these agents before the ceiling hemoglobin of 12 g/dL is reached.

**...the increased viscosity of blood associated with increased hemoglobin concentrations may result in more thrombotic complications. This risk may outweigh the lack of immediate benefit of ESAs...**

The FDA's erythropoietin-stimulating agent (ESA) warnings pertain to the labeled indications for use of these agents, which include use in patients with renal disease, cancer, and after surgery to prevent blood transfusions. In patients with head and neck cancers, ESA use with hemoglobin levels greater than 12 g/dL was associated with increased tumor growth. In patients with cancers not receiving chemotherapy, ESA use was associated with no fewer blood transfusions, yet decreased survival.

In patients with chronic kidney failure, the FDA found increased deaths, non-fatal heart attacks, strokes, heart failure, and blood clots when ESAs were adjusted to maintain higher red blood cell levels (hemoglobin more than 12 g/dL). Patients scheduled for orthopedic surgery who received ESAs to reduce blood transfusions during and after surgery had more blood clots than those not given an ESA. The increased risk of thrombosis is a concern that has not received as much attention. This risk should be considered when using ESAs for labeled and off-labeled uses.

ESAs do not act quickly. They take several weeks to increase red blood cell production. As with the finding in cancer patients not undergoing chemotherapy, ESA use may not prevent blood transfusions in the acute treatment period. Even though the effect is delayed, ESAs are often used because of the perception that there is little risk and they could eventually prevent the need for blood, which has risk, albeit lower than in the past.

Current warnings suggest that the increased viscosity of blood associated with increased hemoglobin concentrations may result in more thrombotic complications. This risk may outweigh the lack of immediate benefit of ESAs in situations where there is unproven benefit, like many off labeled uses.

## INSIDE THIS ISSUE

***Formulary update,*** *from page 1*
third intramuscular (IM) second generation antipsychotic marketed with a rapid onset of action. **Ziprasidone IM injection**, which was listed in the *Formulary* in January 2003, was the first second generation, rapidly acting injectable antipsychotic. **Olanzapine IM injection** was added in the *Formulary* in March 2006. Oral aripiprazole was added in the *Formulary* in April 2004.

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia, bipolar disorder, and agitation associated with schizophrenia or bipolar disorder, is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at $D_2$ and 5-$HT_{1A}$ receptors and antagonist activity at 5-$HT_{2A}$ receptors. Actions at receptors other than $D_2$, 5-$HT_{1A}$, and 5-$HT_{2A}$ may explain some of the other clinical effects of aripiprazole, eg, the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic $alpha_1$ receptors.

Although intramuscular aripiprazole has a labeled indication for the treatment of agitation associated with schizophrenia or bipolar disorder, it is also used off-label to begin or continue oral aripiprazole therapy. Like other first- and second-generation antipsychotics, aripiprazole could be used off-label for the treatment of agitation in dementia, in the intensive care unit setting, and in other medical conditions. Recent warnings regarding increased risk of death in the elderly should prohibit the off-label use of second generation antipsychotics for dementia. This same rationale prohibits use for agitation in the ICU or other patients with severe medical conditions. ICU and severely ill medical patients may have risk factors that would make use in this setting unreasonable at this time.

Studies show greater efficacy than placebo for the labeled indication. There are no published studies directly comparing aripiprazole IM with olanzapine or ziprasidone. There are a few studies comparing aripiprazole IM to haloperidol (either directly or indirectly). Aripiprazole has been shown to have equal efficacy to haloperidol with a different adverse effect profile.

Aripiprazole IM is associated with less extrapyramidal symptoms (EPS) compared with haloperidol. It also is associated with less sedation. It is associated with a greater incidence of headache, dizziness, and nausea and vomiting.

Aripiprazole IM costs 10 times more than haloperidol IM/IV, is similarly priced to ziprasidone IM, and is half the cost of olanzapine IM. Aripiprazole IM is less expensive than aripiprazole liquid or ODT.

Cost estimates are based on using 1 vial (ie, maximum dose of 9.75 mg), but if higher doses (10 mg or 15 mg) are prescribed, it is more expensive than olanzapine. There is no rationale for these higher doses. The oral dose should not be used when prescribing the IM dose, which is a common mistake made for all second-generation antipsychotics. Aripiprazole should not be given intravenously.

Based on a recommendation that 1 IM second-generation antipsychotic be listed in the *Formulary*, aripiprazole injection was added in the *Formulary* and olanzapine injection and ziprasidone injection were deleted and designated nonformulary and not available.

**Hyoscyamine** is a nonspecific antimuscarinic anticholinergic drug that has been on the market since 1938. Because it has been on the market for so long, the labeling information is limited, and there is not much published regarding its therapeutic uses. Many of the labeled indications (eg, a drying agent for acute rhinitis) would be considered inappropriate today.

Hyoscyamine was requested for use post radical prostatectomy for detrusor relaxation in the bladder to prevent urinary spasms and urgency. The drugs used for this indication are the same drugs that are used for overactive bladder.

When drugs used for overactive bladder were reviewed in 2004, tolterodine extended-release (Detrol® LA) was selected for addition in the *Formulary* based on its prevalence in the outpatient setting. Newer agents like tolterodine ER are promoted as having less systemic anticholinergic adverse effects than older less specific agents, like hyoscyamine.

Common anticholinergic adverse effects associated with hyoscyamine include dry mouth, constipation, tachycardia, drowsiness, decreased sweating, and delirium. Hyoscyamine is listed as a drug that should be avoided in the elderly because of its systemic anticholinergic effects.

There are no published studies comparing hyoscyamine with other therapeutic alternatives to help guide a decision as to whether hyoscyamine should be added in the *Formulary*. Because there was insufficient evidence to support its addition and because of concerns about possible adverse effects, hyoscyamine was not added in the *Formulary*.

**Iron sucrose injection** is 1 of 3 versions of parenteral iron therapy on the market. The other 2 agents are iron dextran and sodium ferric gluconate in sucrose injection.

Parenteral iron is commonly used in combination with an erythropoietin in many clinical settings. Use in patients with renal failure and renal dysfunction is a major area of use. Iron dextran was the only choice for parenteral iron therapy until 1999, when ferric gluconate injection was marketed. Ferric gluconate injection was added in the *Formulary* as an alternative to iron dextran in patients who could not tolerate iron dextran. In 2000, iron sucrose injection was marketed as an alternative to ferric gluconate.

The labeled indications for iron sucrose injection are for the treatment of iron deficiency anemia in the following patients: non-dialysis-dependent chronic kidney disease patients receiving an erythropoietin; non-dialysis-dependent chronic kidney disease patients not receiving an erythropoietin; hemodialysis-dependent chronic kidney disease patients receiving an erythropoietin; and, peritoneal dialysis-dependent chronic kidney disease patients receiving an erythropoietin. However, iron sucrose has been used off-label in any situation when parenteral iron supplementation is needed.

Clinical trial data show that iron sucrose injection is effective. It has been tolerated in patients who have not tolerated iron dextran and was shown to be as effective as ferric gluconate in a head-to-head trial. There are no data proving that iron sucrose is safer than ferric gluconate.

The costs of iron sucrose injection and ferric gluconate are the same based on a mg-of-iron basis. There is also more experience using ferric gluconate in pediatric patients. Therefore, iron sucrose injection was not added in the *Formulary*.

**Neoral**® and **Gengraf**® are the only brands (or generic versions) of **modified cyclosporine capsules** that will be listed in the *Formulary*. Normally all drugs available with bioequivalent generics are automatically interchanged to the least expensive generic product (ie, generic interchange). However, for controversial drugs, this interchange is reviewed by the P&T Committee.

Since 2000, when the first generic cyclosporine equivalent to Neoral® was marketed (ie, Gengraf®), both Neoral® and Gengraf® have been available at Shands at UF. Patients who are admitted on a generic version of modified cyclosporine capsules (ie, products made by Ivax, Pliva, or Sandoz) must either use their own supply from home under the Patients Own Medication policy or be converted to either Neoral® or Gengraf®.

*(continued on next page)*

***Formulary update,*** *from page 2*

Although the Food and Drug Administration (FDA) has tested the bioequivalency of all generic modified cyclosporine capsules and deemed them interchangeable, some transplant physicians are concerned that this may result in unnecessary variability in serum concentrations. For this reason, they do extra monitoring after converting to modified cyclosporine made by another manufacturer. The FDA has stated that this extra monitoring is unnecessary. Regardless, it is occurring.

Since most of the patients who have received transplants at Shands at UF are receiving either Neoral® or Gengraf®, stocking these products should cover many of the patients admitted. Some third-party payors give patients economic incentives to use a less expensive version of modified cyclosporine capsules. These patients' copays are considerably less per month. When these patients are admitted, they must be switched to Neoral® or Gengraf® or use their supply from home.

**Intravenous potassium** criteria for use have been modified to reflect current practice. The Parenteral Potassium Administration Protocol was modified to allow larger potassium doses in children. The old policy limited potassium replacement doses to 0.5 mEq/kg/dose. The revision allows 0.5 mEq/kg/hour or 20 mEq per hour, whichever is less.

However, there is a provision for 1 mEq/kg/hr doses in patients with severe hypokalemia in special circumstances. These special circumstances are patients having cardiac arrhythmias, patients with known high risk for cardiac arrhythmias, and patients with poor cardiac function and a measured potassium concentration less than 3.1 mmol/L.

Operationally, 2 separate syringes of potassium chloride 0.5 mEq/kg will be sent. Physician-to-nurse communications of special circumstances will be needed to infuse these syringes over half an hour (ie, 1 mEq/kg/hr).

Additional policy changes also allow a standard premade bag of 40 mEq/100 mL for patients receiving continuous renal replacement therapy (CRRT). The maximum dose of 40 mEq/hr will be allowed for patients greater than 40 kg. For patients less than 40 kg, the maximum dose will be 20 mEq/hr. The potassium dose will be stopped when CRRT is not functional to prevent hyperkalemia.

Finally, the total amount of potassium in large volume parenterals, excluding TPN, was clarified to allow a maximum of 1 mEq/kg for non-ICU pediatric patients and 2 mEq/kg in ICU pediatric patients.

**PRESCRIBING**

# "Doctoring orders"

It is not clear where the term "doctoring" came from, but a favorable connotation is to use it to mean "to alter." This article deals with altering medication orders after they are written. In this case, "doctoring" orders is usually not the less favorable connotation of "falsifying," but simply adding something to an order or correcting something assuming that it can be fixed before the order is carried out.

In order to understand the issues surrounding the "doctoring" of orders, one has to understand how medication orders are processed. After a prescriber writes an order for a medication, it is flagged to be processed by a ward clerk or nurse. Medication orders are faxed to the Pharmacy for processing. After the order is faxed, it is supposed to be noted that it has already been faxed (ie, stamped as faxed). Unfortunately, the notation that an order has been faxed is not always done.

If a drug is left off a set of orders, if a dose or frequency change is necessary, or if the patient no longer needs the medication, it is not acceptable to go back and alter the original order under the assumption that nobody has seen it yet. This assumption can lead to medication errors.

Once a prescriber has walked away from an order that has been written, they must assume that the order has already been processed. In this case, make the assumption that the order has already been faxed to the Pharmacy. If a drug needs to be added, a separate order needs to be written. If a new order is not written, there is a good chance the "doctored" order will be overlooked, at least until orders are verified by the nursing staff. If an order is "doctored" but not sent to the Pharmacy, it is possible that the original order will be dispensed and that the patient will receive the unintended dosage.

In order to prevent potential problems, avoid "doctoring" orders. Assume that once you step away from an order, it has already been processed.

**PRESCRIBING**

# Meningococcal vaccination in the hospital setting

An estimated 0.5-1.1/100,000 people are affected by meningococcal disease in the United States. Approximately 10-15% of these people die despite antibiotic treatment. Therefore, vaccination against this disease in people most at risk is important.[1]

The Centers for Disease Control and Prevention (CDC) along with the Advisory Committee on Immunization Practice (ACIP) recommend vaccination against meningococcal disease in a variety of patient populations, including those who have complement component deficiencies or splenectomies. Post-splenectomy patients account for the majority of meningococcal vaccine administrations in hospitalized patients. These patients have an impaired ability for phagocytosis and antibody function and are, therefore, at risk for a variety of infections caused by encapsulated organisms including *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae.* Vaccination against these organisms is important in the prevention of infection in these high-risk, post-splenectomy patients.[1,2]

Currently 2 meningococcal vaccines are available.[1,3,4]

Due to increased demand, Menomune® is in short supply and is being allocated to assure proper vaccination of patients at high risk for the development of *N. meninigitidis* infections. Menomune® is limited to 10 single dose vials every 30 days.[2,5,6] *(See table on next page.)*

This meningococcal vaccine shortage has left many healthcare institutions needing to substitute 1 vaccine for another to assure vaccination of those at high risk for infection. However, substitution is often not implicit since the recommended population age is different for both products.

As a result, the ACIP released a statement that Menomune® is an acceptable alternative if Menactra® is unavailable. In the event that Menomune® is the preferred vaccine and is not available, risks versus benefits must be weighed before Menactra® is administered in each patient.[1,7]

As with any vaccine, administration must be appropriately documented. The CDC requires the following information be included in the patient's permanent medical record: date of administration, name or common abbreviation of vaccine, vaccine lot number, vaccine manufacturer, administration site, Vaccine Information Statement (VIS) edition date and date provided to the patient/guardian, and name and address of the healthcare provider.[7] According to current hospital policies

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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**
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*Prescribing, from page 3*
and procedures, the pharmacy shall dispense a VIS specific to the vaccine and a pharmacy-generated computer label upon receiving an order for the vaccine. This label will indicate that the patient has been provided a VIS and will also have the VIS date, nurse, and manufacturer/lot number blanks that must be completed before the vaccine is delivered to the nursing unit. The nurse must initial in the appropriate blanks of the pharmacy label before the vaccine is administered. This label must be placed in the patient's Medication Administration Record (MAR). In the event a pharmacy label is unavailable, a written note that contains the above information must be signed by the nurse and placed in the patient's MAR.[8] Accurate documentation of vaccine administration must be exercised to comply with federal regulations and assure patient safety.

## TABLE 1: MENINGOCOCCAL VACCINES

| | Menomune® | Menactra® |
|---|---|---|
| | ▪ Meningococcal polysaccharide vaccine (MPSV4) | ▪ Meningococcal conjugate vaccine (MCV4) |
| **Activity** | ▪ *N. meningitidis* serotypes A, C, Y, and W-135 | ▪ *N. meningitidis* serotypes A, C, Y, and W-135 |
| **ACIP recommended population** | ▪ Patients aged 2-10 years and patients older than 55 years of age | ▪ Adolescents and adults 11 through 55 years of age |
| **Dose** | ▪ 50 mcg | ▪ 4 mcg |
| **Route of administration** | ▪ Subcutaneous | ▪ Intramuscular |
| **Need for revaccination** | ▪ May be needed in 2-5 years if first vaccination was received prior to the age of 4 or if the patient remains at high risk for infections | ▪ No need for revaccination |

Menactra® is currently more readily available than Menomune®, which is being reserved for our pediatric patients who are 2–10 years old. All patients ages 11–55 years should receive Menactra®, and risks versus benefits must be weighed before administration of Menactra® in patients who are 2–10 years of age or older than 55 years of age who qualify for Menomune® but cannot receive the product due to the shortage. Regardless of which product is administered, appropriate documentation of administration remains crucial.

*By Mona Patel, PharmD*

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