

# Drugs & Therapy

B • U • L • L • E • T • I • N

## FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met August 21, 2007. 6 drugs or dosage forms were added in the *Formulary*, and 7 drugs or dosage forms were deleted. 8 drugs were designated nonformulary and not available. Therapeutic interchange was approved for 1 drug, and criteria-for-use were changed for 4 drugs.

### ◆ ADDED

**Buprenorphine-Naloxone**  
(Suboxone® by Reckitt Benckiser Pharmaceuticals)†

\*Restricted to Shands Vista or patients admitted to Shands at UF on Suboxone® for opioid maintenance or chronic pain with a history of opioid dependency

**Caffeine Tablets** (generic)

**Cefixime**  
(Suprax® by Lupin Pharma)

**Hydroxocobalamin**  
(Cyanokit® by Dey)

**Insulin Glargine Pen**  
(Lantus® SoloStar® Pen)

**Insulin Lispro-Insulin Lispro Protamine Pen**  
(Humalog® 75/25 Pen)

### ◆ DELETED

**Antihemophilic Factor**  
(Monarc® M by Baxter)†

**Antihemophilic Factor, Porcine**  
(Hyate® C by Ipsen)†

**Buprenorphine Sublingual Tablets** (Subutex® by Reckitt Benckiser Pharmaceuticals)†

**Cyanide Antidote Kit** (by Akorn)†

**Gonadorelin** (Factrel® by Baxter)†

**Insulin Aspart-Insulin Aspart Protamine Pen**  
(Novolog® 70/30 Pen)†

**Insulin Glargine Vial**  
(Lantus® Vial)†

†Nonformulary and not available

(continued on next page)

## PHYSICIAN-APPROVED PROTOCOLS

### Erythropoiesis-stimulating agent protocol

A physician-approved protocol (PAP) for the erythropoiesis-stimulating agents (ESAs) was approved by the P&T Committee to improve dosing and monitoring of these agents in the inpatient setting. Any order for an ESA will activate this protocol. This policy will not apply to outpatient clinics.

As mentioned in the *Formulary Update*, this PAP also allows for the therapeutic interchange of ESAs. Based on current hospital costs, darbepoetin

ordered. The second dose and all subsequent doses will be given on either a Monday or Thursday (see table below).

Doses may be delayed (ie, given on the following Thursday or Monday) if a patient's hemoglobin (Hgb) value is considered too high.

The FDA has recently issued a safety warning regarding cardiovascular risks when Hgb values are increased too much with ESAs. The PAP will allow pharmacists to decrease or hold doses based on

#### DAY ESA 1<sup>ST</sup> ORDERED ..... DAY OF NEXT WEEKLY DOSE

Monday .....	Monday
Tuesday .....	Monday of the following week (6 days)
Wednesday .....	Thursday of the following week (8 days)
Thursday.....	Thursday
Friday.....	Thursday of the following week (6 days)
Saturday.....	Monday of the following week (9 days)
Sunday .....	Monday of the following week (8 days)

(Aranesp®) will be the preferred ESA. Orders for epoetin (Procrit®) will be converted to a weekly dose of darbepoetin unless "Do Not Substitute" is included in the epoetin order.

The ESA PAP will also allow for standardization of doses. An equivalent ratio of 250 units of epoetin per 1 mcg of darbepoetin will be used, but with rounding the doses to the nearest syringe size, the ratio can be higher. A maximum dose of 100 mcg per week of darbepoetin will be used. Orders written for darbepoetin will be rounded down to the nearest syringe size to prevent waste. All darbepoetin dosages written for every other week will be standardized to weekly dosing by dividing the dose in half and rounding to the nearest syringe size.

Darbepoetin doses will be administered on Mondays and Thursdays at 1800 to allow implementation of the PAP with adequate monitoring before any needed dosage modifications. First doses will be given on the day they are

laboratory test findings and order laboratory tests when they have not been done to decrease any possible risks.

If a patient's Hgb is greater than 10 g/dL (or greater than 12 g/dL for chronic kidney disease), the day of administration will be delayed (or the first dose will not be administered). The complete PAP outlining the specific steps for each aspect of the PAP is available on the Pharmacy Intranet page (<http://intranet.shands.org/pharm/menu.htm>). Folic acid, hemoglobin, serum ferritin, serum iron, total iron-binding capacity, reticulocyte count, and vitamin B-12 tests can be ordered to monitor the effect of the ESA and/or the ability of the patient to respond to an ESA.

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## ◆ INSIDE THIS ISSUE

◆ The cost of Acthar Gel

◆ **NONFORMULARY AND NOT AVAILABLE**

**Propoxyphene** (Darvon<sup>®</sup>, Darvocet<sup>®</sup>, & generics)<sup>†</sup>

<sup>†</sup>All propoxyphene-containing products.

◆ **THERAPEUTIC INTERCHANGES**

**Darbepoetin** (Aranesp<sup>®</sup>) for **Epoetin** (Procrit<sup>®</sup>)

◆ **CRITERIA-FOR-USE CHANGES**

**Imipenem**  
(Primaxin<sup>®</sup> by Merck)

**Itraconazole**  
(Sporanox<sup>®</sup> by Ortho Biotech)

**Meropenem** (Merrem<sup>®</sup> by AstraZeneca Pharmaceuticals)

**Voriconazole**  
(Vfend<sup>®</sup> by Pfizer)

**Buprenorphine sublingual tablets** are opioid agonist-antagonists that are restricted for use for opioid detoxification, opioid maintenance therapy, and the treatment of chronic pain in patients with a history of opioid dependency. Buprenorphine is used primarily at Shands Vista, but there have been patients admitted to Shands at UF for a medical problem who require continuation of their buprenorphine therapy. A patient with a history of opioid addiction who is admitted to a hospital for a primary medical problem other than opioid addiction (eg, myocardial infarction) may be administered opioid-agonist medications (eg, methadone or buprenorphine) to prevent opioid withdrawal that would complicate the primary medical problem.

**Buprenorphine-naloxone sublingual tablets** are the preferred product in the outpatient setting because the tablets cannot be abused by grinding them up and injecting the solubilized tablets. By switching from buprenorphine to buprenorphine-naloxone sublingual tablets, continuity of care at discharge is more seamless.

With buprenorphine (only) sublingual tablets, there was concern that patients could be discharged on this product. This could predispose a patient to abuse. In order to make the medication reconciliation process easier, Subutex<sup>®</sup> was designated nonformulary and not available and Suboxone<sup>®</sup> was added in the *Formulary*.

**Caffeine tablets** were added in the *Formulary* as an option for the off-labeled treatment of post-dural

puncture headaches. Caffeine is a naturally occurring xanthine derivative with central nervous system and respiratory stimulatory effects. It is also a mild diuretic.

A 400-mg oral dose (ie, two 200-mg tablets) of caffeine has been suggested for the treatment of post-dural puncture headaches. To put this dose in perspective, a cup of coffee has approximately 50-100 mg of caffeine, and a caffeinated soft drink usually has about 35-50 mg of caffeine. The mechanism of caffeine in the treatment of post-dural puncture headache is unknown, but its presumed mechanism is vasoconstriction.

Although there is more data for the intravenous route of administration of caffeine for the treatment of post-dural puncture headache, oral therapy is an alternative. The limited availability and high cost of IV caffeine, which has a labeled indication for use in neonatal apnea, limits its routine use in adults.

**Cefixime** is a third-generation cephalosporin that was re-added in the *Formulary* for the oral treatment of gonorrhea. When cefixime was removed from the market in 2002, it left a gap in the oral management of gonorrhea. Injectable ceftriaxone remains a viable alternative, if patients can receive an injection. Ironically, injectable ceftriaxone is less expensive. Generic ceftriaxone injection is available from multiple vendors, whereas oral cefixime is available from only 1 company. It is available only as an oral suspension.

Oral fluoroquinolones used to be an oral option for the treatment of gonorrhea. However, because of high level fluoroquinolone resistance among *Neisseria gonorrhoeae* isolates, fluoroquinolones are no longer recommended by the Centers for Disease Control (CDC).

**Hydroxocobalamin** was reviewed proactively as an alternative to the traditional **Cyanide Antidote Kit** that contains amyl nitrite, sodium nitrite injection, and sodium thiosulfate. The Regional Poison Control Center recommends hydroxocobalamin as the treatment of choice for cyanide exposure. The most common exposure to cyanide is from house fires; however, cyanide exposure can occur in industrial settings or even as part of a terrorist attack.

Following exposure, cyanide quickly and reversibly binds to ferric ion in the cytochrome oxidase system of mitochondria. This inhibits the body's ability to perform aerobic metabolism, leading to lactate formation, cellular hypoxia, and metabolic acidosis.

The traditional Cyanide Antidote Kit consists of inhaled amyl nitrite for immediate effect, then sodium nitrite injection, followed by sodium thiosulfate. The nitrites induce methemoglobinemia, which preferentially binds cyanide. Sodium thiosulfate facilitates

the elimination of bound cyanide. This treatment is associated with adverse effects and is complicated to use.

Hydroxocobalamin is given as an IV injection and converts cyanide to cyanocobalamin (Vitamin B<sub>12</sub>), which can be excreted in the urine. It can be given as two 2.5-gram doses. Each dose is diluted in 100 mL of normal saline (or other diluent) and given over 7.5 minutes. It can be administered by emergency medical service personnel while patients are being transported to a hospital.

The most common adverse effects reported in clinical trials were red-colored urine, which occurred in all patient receiving at least 5 grams, and erythema, which occurred in nearly all patients receiving a 5-gram dose or greater. All adverse events were considered mild to moderate in severity and resolved following discontinuation of therapy or supportive care.

Although hydroxocobalamin costs nearly 4 times more than Cyanide Antidote Kits, its improved safety profile and ease of administration in an emergency setting justify its addition in the *Formulary*. Cyanide antidote kits were designated nonformulary and not available.

Several additional changes were made to the insulin products to harmonize what is listed in the *Formulary* with Shands AGH and promote patient safety.

**Lantus<sup>®</sup> SoloStar<sup>®</sup> pens** will replace **Lantus<sup>®</sup> vials**, which were deleted and designated not available. In general, pens are more convenient than vials. The SoloStar<sup>®</sup> pen is sufficiently different from other insulin pens listed in the *Formulary* to avoid any possible confusion. **Insulin glargine** is a long-acting insulin analog.

**Humalog<sup>®</sup> 75/25 pens** will replace **Novolog<sup>®</sup> 70/30 pens** as the mixed combination of a rapid onset insulin analog (ie, **insulin lispro** instead of **insulin aspart**) and an intermediate acting insulin analog (ie, **insulin lispro protamine** instead of **insulin aspart protamine**). Humalog<sup>®</sup> 75/25 provides the same effect on blood glucose as Novolog<sup>®</sup> 70/30 in a pen dosage form.

Novolin<sup>®</sup> 70/30 vials, a mixture of regular insulin and isophane insulin, remain in the *Formulary*. The differences in the brand names, the dosage forms (ie, pen versus vial), and the numbers after the brand name (ie, 75/25 versus 70/30) should help avoid mix-ups.

Two **antihemophilic factors** were deleted from the *Formulary* and designated nonformulary and not avail-

(continued on next page)

able. **Monarc® M** is a Factor VIII product derived from human plasma donations, which are then purified using monoclonal antibodies. Although this technology reduces the risk of many possible blood-borne pathogens, there have been lingering concerns that some infectious agents may still be transmitted by these products. Thus, recombinant Factor VIII products (ie, recombinant antihemophilic factor) are the preferred products.

Both Adult and Pediatric Hematology physicians agree that monoclonal antibody purified antihemophilic factor is obsolete and does not need to be listed in the *Formulary*. These products have not been used and cannot be returned for credit when they expire.

**Hyate® C** was **porcine antihemophilic factor** (ie, porcine Factor VIII). This product was discontinued in June 2004 and is now no longer commercially available.

Porcine Factor VIII was used when patients had antibodies to [human] Factor VIII (eg, acquired hemophilia). This condition is now treated with recombinant Factor VIIa (ie, NovoSeven®), which is listed in the *Formulary*. NovoSeven® availability has made porcine Factor VIII obsolete. Thus, the manufacturer discontinued the product for business reasons.

**Gonadorelin** is a naturally occurring gonadotropin-releasing hormone. It had a labeled indication as a diagnostic agent for hypogonadism and was used in the diagnosis and treatment of infertility in men and women with hypogonadism.

This product is no longer commercially available. It has been on our shortage list for at least a year and has not been used at Shands at UF for several years. Thus, gonadorelin was deleted from the *Formulary* and designated nonformulary and not available.

**Propoxyphene** is a synthetic opioid that has been on the market for decades. It is used alone or in combination with acetaminophen for the treatment of mild to moderate pain.

Although propoxyphene has not been listed in the *Formulary* for over 20 years, it has continued to be requested for nonformulary use and stocked. The nonformulary and not available (NFNA) category did not exist when propoxyphene was originally deleted from the *Formulary*; therefore, it was not designated NFNA. Since propoxyphene is a controlled substance, patients cannot use their own supply from home.

There are many studies that show propoxyphene is no more effective than acetaminophen alone. It is also less effective than tramadol, which is an alternative pain reliever listed in the *Formulary*. Propoxyphene continues to be used despite its questionable efficacy,

and risks of adverse effects (eg, associated with overdose, withdrawal symptoms). Propoxyphene is also in the Beer's List of drugs that should be avoided in the elderly. There is currently a debate as to whether propoxyphene should be removed from the market.

Therefore, an audit was done to determine the barriers associated with changing the status of propoxyphene from nonformulary to nonformulary and not available. Data were collected on 30 patients from October 2006 through April 2007; 43% of these patients were greater than 65 years of age. Approximately half of elderly patients were on propoxyphene before admission to the hospital, and approximately 37% of all patients were taking propoxyphene on admission.

There was considerable heterogeneity for the reasons for propoxyphene use and the services that used propoxyphene. Patients were frequently prescribed propoxyphene-acetaminophen with other acetaminophen-containing products. The maximum dose of 4 grams of acetaminophen per day was exceeded in 1 patient. Lack of use of "as needed" orders prevented more patients from excessive acetaminophen exposure.

Based on this evaluation, all propoxyphene-containing products were designated nonformulary and not available.

**Darbepoetin** and **epoetin** are erythropoiesis-stimulating agents (ESAs). Both are biological products made with recombinant technology. Epoetin is the same as native erythropoietin, and darbepoetin is just a slight chemical modification of epoetin that works just like erythropoietin. Both products stimulate red blood cell formation. Darbepoetin has a longer duration of action, which can make a difference in the outpatient setting (ie, fewer trips to the clinic for recurring doses), but in the inpatient setting these products were deemed interchangeable.

Darbepoetin was chosen as the preferred ESA in the *Formulary* at this time based on its cost advantage. Unless a prescriber specifies "Do Not Substitute" for an epoetin order, the order will be converted to an equivalent dose of darbepoetin. Conversion will not occur for children less than 1 year of age. Special populations (eg, Jehovah's Witnesses or oncology patients with chronic kidney disease) will be addressed on a case-by-case basis. A ratio of 1 mcg of darbepoetin for 250 units of epoetin was chosen as the closest equivalent dosage conversion based on a review of the literature. However, based on rounding to the nearest available dosage form, this ratio varies (*see table*).

Darbepoetin doses will be administered weekly. Any biweekly doses will be converted to weekly by dividing the dosage in half.

Darbepoetin doses will also be rounded down to the nearest vial size.

Criteria for using carbapenems (ie, **imipenem** and **meropenem**) and the antifungals **itraconazole** and **voriconazole** were changed based on the recommendations from the Anti-Infective Subcommittee's annual review of the restricted drug policy.

**Carbapenems** are broad-spectrum antibiotics, and misuse has been associated with the development of microbial resistance and increased fungal infections. Based on recent information, carbapenems will no longer be considered first-line agents for the treatment of necrotizing pancreatitis. Cefepime plus metronidazole is the recommended combination for this use. Carbapenem use for necrotizing pancreatitis will require approval by an Infectious Diseases Consult or Dr. Ramphal.

**Itraconazole** should not be used for the treatment of aspergillosis as **voriconazole** is appropriate for the management of probable and documented mold infections (including as first-line therapy for invasive *Aspergillus* infections). Itraconazole use is limited to the treatment of invasive blastomycosis or histoplasmosis after clinical stabilization with an initial course of or intolerance to lipid amphotericin B (Abelcet®). It may also be useful for probable or definite mold infections in patients intolerant to voriconazole. It should be remembered, however, that itraconazole is not effective against zygomycetes. Itraconazole should be used cautiously in patients with a creatinine clearance less than 30 mL/min because of the accumulation of hydroxypropyl-beta-cyclodextrin vehicle in the formulation of itraconazole.

**Voriconazole** should be used for the management of probable and documented mold infections, including as a first-line agent for the treatment of invasive *Aspergillus* infections. Like itraconazole, it is not effective against zygomycetes. Lipid amphotericin B is the drug of choice for zygomycetes. Voriconazole should be used cautiously in patients with an estimated creatinine clearance less than 30 mL/min because of the accumulation of hydroxypropyl-beta-cyclodextrin vehicle.

EPOETIN ALFA (UNITS/WEEK)	DARBEPOETIN ALFA (MCG/WEEK)
Less than 2500	6.25
2500-4999	12.5
5000-10,999	25
11,000-17,999	40
18,000-33,999	60
34,000-89,999	100
Greater than 90,000	100

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## NEWS

# “Old” does not always equal “less expensive”: The Case of Acthar Gel

One of the goals of the Pharmacy and Therapeutics Committee is to promote cost-effective drug therapy. In general, this means promoting older, generic drugs when they are equally safe and effective. However, there are some striking cases when “older” does not equal “less expensive.” Recent changes in the cost of H.P.\* Acthar® Gel show how a product with rare indications and 1 supplier can be very expensive to use.

Corticotropin was approved by the FDA in 1950 and Acthar® Gel has been available for decades. You can tell how old the product is by how brief the official product information is (see [http://www.acthar.com/Pdf/Acthar\\_PI.pdf](http://www.acthar.com/Pdf/Acthar_PI.pdf)). Acthar® Gel has labeled indications for the diagnostic testing of adrenocortical function and conditions responsive to corticosteroid therapy. It has commonly been used off-label to treat infantile spasms and exacerbations of multiple sclerosis. The “bottom line,” however, has been that it has not been a commonly used product.

Questor Pharmaceuticals recently announced that it will be raising the cost

of a 5-mL multi-dose vial (80 units/mL), from its previous price of about \$1,500 per vial to \$23,000 per vial! This is a greater than 15-fold increase. The manufacturer states that it feels that this is now more in line with other drugs that are used to treat rare disorders.

The dramatic increase in cost of Acthar® Gel should remind prescribers that it should be used only for “rare disorders” and that other therapeutic alternatives should be considered whenever possible.

### *PAPs, from page 1*

Chart documentation of all PAP-related modifications to the original order will be completed by placement of a P&T-authorized order signed by a pharmacist in both the Orders and the Progress Notes sections. The PAP will allow dose modifications, interval modifications (and day of administration specification), and ordering of laboratory tests as needed. The PAP will only allow supplementation with iron, folic acid, or B-12 with prescriber authorization or a verbal order.

The PAP will not be implemented for patients less than 1 year of age. Also, it will not be implemented for special populations (eg, Jehovah's Witnesses or oncology patients with chronic kidney disease). These

patients will be addressed on a case-by-case basis. Therapy and goals of therapy will be determined jointly by the prescriber and PAP pharmacist. Therapy and outcomes will be tracked with the intention of incorporating the needs of special populations into the next revision of the ESA PAP.

The purpose of the ESA PAP is to standardize dosing and monitoring, which should improve patient safety. This process should decrease the overuse of ESAs when patients are unable to respond to these products, but will improve the response to ESA for some patients (eg, those with iron deficiency). The PAP will also decrease the risk of Hgb values reaching levels that have been associated with adverse patient outcomes.