

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met June 18, 2013. 1 drug was added in the *Formulary 2* drugs were deleted, and 9 drugs were designated nonformulary and not available. 1 interchange was approved and 3 drugs were designated a high-priority nonformulary drug. Criteria for use were established or changed for 4 drugs.

◆ ADDED

Nimodipine Liquid (Nymalize®)

◆ DELETED

Coagulation Factor IX, Human (Mononine®)*

*Nonformulary and not available

Ipratropium-Albuterol Aerosol (Combivent®)*

*Nonformulary and not available

◆ NONFORMULARY AND NOT AVAILABLE

Acyclovir Sublingual (Sitavig®)†
†Patients may use their own supply

Brinzolamide-Brimonidone
Ophthalmic Drops (Simbrinza®)†
†Patients may use their own supply

Ezetimibe-Atorvastatin (Liptruzet®)‡
‡Interchanged or patients may use their own supply

Liposomal Vincristine (Marqibo®)§
§May be used in the Infusion Center

Lucinactant (Surfaxin®)

Norethindrone-Ethinyl Estradiol
(WC3040)†
†Patients may use their own supply

Norethindrone-Ethinyl Estradiol-Ferrous Fumarate
(Minastrin-24 Fe®)†
†Patients may use their own supply

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GENERICS

Pay for delay

Recent statistics show a slowing in the amount of money spent on prescription drugs. As drugs come off patent, the price drops slightly with the first generic, then dramatically with competition (ie, more than one generic for the same drug). In some situations the first generic is awarded a 6-month exclusivity period, which can be lucrative for the generic manufacturer.

In the early days of the Hatch-Waxman law that provided a pathway for the approval of generics for small molecules, it was common for court disputes to delay the availability of generics. Brand name drug manufacturers challenged the generic companies (ie, that the generic was violating the brand patent) and asserted that the

company NOT to market their generic. The generic company is paid for doing “nothing,” usually much more than they would have received for making and selling the generic. This is a good deal for the generic company, and an excellent deal for the brand name company that gets to prolong their patent monopoly and maintain large profits based on high prices of brands to consumers. The brand name company makes much more than what they pay the generic company. Only consumers lose.

The Federal Trade Commission (FTC) estimates that “pay-for-delay” arrangements have cost consumers \$3.5 billion a year. The FTC tried to prevent pay-for-delay arrangements – but had not been successful.

The Supreme Court recently ruled that consumer advocates and regulatory agencies can sue companies involved in “reverse payments” based on antitrust grounds. This decision does not outlaw “reverse payments,” but it does make them more risky for brand and generic companies and, presumably, less likely.

The Supreme Court ruling was based on the case of AndroGel®. The patent for this topical testosterone replacement therapy was challenged in 2006. The maker of AndroGel® paid generic companies millions of dollars not to market less expensive generic versions. Meanwhile AndroGel® generated more than a billion dollars in sales last year. The agreement with the generic companies was to last through 2015.

Arrangements like “pay for delay” contributed to the difficulty in anticipating when a drug’s patent would expire, and multiple generics will become available. This recent decision may make this process somewhat more predictable and should decrease the likelihood of future pay for delay arrangements.

◆
“The brand company pays the generic company NOT to market their generic. ...Only consumers lose.”

brand patent was still in force. The brand company then received a delay while this issue was sorted out in court. Generic companies learned to challenge patents early, long before the patent should have expired, in order to avoid the last-minute patent challenge and an unnecessary patent extension. Also, this put the brand name patent at risk well before anticipation of the scheduled expiration of the patent.

There has been a practice called “pay for delay” or “reverse payments” that has been an impediment to the path of multiple generic alternatives. When a generic company files a lawsuit challenging the brand name patent, the brand and generic companies agreed to a mutually beneficial deal and avoided the costs and risks of litigation.

The generic company and the brand name company benefitted. The brand name company pays the generic

◆ INSIDE THIS ISSUE

◆ Editorial change

◆ **INTERCHANGES**

Ezetimibe-Atorvastatin

(Liptruzet®)‡

‡Interchanged to individual ingredients

◆ **HIGH-PRIORITY**

NONFORMULARY DRUGS

Dimethyl Fumarate (Tecfidera®)¶

¶High cost and low anticipated use

Glycerol Phenylbutyrate (Ravicti®)¶

¶High cost and low anticipated use

Mipomersen (Kynamro®)¶

¶Restricted distribution; patients must use their own injection

◆ **CRITERIA FOR USE CHANGES**

Darbepoetin Alfa (Aranesp®)**

**Anemia or critical illness (hemoglobin is equal to or less than 8.5 mg/dL)

Meperidine (Generic)**

**High-dose for rigors for an investigational hypothermia device protocol

Midazolam 5 mg/mL (Generic)**

**Restricted storage areas

Parenteral Nutrition

(Generic)††

††Physician Approved Protocol (PAP) approved

Nymalize® is a new **nimodipine oral solution** with a labeled indication for the treatment of patients experiencing symptoms resulting from subarachnoid hemorrhage. Nimodipine previously was available only as a liquid-filled gel capsule. For many years, an extemporaneously compounded liquid has been used. However, this liquid is difficult to make. At some institutions, a syringe was used to aspirate the liquid-filled capsules and then administer the liquid orally in patients who could not swallow a capsule.

Over the years, the FDA has received reports of serious and sometimes fatal consequences from intravenous (IV) injection of the liquid contents of nimodipine capsules. IV administration of nimodipine meant for oral use can result in death, cardiac arrest, severe decreases in blood pressure, and other heart-related complications. In August 2010, the FDA reminded health care professionals about the risks of IV administration of nimodipine from oral capsules. In 2006, a boxed warning was added to the drug to warn against such use. Nymalize® is administered orally, or via nasogastric or gastric tube, and

there is no need for a needle to be used, which is what caused past medication errors.

The approval of Nymalize® was based on clinical studies evaluating the use of nimodipine oral capsules in patients with subarachnoid hemorrhage. The most common adverse event observed in the studies was decreased blood pressure. A patient's blood pressure should be carefully monitored during treatment. With the addition of Nymalize®, the extemporaneously compounded nimodipine liquid will no longer be used at UF Health Shands Hospital.

Mononine® is **coagulation Factor IX** from pooled **human** plasma. For many years, the Factor IX product that has been used (and has been stocked) at Shands Hospital is BeneFix®, which is a recombinant Factor IX. Both Mononine® and BeneFix® have labeled indications for the prevention and control of bleeding in Factor IX deficiency (Hemophilia B or Christmas disease).

Mononine® was not officially deleted from the *Formulary*, even though the use of this product, like all factor products from pooled plasma, has migrated to recombinant products. Plasma-derived products have the theoretical risk of transmitting viral and other pathogens, although these risks are low with appropriate viral clearing methods and donor screening. Before viral inactivation methods and donor screening, patients did develop viral infections, like human immunodeficiency virus (HIV), from factor products from pooled plasma. These products still carry this stigma.

The cost difference between Mononine® and 3-factor prothrombin complex concentrate (PCC) is minimal. Three-factor PCC contains Factors II, IX, and X. Although primarily used off-label (eg, for warfarin reversal), PCC has a labeled indication for the treatment of Factor IX deficiency. Patients who cannot receive BeneFix® can be treated with PCC, although these patients should be rare. Therefore, Mononine® was deleted from the *Formulary* and designated nonformulary and not available. Like all coagulation factors, patients can provide their own supply for inpatient use.

Combivent® aerosol is a combination bronchodilator containing **ipratropium** (anticholinergic) and **albuterol** (beta-agonist) with a labeled indication for use in patients with chronic obstructive pulmonary disease (COPD). Combivent® is used in patients who were on a regular aerosol bronchodilator and who continue to have evidence of bronchospasm and required a second bronchodilator.

The aerosol version of Combivent® has been discontinued because it contains chlorofluorocarbons (CFCs), which have been associated with ozone depletion in the atmosphere. Since the CFC-containing aerosol is no longer available, Combivent® Respi-mat®, a propellant-free inhalant, is now available as an alternative for use in the ambulatory setting.

Although Combivent® Respi-mat® contains the same ingredients as the aerosol, it delivers drugs more efficiently. One inhalation 4 times a day of the Respi-mat® is equal to 2 inhalations 4 times a day of the aerosol. The Respi-mat® cannot be used in ventilated patients, and it requires manual dexterity to administer.

DuoNeb® is the nebulized dosage form of the combination of ipratropium and albuterol that must be administered by a respiratory therapist. It is equally effective and is less costly. An equivalent dosage would be one 3-mL vial administered 4 times a day.

Combivent® aerosol was deleted from the *Formulary* and designated nonformulary and not available. DuoNeb® is the recommended alternative. Combivent® Respi-mat® remains nonformulary and not available, but patients may use their own supply from home.

Sitavig® is a **buccal** tablet dosage form of the antiviral **acyclovir**. Acyclovir is primarily active against herpes viruses. Sitavig® has a labeled indication for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults. Sitavig® has a mucoadhesive that attaches the tablet to the gum near the site of the lesion on the lip and delivers a high concentration of acyclovir. It is administered as a single application. The most common adverse effects are headache and pain at the site of application.

Acyclovir oral tablets and valacyclovir capsules are alternative antivirals listed in the *Formulary*. Sitavig® was designated nonformulary and not available, however, patients may use their own supply.

Simbrinza® is a combination of **brinzolamide** (a topical ophthalmic carbonic anhydrase inhibitor) and **brimonidine** (an alpha-2 adrenergic receptor agonist) with a labeled indication for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The recommended dosage is 1 drop in the affected eyes 3

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Formulary update, from page 2

times a day. The most common adverse reactions are blurred vision, eye irritation, dysgeusia, dry mouth, and eye allergy. Patients with a sulfonamide allergy should not use Simbrinza[®] because the brinzolamide component is a sulfonamide.

Brimonidine is listed in the *Formulary* as a single agent, while brinzolamide is a nonformulary drug.

Dorzolamide (Trusopt[®]) is the topical ophthalmic carbonic anhydrase inhibitor in the *Formulary*. It can also be given 1 drop 3 times a day. Dorzolamide is also a sulfonamide.

Simbrinza[®] was designated nonformulary and not available. Patients may use their own supply or prescribers should consider using brimonidine and dorzolamide as individual agents as an alternative.

Liptruzet[®] is a fixed combination of ezetimibe and atorvastatin. Ezetimibe (Zetia[®]) is a cholesterol absorption inhibitor. Atorvastatin is a hydroxymethylglutaryl CoA (HMG-CoA) reductase inhibitor that decreases the production of cholesterol by competing with HMG-CoA for HMG-CoA reductase (a hepatic microsomal enzyme) and reducing the quantity of the cholesterol precursor, mevalonic acid. Both ingredients are currently listed in the *Formulary*. Liptruzet[®] will be interchanged to the individual ingredients or patients can use their own supply from home.

Marqibo[®] is a once-weekly, intravenous liposomal injection of vincristine. It has a labeled indication for the treatment of adults with Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following 2 or more anti-leukemia therapies. This indication is based on an improvement in overall response rate; improvement in overall survival has not been shown.

Serious adverse events such as leukopenia with fever, hypotension, respiratory distress, and cardiac arrest occurred in 76% of the patients studied. The most common adverse effects observed during clinical studies include constipation, nausea, low blood cell counts, fever, nerve damage, fatigue, diarrhea, decreased appetite, and insomnia.

The prescribing information carries a boxed warning alerting that Marqibo[®] must be administered only intravenously because it can be fatal

if administered in other ways, such as intrathecally. The boxed warning also states that Marqibo[®] has different dosage recommendations than vincristine sulfate injection alone. To avoid overdose, it is important for health care professionals to verify the drug name and the dose before administration. Special requirements for preparation of Marqibo[®] are detailed in the label.

Liposomal vincristine was designated nonformulary and not available for inpatient use. The potential for medication errors (ie, confusion with conventional vincristine) should limit liposomal vincristine use to the outpatient setting. If used in the Infusion Center, safety mechanisms will be established to assure safe use in patients with no other option in whom it is economically feasible.

Lucinactant is a synthetic surfactant with a labeled indication for the prevention of respiratory distress syndrome (RDS) in premature neonates. Lucinactant contains sinapultide, an amino acid peptide designed to mimic the action of surfactant protein-B (SP-B). Marketed surfactants contain 2 main surfactant proteins (SP-B, SP-C) that contribute to lung surface activity with SP-B playing the dominant role in improving outcomes. Until recently, surfactant replacement therapies for the prevention and treatment of RDS were derived from animals or were non-protein-containing synthetic products.

Non-protein containing synthetic surfactants proved to be inferior to animal-derived products and were removed from the market. Animal-derived products are efficacious, but they may be associated with infectious and immunologic complications that can contribute to chronic lung disease progression. There are also variations in the amount of surfactant proteins between different formulations and brands of surfactant, but it is unclear if this affects clinical outcomes.

The recommended dose of lucinactant is 5.8 mL/kg through the endotracheal (ET) tube given at least 6 hours apart for a maximum of 4 doses within the first 48 hours of life. Two clinical trials, STAR and SELECT, compared lucinactant to animal-derived products in neonates at high risk of RDS. The STAR trial demonstrated that lucinactant was similar in safety when compared to poractant alfa. However, the study was underpowered and noninferiority could not be established. The SELECT trial demonstrated lucinactant was more effective than beractant and colfosceril palmitate with a similar safety profile. A

1-year follow-up study showed that lucinactant was not associated with increased neonatal complications or mortality. Both the STAR and SELECT trials demonstrated that lucinactant had a higher incidence of administration-related adverse reactions compared to other surfactants.

Lucinactant requires a large volume for each dose and prolonged administration increases the risk for administration-related adverse events. It is currently unavailable for purchase and there is no information regarding price comparisons to other surfactants. There is also insufficient evidence showing its superiority over animal-derived surfactants, especially calfactant, the surfactant product listed in the *Formulary*. Therefore, lucinactant was designated nonformulary and not available.

WC3040, which is made by Warner Chilcott (thus the "WC"), does not have a brand name yet. This chewable combination oral contraceptive contains **norethindrone** (a progestin) and **ethinyl estradiol** (an estrogen) in 24 tablets similar to Loestrin 24 Fe[®]. Four tablets contain **ferrous fumarate** for iron replacement. News reports state that this product will be marketed in August 2013.

WC3040 was designated nonformulary and not available and, like most oral contraceptives, patients may use their own supply from home during their hospitalization.

Minastrin-24-Fe[®] is an oral contraceptive containing **norethindrone**, **ethinyl estradiol**, and **ferrous fumarate**. Each packet has 24 capsules containing norethindrone and ethinyl estradiol and 4 ferrous fumarate capsules. News reports suggest that this product will not be marketed until after 2013.

Like most oral contraceptives, Minastrin-24-Fe[®] was designated nonformulary and not available, but patients may use their own supply from home while they are hospitalized.

Dimethyl fumarate is an oral capsule with a labeled indication for the treatment of relapsing remitting forms of multiple sclerosis (MS). It is an immunomodulator that has been used in higher doses in other countries for the treatment of psoriasis.

Results from 2 clinical trials showed that dimethyl fumarate decreased the number of relapses in patients with MS compared to placebo. One trial showed that patients showed less disability compared with placebo.

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Formulary update, from page 3

Dimethyl fumarate can cause leukopenia and may increase the risk of infections, although more infections were not seen in clinical trials. White blood cell counts should be monitored on dimethyl fumarate.

Common adverse effects include flushing, nausea, vomiting, and diarrhea, especially at the beginning of therapy. These effects may decrease over time.

Dimethyl fumarate was designated a high-priority nonformulary drug. If usage increases, its formulary status will be re-evaluated.

Glycerol phenylbutyrate is as an alternative to sodium phenylbutyrate (Buphenyl®) or NaPBA. It has not been shown to be superior for treatment of chronic urea cycle disorder (UCD). Glycerol phenylbutyrate was approved with a labeled indication for the treatment of chronic UCD to be used with protein restriction and amino acid supplementation in patients 2 years of age and older.

NaPBA is approved for patients over 20 kg and can be used off label without age or weight restrictions. Glycerol phenylbutyrate is contraindicated in patients younger than 2 months. NaPBA is approved for UCD related to carbamoyl phosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase. Glycerol phenylbutyrate does not specify what specific subtypes it is approved for; however, it has not been evaluated in N-acetylglutamate synthase (NAGS) deficiency.

Both agents have the same mechanism of action; they are prodrugs that are converted to phenylacetylglutamine when taken orally. Phenylacetylglutamine is a substitute for urea and is excreted in the urine carrying with it 2 moles of nitrogen per mole of phenylacetylglutamine.

Glycerol phenylbutyrate has been evaluated against NaPBA in non-inferiority clinical trials and in uncontrolled trials. The study primarily cited when the FDA approved glycerol phenylbutyrate was an actively controlled, 4-week non-inferiority study comparing glycerol phenylbutyrate and NaPBA at equivalent doses in 44 adults. Glycerol phenylbutyrate was found to be non-inferior to NaPBA based on 24-hour AUC of mean venous ammonia levels.

Glycerol phenylbutyrate has also been compared to NaPBA in pediatric patients aged 2-17 years in 2 short-

duration, open-label, and switchover studies. The 24-hour AUCs were not significantly different between the drugs. Glycerol phenylbutyrate has not been evaluated in superiority studies in pediatric or adult patients.

A pooled analysis of all studies showed lower 24-hour AUC of ammonia in all subgroups and was statistically significant as well as plasma glutamine. However, these studies were powered to be non-inferiority and not superiority studies. Glycerol phenylbutyrate is an oral liquid and NaPBA is available as an oral tablet or powder. Glycerol phenylbutyrate is administered 3 times daily, the same frequency as NaPBA.

The adverse reactions most commonly reported with glycerol phenylbutyrate are flatulence, diarrhea, and headache and have not been shown to be significantly different from NaPBA.

The use of glycerol phenylbutyrate is expected to be uncommon. Because of its expense, glycerol phenylbutyrate was designated a high-priority nonformulary drug. Prescribers will be encouraged to use the patient's supply from home.

Mipomersen is an injectable oligonucleotide inhibitor of apolipoprotein B-100 synthesis with a labeled indication as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), and non-high density lipoprotein-cholesterol (non HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH). Mipomersen injection is given once a week.

The efficacy of mipomersen was evaluated in a clinical trial of 51 patients with HoFH. Levels of HDL-C fell by about 25% during the first 26 weeks in patients receiving mipomersen.

Mipomersen has a boxed warning on the serious risk of liver toxicity, which is associated with enzyme abnormalities and fatty liver. Chronic use would progress to liver disease.

The most common adverse effects include injection site reactions, flu-like symptoms, nausea, headache, and elevations in serum transaminases. The FDA is requiring postmarketing studies to determine long-term safety.

Mipomersen was approved with a risk evaluation and mitigation strategy (REMS) with elements to assure safe use including prescriber and pharmacy certification and documentation of safe-use conditions, which requires a prescription form for each new prescription. It is only available from certified pharmacies.

Each prescription requires a separate authorization form for each patient. The product can be shipped to the patient's home or an alternative address (such as UF Health Shands Hospital) if the patient is an inpatient. UF Health Shands Hospital cannot stock this product. Therefore, mipomersen was designated a high-priority nonformulary drug.

Darbepoetin alfa is a hyperglycosylated recombinant form of the renal hormone erythropoietin. It is produced by recombinant technology in a Chinese hamster ovarian cell system. The labeled indications for use include the treatment of anemia secondary to chronic kidney disease and concomitant myelosuppressive chemotherapy.

At UF Health Shands Hospital, inpatient use of darbepoetin alfa is restricted to anemia associated with chronic kidney disease/end-stage renal disease ON dialysis, anemia associated with chronic kidney disease/end-stage renal disease NOT on dialysis, anemia in critically-ill patients (expected ICU stay of at least 7 days), anemia associated with low-risk myelodysplastic syndrome (MDS), and anemia associated with chemotherapy.

The off-label use of darbepoetin in patients experiencing anemia of critical illness has been common at Shands. The majority of use has been observed within the thoracic and cardiovascular (TCV) surgery patients. It is estimated that approximately 90% of critically ill patients that remain in an intensive care unit (ICU) greater than 3 days will experience anemia, thereby leading to decreased tissue and vital organ oxygenation. Interest in the use of erythropoiesis-stimulating agents for the treatment of anemia of critical illness emerged with observations of impaired erythropoiesis secondary to a blunted endogenous erythropoietin effect that is responsive to exogenously administered erythropoietin. Additionally, it has been theorized, but not well demonstrated in the literature, that the use of erythropoiesis-stimulating agents may decrease red blood cell transfusions and associated transfusion-related complications.

Current recommendations surrounding red blood cell transfusions indicate using a restrictive transfusion strategy in the critically ill patient population. A hemoglobin threshold of less than 8 g/dL is a safe and effective marker for transfusion if clinically indicated in the TCV population.

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This is the last issue of the *Bulletin*

...that I will be writing and editing.

I am retiring from UF Health Shands Hospital and will no longer be the Editor of the *Bulletin*. I will not have the privilege of writing and editing this newsletter that I started 27 years ago. I will also no longer be staffing the Pharmacy and Therapeutics Committee. I will miss both.

It is time for somebody else to take over. Dr. Carrie Lagasse will be the Editor beginning with the September issue.

It has been an interesting experience, and I have learned a lot. I have learned a lot about drug therapy, writing, and editing. I have learned a lot about written communication. From the beginning of the *Bulletin*, the goal has been modest: to communicate to the medical staff the decisions of the P&T Committee, and, more importantly, **why these decisions were made**. Also, it was important to keep each topic focused and the length of each article short.

It was a challenge to write much of the content and edit it. I would like to thank those who have helped me proof

my work. I would especially like to thank Dr. Rob Kilroy, who has done the final check of the newsletter for many years. I picked Rob for this role because of his knowledge about the policies of the Department of Pharmacy Services. He also has an amazing attention to detail. I cannot thank him enough. If there are mistakes in this issue, it is because I did not want him to see this article before it was published.

I have received a lot of feedback about the content of the *Bulletin*, both positive and negative. I have particularly “enjoyed” the negative feedback. That is how I have measured the *Bulletin's* success. Readers have been examining the content carefully and taking the time to let me know what can be improved.

One time I received a particularly harsh email about a P&T Committee proposal that was posted in the *Bulletin*. I forwarded those comments to others and added to the email, “at least he read the newsletter.” I meant that although the commenter did not agree with the proposal, at least he was aware of the proposal because it was in the news-

letter. By reading the article, he had a chance to provide input, but what I wrote in the email could have been taken another way. The email was forwarded to the commenter. I was embarrassed. I learned to try, every time, to write something exactly as it is intended. Also, I learned that email is a horrible way to communicate some issues, and not to write anything in an email that you do not want forwarded.

I am sure that the Dr. Lagasse will do a better job than I have and will continue to inform you about drug-related matters at UF Health Shands Hospital. Before we had a newsletter, I was told that if we had a newsletter, it would solve many drug-related problems. I do not think the *Bulletin* has solved anything, but I am glad we tried to keep you informed.

Since the inception of the *Bulletin*, I have rarely put my byline on the articles I wrote. I am going to break this tradition this [last] time.

by Randy C. Hatton, PharmD

Formulary update, from page 4

At UF Health Shands Hospital, all darbepoetin alfa orders are reviewed by a pharmacist once weekly as part of a physician approved protocol (PAP). The reasons for use and hemoglobin concentrations prior to subsequent administrations are reviewed. Pharmacists' actions are documented in each patient's medical record. The P&T-Committee-approved restrictions require holding scheduled administrations when hemoglobin values are greater than or equal to 12 g/dL in patients with chronic kidney disease, or when hemoglobin values are greater than or equal to 10 g/dL in patients receiving darbepoetin alfa for all other indications.

With the current “transfusion triggers,” darbepoetin alfa's criteria for use were modified. Serious adverse effects including venous thromboembolism, myocardial infarction, and stroke have been associated with target hemoglobin values greater than 11 g/dL. For these reasons, darbepoetin alfa's criterion for use in the treatment of anemia of critical illness was lowered. Patients now require a hemoglobin value at or below 8.5 g/dL

for continued use for anemia of critical illness. Pre-operative use will not be restricted. However, the continued use of darbepoetin for anemia of critical illness will be re-evaluated in the future. Because of the slow onset of darbepoetin, its use in this setting does not appear rational.

The cost of darbepoetin alfa is significant. When used for the treatment of anemia of critical illness, darbepoetin alfa 100 mcg subcutaneous once weekly is recommended. As observed in the literature, a typical therapeutic course of darbepoetin alfa in anemia of critical illness ranges from 3 to 4 weeks. Three to 4 doses cost more than a thousand dollars.

Meperidine is an opioid that has been restricted at Shands since 2002. It has a short duration of action and is associated with central nervous adverse effects, like seizures, even in patients with good renal function. For this reason, its use is limited to short procedures for pain and sedation, and for the treatment of rigors. Usual doses for rigors are 25 mg, which can be repeated a few times depending on the patient's symptoms.

Thus, doses are limited to 100 mg per day. The VA has national guidelines that limit meperidine's use to less than 24 hours and up to 600 mg per day for pain. The P&T Committee evaluated a request to allow the investigational use of meperidine to treat/prevent hypothermia rigors as part of an investigational hypothermia protocol for ischemic stroke patients. The protocol is for the evaluation of a hypothermia device.

The P&T Committee expressed concern about the safety of the dose of meperidine that will be used in this study to manage rigors associated with the device-induced hypothermia. Patients will receive a 1-mg/kg loading dose over 10 minutes, then an infusion of 30 mg per hour. The dose will be adjusted and the maximum dose per day is 1500 mg. Hypothermia will last for 36 hours. This dosage is above the labeled maximum and was inconsistent with previous UF Health Shands Hospital restrictions and VA national standards.

There are limited published data to support this dosage. In 2 studies, 37 patients total have successfully

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Volume 27, No. 7 July 2013

This publication is produced by the Drug Information and Pharmacy Resource Center under the direction of the Department of Pharmacy Services and the Pharmacy and Therapeutics Committee.

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received this regimen. These patients were not explicitly monitored for seizures, but no seizures were reported. Patients were heavily sedated and developed a higher rate of pneumonia, which might have been from aspiration.

The P&T Committee approved the investigational use of meperidine for rigors at this high dose with adequate informed consent. The FDA verified that the sponsor's Investigational Device Exemption (IDE) includes approval for the Investigational New Drug (IND) application for meperidine outside of its labeling.

Midazolam is a very short-acting benzodiazepine used for sedation, anxiolysis, and amnesia during short procedures or as an aid in the induction of anesthesia. It is usually given intravenously, and the dose is given slowly and in small increments to monitor the patient's level of sedation. Oral or nasal midazolam are sometimes used, particularly in children, when IV access is not available or to facilitate a more invasive procedure.

In 2012, there was a shortage of midazolam 5-mg/mL, and it was no longer stocked. Due to previous patient

safety reports with this item (ie, practitioners were unfamiliar with the 5-mg/mL vial and thought that 1 mL always contained 1 mg), it was decided not to restock this item after the shortage ended. Since then, there have been multiple requests from the pediatric emergency department (ED), pediatric anesthesia, and pediatric pulmonary to use this higher concentration of midazolam for intranasal midazolam administration, and it appears that this product is needed in these areas and not having it may result in unintended consequences. It is no longer in short supply.

The P&T Committee approved restocking this dosage form, provided safety checks can be implemented, including the following. Midazolam 5 mg/mL will be limited to the pediatric ED and pediatric pulmonary and pediatric anesthesia areas (including UF Health Children's Surgical Center). Omnicell alerts stating "concentrated: for intranasal use only" will be created. Bar code technology will be used when stocking midazolam in Omnicell cabinets as oral syringes to minimize the risk of inadvertent IV administration.

Parenteral nutrition is the intravenous administration of nutrients (proteins, carbohydrates, lipids) and electrolytes to meet a patient's metabolic needs. In May, the P&T Committee approved restrictions on the use of PN in adults and children in adult units. In June, the P&T Committee approved a proposal that allows prescribers to order PN via a physician approved protocol (PAP). The PAP is for adults and children in adult units.

Pharmacists will initiate and modify PN therapy after an order for the PAP is placed. A note will be written at least every third day, and the PAP allows the ordering of PN solutions and necessary laboratory monitoring.

This proposal has already been approved by the Standing Orders Committee and the Medical Executive Committee. The Parenteral Nutrition Physician Approved Protocol is an option that prescribers can order for the management of patients who are eligible for PN.