

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met February 20, 2007. 3 drugs were added in the *Formulary*, and no drugs were deleted. 1 dosage form was designated nonformulary and not available.

◆ ADDED

Decitabine
(Dacogen® by MGI Pharma)

Duloxetine
(Cymbalta® by Eli Lilly)

**Meningococcal Polysaccharide
Diphtheria Toxoid Conjugate
Vaccine**
(Menactra® by Sanofi Pasteur)

◆ DELETED

None

◆ NONFORMULARY AND NOT AVAILABLE

Insulin Detemir PENS (Levimir®
FlexPen® by Novo Nordisk)*

*Only the FlexPen® is not available;
vials may be used nonformulary.

Decitabine is a cytosine analogue; however, it is thought to work in the treatment of myelodysplastic syndrome by a mechanism that is relatively unique. Although the mechanism of action is not fully described, at lower doses decitabine is considered to be an inhibitor of DNA methylation, similar to azacitidine. In some cancers, hypermethylation is thought to block tumor suppression.

Decitabine has a labeled indication for the treatment of myelodysplastic syndromes (MDS). MDS are a group of clonal bone marrow stem cell disorders characterized by increased bone marrow cellularity, peripheral cytopenias, and abnormal blood cell function.

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FORMULARY PROPOSAL

Using generic cyclosporine

Generic interchange is a standard practice at Shands at UF. The responsibility to use A-rated generic drugs has been delegated to the Director of Pharmacy Services. However, the Pharmacy and Therapeutics Committee will review any generic interchange that is perceived as controversial. Also, any attending physician can request that a generic interchange practice be reviewed by the P&T Committee.

The generic interchange of cyclosporine is an interchange that is “controversial.” Although almost all drugs that are available as generics are used because of the significant cost savings (ie, 70% or more), oral cyclosporine products continue to be requested as a brand-name product (eg, Neoral®) with directions not to substitute. In the community setting, writing “Medically Necessary” on the face of a prescription prevents generic interchange. Our own outpatient data show that the co-pays associated with brand-name stipulation results in patients paying

nearly \$400 per year more for brand-name cyclosporine.

Generic drug products that are A-rated by the Food and Drug Administration’s standards for bioavailability can be safely interchanged without the need for any dosage modifications or additional monitoring. The FDA’s standards for bioequivalence are rigorous and are considered adequate, even for difficult-to-make dosage forms like oral cyclosporine products.

Based on the evidence, the current proposal is to carry 1 generic cyclosporine product in the *Formulary* and interchange all patients to this product. Attending physicians who would like to comment on this proposal should submit their comments in writing to Secretary, P&T Committee, PO Box 100316, or by email to dis@shands.ufl.edu. Evidence to support any concerns should be provided. The deadline for any comments to be considered by the P&T Committee is April 5, 2007.

POLICIES AND PROCEDURES

Off-label drug use promotion banned

Drug manufacturers’ sales representatives can promote drugs only for their labeled indications. Generally, off-labeled uses cannot be marketed. Companies can disseminate peer-reviewed journal articles about an off-label indication of its product, provided the company commits itself to file, within a specified time frame, a supplemental application based on appropriate research to establish the safety and effectiveness of the off-labeled use.

Sales representatives have been observed handing out unsolicited articles regarding off-labeled uses and discussing off-labeled uses at Shands at UF. This practice is considered inappropriate promotion at SUF, and the P&T Committee revised the sales representative policy to consider this an infraction that will result in progres-

sive sanctions, which could result in the sales representative or company being banned from Shands. When a drug is added in the *Formulary*, criteria for use that sales representatives must follow are approved. Unless otherwise specified, these criteria for use are the labeled indications.

Drug manufacturers’ sales representatives are now banned from off-label promotion of products including any verbal or printed communications that
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◆ INSIDE THIS ISSUE

- ◆ MDRD for renal dosage adjustments
- ◆ Drugs down the tube

Formulary update, from page 1

Several treatment approaches for MDS have become available in recent years, but few have been demonstrated to definitely improve survival. Treatment options for patients who are not candidates for bone marrow transplantation include: supportive care, growth factors such as erythropoietin and granulocyte colony-stimulating factor, immunomodulation with lenalidomide or thalidomide, immune suppression with antithymocyte globulin and/or cyclosporine, or chemotherapy.

Historically, the chemotherapy approach used in the treatment of MDS consisted of intensive chemotherapy similar to that used in acute leukemia. More recently, a lower intensity chemotherapeutic approach, employing the hypomethylating agents (eg, azacitidine or decitabine), has been used.

Decitabine has a labeled dose of 15 mg/m² IV every 8 hours for 9 doses for the treatment of all patients with MDS. In Phase II trials, response rates (complete plus partial response) ranged from 30% to 45%, with complete response rates of 8% to 20%. In the pivotal Phase III trial comparing decitabine to supportive care, the response rate was 17% (versus 0%), with a complete response rate of 9% (versus 0%). An additional 13% to 14% of patients experienced hematologic improvement. In responders, responses lasted a median of 10 months, and a prolongation in time to evolution to AML or to death was observed in patients receiving decitabine compared to supportive care. Toxicity in these studies was relatively modest and was mostly related to myelosuppression.

While response rates in the pivotal Phase III study were relatively modest, emerging data indicate that the FDA-approved dose may not be the most effective dose. Alternative dosing strategies employing lower total daily doses appear to produce higher response rates. In a recent report, decitabine dosed at 20 mg/m² IV daily for 5 days produced a CR rate of 39%. This dosing approach also appears to maximize hypomethylation status.

The anticipated use of decitabine in the inpatient setting is anticipated to be very low. A course of therapy is anticipated to cost approximately \$6000 to \$12,000. After 1 year, the need for both decitabine and azacitidine will be re-evaluated.

Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) with labeled indications for the treatment of major depressive disorder and the management of neuropathic pain associated with diabetic peripheral neuropathy. The FDA recently approved a new labeled indication for generalized anxiety

disorder (GAD). Duloxetine has also been used off-label for the treatment of fibromyalgia, as well as the treatment of stress urinary incontinence in female patients.

The usual adult daily dosage of duloxetine for the treatment of depression is 40 to 60 mg. This may be given in 2 divided doses, or once daily. The usual adult dosage for the treatment of diabetic peripheral neuropathic pain is 60 mg once daily. There are no data available on the usage of duloxetine in pediatric patients.

Clinical trial data show that duloxetine is effective compared to placebo. There are limited published data comparing duloxetine to other treatment options. These data do not show that duloxetine is superior to other active treatments (ie, venlafaxine or SSRIs) for depression. There is also a lack of published data on the use of duloxetine in treatment-resistant depression. However, it appears that duloxetine is as effective as other treatment options available for depression.

Duloxetine is approximately the same cost per day as the most similar treatment option, venlafaxine extended-release.

Although duloxetine does not offer any obvious advantages compared to other antidepressant options listed in the *Formulary*, there is little information to guide the conversion from duloxetine to an alternative antidepressant. Therefore, duloxetine was added in the *Formulary*.

Meningococcal polysaccharide diphtheria toxoid conjugate vaccine is conjugated with diphtheria toxin to provide a stronger immune response that should last longer than the unconjugated meningococcal vaccine (ie, Menomune®). Both the conjugated and unconjugated meningococcal vaccines contain the same 4 serogroups for the polysaccharides from *Neisseria meningitidis* (ie, A, C, Y, W-135). Menomune® has been listed in the *Formulary*, but because of a nationwide shortage, we have been receiving a limited allocation.

Menactra® currently only has a labeled indication for meningococcal prophylaxis in children or adolescents greater than or equal to 11 years of age and in adults less than 56 years of age. Menomune®'s use is not limited to the same ages as Menactra®. Menactra® had been on a nationwide shortage; and, thus, the Centers for Disease Control recommended that routine vaccination with Menactra® be limited to patients at highest risk until supply issues were resolved. There currently is no shortage of Menactra®.

Menactra® was proactively reviewed in order to make the most appropriate vaccines available for use at Shands at UF. Inpatient use of meningococcal vaccines is primarily for patients with anatomic (eg, trauma) or functional

asplenia and patients with terminal complement deficiency. Because of the shortage of Menomune®, patients 11 to 55 should receive Menactra® and patients less than 11 or greater than 55 should receive Menomune®. Thus, both products remain listed in the *Formulary*. Orders that specify either the brand name or conjugated or unconjugated meningococcal vaccine will prevent the need for order clarifications.

The percentage of subjects reporting systemic adverse effects is similar for both meningococcal vaccines. Local adverse effects are more common in patients aged 11 to 18 who receive Menactra® than among those who received Menomune®. These local reactions occur at a rate that is similar to tetanus-diphtheria toxoid (Td).

8 cases of Guillain-Barre Syndrome within 6 weeks of Menactra® have been reported. Even though this incidence is similar to that expected in nonvaccinated patients, the temporal relationship suggests an association with Menactra® administration. Therefore, Menactra® is contraindicated in patients with previous history of Guillain-Barre Syndrome.

Insulin detemir pens were designated nonformulary and not available for medication safety reasons. A Levemir® FlexPen® looks very similar to a Novolog® FlexPen®, which could lead to errors. This decision follows previous formulary decisions to choose insulin products that look dissimilar as a means of decreasing possible mistakes with injectable insulin products.

Insulin glargine (Lantus®) is the long-acting recombinant insulin analogue alternative to Levemir® listed in the *Formulary*. Data suggest that insulin detemir may require twice-daily dosing compared with once-daily insulin glargine.

Policies and procedures, from page 1

discusses off-labeled drug use. This explicitly prohibits the distribution of articles, including peer-reviewed articles, or any other reference material that contains information on off-labeled drug uses. Representatives cannot verbally discuss any off-labeled drug use at Shands at UF. This policy applies to Shands at UF and does not have anything to do with enforcement of federal law.

Any sales representative observed violating this policy should be reported to the Director of Pharmacy Services. Any sales representative unfamiliar with the current policies that permits them to visit Shands at UF should contact the Pharmacy Department's Resource Utilization Coordinator for additional details.

MDRD vs Cockcroft-Gault dosing with impaired renal function

It is hard to imagine a day when clinicians will individualize drug therapy based on a patient's genetic makeup when we still have a difficult time adjusting drug dosages based on a patient's renal function. Many drugs and their metabolites are eliminated by the kidneys, and clinicians should adjust the dosages of these medications when renal function is impaired. In general, one needs to consider adjusting medication dosages when the glomerular filtration rate (GFR) is below 60 mL/min. However, GFR is rarely measured, and prescribers often rely on estimates of GFR to make renal dosage adjustments and make other clinical decisions.

Since direct measurement of actual GFR is rarely done, several indirect methods are used to estimate renal function. Creatinine clearance is often used as a substitute for GFR measurement. Creatinine clearance is measured by collecting a timed urine sample (eg, 24-hour sample) and measuring the rate of creatinine excretion. Because of the difficulty and inconvenience of accurately collecting a 24-hour urine sample, several alternative methods have been developed. These equations estimate GFR from the serum creatinine (refer to table with equation below). The most widely recognized formula is the Cockcroft-Gault formula, but the MDRD eGFR equation

is becoming the standard for clinical use. Since creatinine is produced by muscle metabolism, all estimates of renal function that are based on the serum creatinine measurement can be misleading in patients who do not have normal muscle creatinine production rates (eg, liver disease, malnutrition, and limb amputations).

Although the Cockcroft-Gault method of estimating GFR has been so widely used that the official labeling for many drugs use this method to stipulate dosage reductions with decreased renal function, it has several limitations. As noted previously, the Cockcroft-Gault equation over-estimates renal function in patients with impaired creatinine production (ie, liver disease). A more important limitation of the use of the Cockcroft-Gault equation in automated systems is its dependence on the patient's weight, which is often not available to clinical laboratory computer systems. Finally, the Cockcroft-Gault formula is not highly accurate and can yield estimates that vary from the actual GFR by more than 30% in many patients.

A more accurate formula to estimate the actual GFR is the MDRD eGFR (estimated GFR) formula. This was developed as a result of extensive testing and actual GFR measurements in large-scale clinical studies. It has been validated in many patient populations and more accurately predicts the actual

GFR than the Cockcroft-Gault formula. Many clinical laboratories, including the laboratory at Shands at UF, now routinely report the MDRD eGFR whenever a serum creatinine is reported.

An important question for the clinician when medication dose adjustment for a patient with reduced renal function is which estimate of GFR to use — the Cockcroft-Gault or the MDRD eGFR. The FDA-approved labeling for most medications uses the Cockcroft-Gault formula, but the MDRD eGFR is the more accurate measurement of actual GFR and is more widely available to the clinician.

Studies have shown that initial dosage adjustments based on estimated creatinine clearance are helpful. When determining an initial dose, either the MDRD eGFR or the Cockcroft-Gault equation can be used. No studies have shown dramatic differences in clinical outcome from the use of one versus the other formula.¹⁻³ When the serum concentrations of medications with dose-dependent toxicities and efficacy can be measured using therapeutic drug monitoring (eg, aminoglycosides and vancomycin), this should be done. Of course, clinicians should make the final dosage adjustment after considering the relative risks for overdosage and underdosage. Most importantly, clinicians should identify patients with impaired renal function and make appropriate dosage modifications to minimize dose-dependent adverse effects.

COCKCROFT-GAULT EQUATION**

$$\text{Estimated Creatinine Clearance (mL/min)} = \frac{[140 - \text{Age (yr)} \times \text{weight (Kg)}]}{[72 \times \text{Serum Creatinine (SCr)}]}$$

*Multiply by 0.85 for females

†Use Ideal body weight (kg) = men = 50 kg + (2.3 kg x inches greater than 5 ft)
women = 45.5 kg + (2.3 kg x inches greater than 5 ft)

‡Normalize for BSA (1.73 m²)

MDRD eGFR

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 186 \times [\text{Serum Creatinine}]^{-1.154} \times \text{Age (yr)}^{-0.203}$$

(x 0.742 if female) (x 1.21 if African-American)

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DRUG INFORMATION FORUM

Getting to the gut of the matter: Administration of medications via enteral feeding tubes

Enteral feeding tubes often are required to provide adequate nutrition to patients with swallowing difficulties or an inability to meet nutritional needs. In such situations, medications may also be administered through enteral feeding tubes. This practice most commonly occurs in hospitalized patients in general medicine (51.5%), intensive care (24%), and pediatric (8%) settings.¹

Although medications are available in a wide variety of dosage forms and

formulations, administering medications via the enteral feeding tube can lead to complications. Complications include tube occlusion, decreased drug activity, alteration of drug properties, interruption of feedings and/or medication schedule, and possibly replacement of feeding tube.^{2,3}

The type of feeding tube placed will determine the choice of medication, as well as the dosage form. Flexible, small-bore nasogastric tubes, such as a Dobhoff, can be placed into the

stomach, duodenum, or jejunum.² Only liquid dosage forms should be administered when using these tubes due to the small, soft lumen.² Crushed tablets and other dosage forms can clog the tube, resulting in tube replacement and a delay in administration of medications and feedings.

The use of large-bore feeding tubes can eliminate the complications related to administration of medications. Several types of tubes may be used,

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Drug information forum, from page 3 including nasogastric (NG) and orogastric (OG) tubes.² These tubes are less likely to clog and are easier to insert because they are stiffer than NE tubes.² However, using large-bore tubes may increase the risk of aspiration.²

Prior to giving medications via the feeding tube, the clinician should evaluate the type of tube, location of tube in the GI tract, site of drug action and absorption, and the effects of food on absorption.²

Certain oral medications should not be crushed, such as sustained-release, enteric-coated, or microencapsulated products. Use of these medications in this manner may result in destruction of the time-release properties, as well as clogging of the tube. An alternative would be to administer the regular-release product, if available, scheduled more often. For example, Cardizem CD[®] is a sustained-release formulation of diltiazem that is given once daily.⁴ If being given via an enteral tube, the dose should be changed to the regular-release product, given four times a day.⁴ Whenever possible, liquid formulations of medications should be chosen to reduce the risk of clogging, as well as ease the administration for the nursing staff. Many products that are not commercially available in a liquid dosage form are compounded by the pharmacy and may be ordered.

Proton-pump inhibitors (PPI) are commonly used medications that are formulated to prevent gastric degradation, as the active drugs are acid-labile.² At Shands at UF, lansoprazole (Prevacid[®]) is the proton-pump inhibitor (PPI) listed in the *Formulary*. Lansoprazole is a delayed-release capsule that contains enteric-coated drug granules and should not be placed down feeding tubes.² An oral-disintegrating tablet (ODT) is available that can be placed on the tongue and allowed to disintegrate, with or without water, until the particles can be swallowed. Alternatively, the ODT can be dissolved in a carbonated liquid to form a suspension and be administered via the feeding tubes.² However, this product should not be used in patients with the small-bore tubes, such as a Dobhoff, as it can cause tube blockage. If a small-bore tube is placed, a liquid formulation compounded by Pharmacy as a 3 mg/mL suspension should be used instead.²

The administration of certain medications with enteral feedings can affect the extent of absorption, such as phenytoin. Phenytoin absorption is decreased when given concomitantly with enteral feedings, reducing serum levels by 50% to 75%.² This can be minimized by flushing the tube and stopping/separating feeds by 2 hours before and after administration

of phenytoin.² In patients who have nutritional deficits, this interruption of feedings can be problematic, especially if the drug is given 3 times a day. The situation can be rectified by changing the schedule to twice-daily or once-daily dosing.

If occlusion of a feeding tube occurs, there are various options available to remove the obstruction. These methods should be attempted prior to replacing the tube. Five milliliters of warm water should be first injected into the tube and clamped for 1 hour.² If that fails, carbonated water can be injected into the tube and clamped for 1 hour.² If a medication-related occlusion is suspected, an alkalized enzyme solution should be administered. The enzyme solution consists of the contents of one Viokase[®] or Creon[®] capsule (pancrelipase) to be mixed with four mL of 8.4% sodium bicarbonate.² This can be ordered from the pharmacy.

By Sarah Bush, PharmD

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