

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met February 19, 2008. 4 drugs or dosage forms were added in the *Formulary*, and no drugs were deleted. 4 drugs or dosage forms were designated nonformulary and not available; 2 interchanges were approved.

◆ ADDED

Exenatide (Byetta® by Eli Lilly)

Insulin Detemir Pen
(Levemir® FlexPen® by
Novo Nordisk)

Intravenous Immune Globulin
(Flebogamma® DIF by Grifols)

Sitagliptin (Januvia® by Merck)

◆ DELETED

None

◆ NONFORMULARY AND NOT AVAILABLE

Carvedilol ER
(Coreg® XR by GlaxoSmithKline)*

*Interchanged to Carvedilol IR

Insulin Detemir Vials
(Levemir® by Novo Nordisk)

Sitagliptin + Metformin
(Janumet® by Merck)†

†Automatically interchanged to the individual ingredients

Zolpidem ER
(Ambien® CR by Sanofi-Aventis)§

§Automatically interchanged to Zolpidem IR

◆ INTERCHANGES

Carvedilol IR (generic) for
Carvedilol ER (Coreg® CR)†

†3.125 mg IR BID for each 10-mg daily dose of Corg® CR

Zolpidem IR (generic) for
Zolpidem ER (Ambien® CR)§

§5 mg IR = 6.25 mg ER, and 10 mg IR = 12.5 mg ER

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POLICIES AND PROCEDURES

Contraindicated combos

The P&T Committee passed a policy that states prescribers and pharmacists will endeavor to avoid the use of drugs in situations in which drug combinations are deemed contraindicated in the official product labeling of either product. If there are circumstances when a UF faculty member feels that the use of contraindicated drug-drug combinations are appropriate, the faculty member must request that this practice be allowed via written communication to the P&T Committee, who will determine if the benefits outweigh the risks. Without P&T approval, the use of contraindicated combinations will not be routinely allowed.

The *CONTRAINDICATIONS* section of the drug product labeling lists those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of drugs to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or, continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities are listed. For example, if hypersensitivity to the drug has not been demonstrated, it is not listed as a contraindication. If no contraindications are known, this section of the labeling states "None known." The current policy refers only to concomitant use of contraindicated drug combinations, not all contraindications.

If the P&T Committee reviews the available evidence and determines that contraindicated drug combinations are reasonable under a specific circumstance, then the practice will be endorsed. It is expected that these circumstances will be rare. However, this policy will not be implemented until May to allow exceptions to be addressed proactively by the P&T Committee.

For example, the concomitant use of sirolimus (Rapamune®), an immunosuppressant commonly used in transplant patients, with voriconazole (Vfend®), an azole antifungal used to treat serious fungal infections (eg, Aspergillosis) is contraindicated in the official labeling for voriconazole. However, there are case reports when these 2 drugs have been used safely together.¹⁻³ In order for the concomitant use of these drugs to be safe, the dose of sirolimus needs to be reduced by as much as 90% and sirolimus levels need to be monitored. Sirolimus is metabolized by the CYP3A4 isoenzyme system of the liver, and voriconazole is a potent inhibitor of CYP3A4 metabolism. By reducing the dose of sirolimus by 90%, sirolimus levels can be maintained in the normal therapeutic range. Without reducing the dosage of sirolimus, serious toxicity can occur.

This type of evidence-based review may determine whether there are circumstances that would permit the use of contraindicated drug combinations. Please submit the potential exceptions to this policy and the supporting evidence to Secretary, P&T Committee, PO Box 100316 or email this information to hatton@ufl.edu.

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INSIDE THIS ISSUE

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- ◆ New Chantix® safety warning

Formulary update, from page 1

Exenatide was evaluated for possible addition in the *Formulary* because of its nonformulary use. The Glycemic Control Committee has recommended that some newer agents, like exenatide, be considered for addition in the *Formulary* because they are unique agents.

Incretin hormones (GIP and GLP-1) are peptides released from the gastrointestinal tract in response to food that enhance glucose-dependent insulin secretion from the pancreas and aid in overall glucose homeostasis. Exenatide is a GLP-1 receptor analogue that is resistant to inactivation by dipeptidyl peptidase 4 (DPP4); it is an incretin mimetic. Exenatide is a synthetic copy of exendin-4, which is a peptide originally isolated from the salivary gland of the Gila monster. The net effect is increased insulin synthesis and secretion in response to carbohydrate consumption.

Exenatide has a labeled indication for the treatment of type 2 diabetes mellitus. Exenatide is approved for monotherapy and for combination therapy (ie, with metformin, and/or a sulfonylurea, and/or a thiazolidinedione). Exenatide must be given twice a day as a subcutaneous injection within the 60-minute period before the morning and evening meals.

There are multiple clinical trials comparing exenatide to placebo. As expected, these studies show a statistically significant reduction in hemoglobin A1C and an increase in the percentage of patients reaching treatment goals (eg, HbA1C <7%) compared with placebo. When compared with insulin glargine and insulin aspart, exenatide had similar efficacy; however, the effects on blood glucose were modest.

Exenatide use is associated with weight loss, while insulin therapy is associated with weight gain. Exenatide has been used inappropriately off-label for weight loss.

Exenatide use is not associated with hypoglycemia, unless it is used in combination with an agent that causes hypoglycemia (eg, a sulfonylurea). Exenatide appears to cause considerably more gastrointestinal complaints and may not be tolerated by some patients. Nausea is most common at the beginning of therapy or upon dose escalation and generally resolves with time, if patients can tolerate therapy initially. In comparative trials, more patients stopped exenatide because of gastrointestinal complaints. Exenatide has been associated with the development of pancreatitis.

Byetta® is available as a unique-looking pen. This should help avoid

any look-alike issues with insulin products listed in the *Formulary*. Exenatide is very expensive, and because it comes as a pen, the entire 30-day dosage unit will be dispensed for each patient. These pens cannot be given to the patient to take home with them because they are not appropriately labeled; thus, product will be wasted at discharge.

The most recent guidelines for the management of hyperglycemia in type 2 diabetes do not address the use of exenatide. Exenatide has a modest effect on hemoglobin A1C, has limited clinical data, and is relatively expensive. It is unreasonable to begin exenatide therapy in the inpatient setting, and patients should often be switched to an alternative therapy during their hospitalization (see Sliding Scale Insulin article on page 5 of this issue of the *Bulletin*).

Insulin detemir and insulin glargine (Lantus®) are alternative “basal” insulins to NPH insulin. Only insulin glargine has been listed in the *Formulary*. Insulin detemir vials have been nonformulary; the pens have been nonformulary and not available. The pens look similar to other products (especially Novolog® pens, which are also a FlexPen®) and could lead to medication errors.

Because insulin detemir was not available, guidelines were developed to convert patients from insulin detemir to insulin glargine. Based on the results of a randomized trial comparing the 2 insulins, the recommended conversion is to take the total daily dose of insulin detemir and reduce this value by 25% to get the daily dose of insulin glargine. This is a conservative dose conversion with the rationale that doses can be titrated upward, if needed. Some have used a unit-for-unit conversion.

There are circumstances that were deemed inappropriate to interchange these products at Shands at UF. For example, cystic fibrosis patients need glucose-lowering effects during the day, but not at night; therefore, once daily insulin detemir can be used in this setting. Insulin glargine, because it has a longer duration (ie, truly a once-a-day drug), could cause hypoglycemia during the night.

Although it is best to consolidate the insulins in the *Formulary* and avoid look-alike products, the concern about the differences in pharmacological effects of these products led to insulin detemir being added in the *Formulary*; the vials were designated nonformulary and not available.

Flebogamma® DIF is a brand of intravenous immune globulin (IVIG) similar to Gamunex®, which is already listed in the *Formulary*. DIF stands for dual inactivation plus nanofiltration, which are processes used to reduce the risk of viral contamination from the

donor plasma. Flebogamma® is not a low IgA IVIG and contains sorbitol as a stabilizer.

IVIGs remain in short supply. The Shands at UF IVIG allocation has been changed and in order to be able to supply product to all patients this brand of IVIG was added in the *Formulary*.

Sitagliptin, like exenatide, was reviewed because of increasing non-formulary use. Sitagliptin is a DPP4 inhibitor, which prolongs the effects of the native incretin hormones by inhibiting their metabolism. Like exenatide, the net effect is increased insulin synthesis and secretion in response to carbohydrate consumption.

Sitagliptin only has labeled indications for adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione, but who have not achieved adequate glycemic control. Sitagliptin is given orally once a day.

Sitagliptin has been compared to placebo (only), placebo as add-on therapy to metformin, placebo as add-on therapy to glimepiride (only) or glimepiride plus metformin, and placebo as add-on therapy to pioglitazone. These studies found statistically significant reductions in hemoglobin A1C, percent of patients reaching goal (when reported), and fasting blood glucose (when reported). In general, more patients experienced gastrointestinal adverse effects, and there were more drop-outs for this reason. The effect on weight was usually neutral or minimal. In active comparator studies with glipizide and metformin, sitagliptin was similar to glipizide and less effective than metformin.

Although DPP4 inhibitors have been associated with skin necrosis in animal models, it has not produced this effect in humans. However, sitagliptin is still a relatively new drug, and whether it causes rare but serious adverse effects is unknown. A theoretical concern is that many other peptides besides the incretin hormones, including neuropeptides, cytokines and chemokines are cleaved by DPP-4. Whether inhibiting this activity could have untoward effects is unknown.

Januvia® tablets cost around \$5 per dose, which is quite expensive compared with other options, like metformin (about 100 times more than metformin). Additionally, sitagliptin is available as a combination product (**Janumet®**), which is a combination of sitagliptin plus metformin. This product comes in 2 dosage forms,

(continued on next page)

Formulary update, from page 2 both containing 50 mg of sitagliptin (ie, 50 mg/500 mg metformin or 50 mg/1000 mg metformin), which cost slightly more than Januvia® daily. Per policy, this product will be interchanged to its individual ingredients; Janumet® is nonformulary and not available.

Carvedilol is an alpha- and beta-blocker primarily used for the treatment of heart failure. It was originally approved to treat high blood pressure, but it was not originally marketed for this use. Carvedilol also has a labeled indication to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤ 40%. Carvedilol has also been used off-label to treat angina.

There are now several generic versions of the immediate-release form of carvedilol (ie, carvedilol IR).

The extended-release dosage form of carvedilol (**Coreg® CR**) was marketed in 2006. The IR-dosage form of carvedilol is given twice a day, while the ER-dosage form is given once daily. Coreg® CR was designated nonformulary and not available and will be interchanged to an equivalent dosage of carvedilol IR (see below). The carvedilol IR dosage is only 62.5% of the Coreg® CR dosage because the extended-release dosage form is less bioavailable.

Zolpidem is a nonbenzodiazepine sedative-hypnotic that works at the GABA-benzodiazepine receptors in the central nervous system and shares many of the effects of benzodiazepines. Zolpidem has a labeled indication for the short-term (7 to 10 days) treatment of insomnia.

Zolpidem has been on the market for many years and there are now several generic versions of the immediate-release (IR) dosage form. The immediate-release version of zolpidem should

be taken immediately before bedtime.

An extended-release version of zolpidem (**Ambien® CR**) was marketed in 2005 as the patent for zolpidem was close to expiring. The CR-dosage form has an immediate-release layer and an extended-release layer, which is designed to affect sleep onset and maintain sleep. Ambien® CR has not been directly compared to zolpidem IR.

Zolpidem IR and ER are Schedule IV controlled substances. Nonformulary controlled substances are problematic. Patients cannot use their own supply from home (ie, their home supply is sent home with a family member or stored with the patient's valuables until discharge). Therefore, Ambien® CR was designated nonformulary and not available and will be automatically interchanged to zolpidem IR tablets. Ambien® CR 12.5 mg at bedtime will be changed to zolpidem 10 mg at bedtime and Ambien® CR 6.25 mg at bedtime will be changed to zolpidem 5 mg at bedtime.

All interchanges are noted in the Orders and Progress Notes sections of the chart. Interchanges are also noted on the Medication Administration Record (MAR) and the Admission/Transfer Reconciliation List of Medications.

COREG® CR CONVERTED TO:	CARVEDILOL IR
Coreg® CR 10 mg daily	Carvedilol 3.125 BID
Coreg® CR 20 mg daily	Carvedilol 6.25 mg BID
Coreg® CR 40 mg daily	Carvedilol 12.5 mg BID
Coreg® CR 80 mg daily	Carvedilol 25 mg BID

NEWS

Publish the good, forget the bad; do you believe everything you read?

Publication bias has long been a controversial issue.¹ Selective publication is a form of publication bias that occurs when authors or investigators fail to publish results of finished trials.

Selective publication has become more of an issue in recent years with the increasing use of meta-analyses and systematic reviews.² Hospitals and clinicians rely heavily on clinical trials reported in the primary literature for decision-making and policy formation when it comes to drug therapy. These decisions can be flawed if clinicians base decisions on incomplete information (ie, not fully reported in the literature). Furthermore, money and resources may be wasted on further research of a drug that has previously been studied.² Selective publication may indirectly harm patients by subjecting them to further risk in future research studies.²

Investigators fail to publish results of clinical trials for multiple reasons. Reasons for unpublished trials include inadequate funding, lack of time, and

inexperience among researchers. Most concerning is that some investigators fail to publish due to unfavorable results. A survey of authors comparing unpublished and published trials found that the most common reasons for not publishing results were lack of interest and unfavorable results.³ Recently investigators have attempted to study selective publication of clinical trials.^{4,5}

Turner and colleagues focused on selective publication of antidepressant studies.⁴ The authors identified phase 2 and 3 clinical trials for 12 antidepressants approved by the Food and Drug Administration (FDA) between 1987 and 2004, involving 12,564 adults. Efficacy data from these clinical trials were then compared to data in the published literature.

Of the 74 FDA-registered clinical trials, 31% were not published; yet 97% (37/38) of studies that the FDA found to be positive were published. In contrast, only 39% (14/36) of studies with results viewed as questionable or negative by the FDA were published. However, 11

of the 14 studies were published as being positive, which was contradictory to the FDA's findings. Overall, positive studies were much more likely to be published in a way that was consistent with the findings of the FDA.

The authors in this study concluded that positive results were more likely to be published in the literature, and studies that were not positive were often published in a way that conveyed a positive outcome.⁴ However, this study failed to uncover reasons behind the selective publication of these clinical trials.

Chan and colleagues found that when study results were reported in the literature, they were often not only incomplete but also biased and inconsistent with the original research protocol.⁵ In fact, 86% of surveyed investigators initially denied incomplete data reporting when confronted by the authors. In addition, statistically significant results were much more likely to be reported compared with nonsignificant results.

(continued on page 4)

Mandatory VTE assessment and orders

The Medical Executive Committee recently approved the mandatory use of an *Adult Venous Thromboembolism (VTE) Prophylaxis Order Form*. This "order form" is actually a combination of a risk assessment tool and order form. The *Adult Venous Thromboembolism (VTE) Prophylaxis Order Form* must be completed for all adult admissions and transfers within the hospital.

All existing VTE prophylaxis orders, both mechanical and pharmacologic, will be removed from all existing adult preprinted physician order sets. The newly approved *Adult Venous Thromboembolism (VTE) Prophylaxis Order Form* will be appended to all adult admission and transfer preprinted physician order sets. A statement will be inserted into all of these admission and transfer order sets that states, "Providers MUST complete the VTE prophylaxis order set."

The action taken by the Medical Executive Committee was the latest step taken to improve the use of anticoagulants at Shands at UF. Anticoagulants have long been recognized as common causes of medication errors and adverse drug reactions.¹ Recently, the Joint Commission included appropriate anticoagulant use as part of its National Patient Safety Goals. Shands at UF has been emphasizing appropriate use of anticoagulants as a quality goal for several years. The approval of the *Adult Venous Thromboembolism (VTE) Prophylaxis Order Form* to assess VTE risk and to provide standardized choices for anticoagulation is intended to improve care.

Recent data from the University Hospital Consortium (UHC) on the rate

of post-operative deep venous thromboses (DVTs) and pulmonary emboli (PE) showed that there is room for improvement at Shands at UF. Although surgical patients have some of the highest risks for VTEs (eg, gynecologic surgery, urologic surgery, general surgery, neurosurgery, hip/knee surgery, major trauma, spinal cord injury, critical care patients), many of the other patients seen at Shands at UF are also at high risk (eg, medical patients, stroke patients). The rate of VTEs must be decreased.

Existing data and guidelines support the aggressive use of VTE prophylaxis. Pharmacologic prophylaxis reduces the rate of DVT and PE by 50-65%. The incidence of bleeding from VTE prophylaxis is rare, as is the risk for heparin-induced thrombocytopenia (ie, unfractionated heparin 2.4%, low-molecular weight heparin <0.1%). VTE prophylaxis has been shown to be cost-effective and to improve the quality of patient care.

Standardized risk assessments and order sets have been shown to be the most effective strategy to improve thromboprophylaxis success. The *Adult Venous Thromboembolism (VTE) Prophylaxis Order Form* begins with risk stratification. Patients are categorized as high risk (eg, major orthopedic procedures, spinal cord injury or multiple trauma, and abdominal/pelvic cancer undergoing operative procedures), moderate risk (non-ICU patient or stable medical patient with at least 1 risk factor [note: risk factors are listed on the form]), and low risk (medical patient [fully mobile or brief admission] or surgical patient [procedure less than 30 minutes, mobile, or no additional risk factor]). Once the patient has been

categorized, several prophylaxis options are listed to choose from by checking the appropriate box. Options include pharmacologic and nonpharmacologic prophylaxis regimens for high- and moderate-risk patients. For high-risk patients, *sequential compression devices (SCDs) at all times while in bed* is added to any pharmacologic therapy selected by the prescriber. Early ambulation is ordered for low-risk patients.

Prescribers can choose "no pharmacologic VTE prophylaxis indicated at this time" but they must document a reason. This shows that there was thought put into the decision to forgo VTE prophylaxis; it was not just an oversight.

A CBC will be ordered every other day for high- and moderate-risk patients receiving pharmacologic therapy to monitor platelet counts. This will aid in the detection of heparin-induced thrombocytopenia. If a prescriber wishes this frequency to be changed, it will have to be noted on the order form.

The *Adult Venous Thromboembolism (VTE) Prophylaxis Order Form* was developed by a small group of physicians and pharmacists; however, it was screened by a wide variety of UF faculty before it was approved by the Medical Executive Committee.

The *Adult Venous Thromboembolism (VTE) Prophylaxis Order Form* is available on the patient care forms Web site for voluntary use. Service-specific and pre-printed orders are being revised and should be made available on the forms Web site by the end of March.

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News, from page 3

When the authors compared published articles to protocols, they found that 62% of trials had at least 1 outcome introduced, omitted, or changed. This study shows that published clinical trials may be unreliable due to the failure of investigators to report all results and to publish only those results that are positively biased.

Journals are combating selective publication by requiring investigators to register all clinical trials prior to patient enrollment. The International Committee of Medical Journal Editors (ICMJE) is a group of the world's leading medical journal editors whose goal is to improve standards in manuscripts submitted to medical journals.⁵ In 2004, members of the ICMJE took a stance on selective publication by

requiring all clinical trials to be registered at or prior to the onset of the trial in a publicly accessible registry to be eligible for publication in their journals.⁵ A sponsor could still fund a trial without registering, but this would forfeit the company's chance of publishing favorable results in these influential journals. The preferred registry of the ICMJE is www.clinicaltrials.gov, which is sponsored by the US National Library of Medicine.⁵

In conclusion, it has been shown in studies that investigators often fail to publish unfavorable results. Clinicians and other healthcare-related decision makers should consider selective publication of trial results when making clinical decisions and forming policies. A thorough literature search should be performed prior to making any impor-

tant decision. This should include a search of registered trials to identify other trials with similar content that may not be published in the primary literature. Investigators should strive to publish all clinical trial results as even those that are unfavorable may impact patient care and safety.

By Michael Latran, PharmD

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Standardized sliding scale insulin orders

Often patients admitted to Shands at UF have diabetes as a comorbid condition. Although diabetes is usually not the reason for admission, it complicates the management of many hospitalized patients. It is important to focus on the patient's blood glucose control while they are in the hospital; hyperglycemia in hospitalized patients has been associated with poor patient outcomes. Hypoglycemia is a complication of medical care that everyone wants to avoid.

Although it may be tempting to continue a patient's outpatient diabetes regimen, it is often necessary to modify their outpatient glycemic control regimen. When patients are hospitalized, their diets change, their activity levels change, they may be infected, they may be NPO for procedures, and they may receive medications that make their blood glucose control more difficult (eg, corticosteroids). Caregivers should reassess a patient's glycemic control regimen and determine how best to manage the patient during their hospitalization. In critical care units, this often requires a constant insulin infusion as part of an aggressive glycemic control regimen. On the medical-surgical wards, however, multiple options exist.

Usually patients on general units can be well managed with a "basal" insulin, like insulin glargine (Lantus®) or NPH insulin. This controls blood glucose levels throughout the day. Basal regimens are often supplemented with "nutritional" insulin regimens that give patients a "bolus" of short-acting regular insulin or an ultra-short-acting insulin analog (eg, insulin aspart [NovoLog®]) when they are taking an oral diet. These "basal" and "nutritional" regimens are the mainstays of glycemic control in patients not getting an insulin infusion.

Sliding scale insulin (SSI) has long been used as a method to supplement a patient's glycemic control regimen based on their measured blood glucose results. SSI regimens alone, without a basal or nutritional regimen are not recommended. SSI regimens alone have been shown to not control blood glucose well. Some institutions have stopped using SSI and improved their use of basal-nutritional blood glucose regimens.

One reason for avoiding SSI regimens is that they are often associated with medication errors and adverse drug reactions. The Institute for Healthcare Improvement (IHI) has included high-alert medications as part of their 5 Million Lives Protected from Harm campaign. From December 2006 to

December 2008, IHI's goal is for participating hospitals to avoid harm in 5 million patients. High-alert medications include anticoagulants (see related article on Mandatory VTE Assessment

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The Medical Executive Committee recently approved the mandatory completion of pre-printed standardized *Subcutaneous Insulin Orders* for all adult inpatients prescribed sliding scale insulin.

and Orders on page 4 of this issue of the *Bulletin*), insulins, sedatives, and "narcotics." IHI provides guidelines for improvement in these areas. IHI recommends that if a SSI regimen is used at an institution that ONLY 1 regimen exist. The existence of multiple regimens leads to confusion, medication errors, and potential patient harm.

The Medical Executive Committee recently approved the mandatory completion of pre-printed standardized *Subcutaneous Insulin Orders* for all adult inpatients prescribed sliding scale insulin. SSI orders in existing adult preprinted physician order sets will be removed. The standardized *Subcutaneous Insulin Orders* will be appended to all adult admission and transfer preprinted physician order sets containing an existing SSI order. An order that states that a "provider *MUST complete the Subcutaneous Insulin Order set*" will be inserted into all

adult admission and transfer preprinted physician order sets containing an existing SSI order.

Prior to the implementation of this policy, data were collected on the previous use of SSI order sets. Nearly 130 different SSI order sets were identified in all areas of Shands at UF. The order sets varied widely and 59% were different in some way. Previous research done at Shands at UF found that SSI order sets alone with no basal or nutritional insulin orders was the second most common cause for hyperglycemic episodes in a sample of medical-surgical patients.¹ Use of the new *Subcutaneous Insulin Orders* set allows the use of SSI, but provides the structure for concomitant basal and nutritional insulin. In other published research, basal-bolus plus SSI was shown to be superior to SSI alone, with 66% of patients reaching the target blood glucose value less than 140 mg/dL compared with only 38% in the SSI alone group.² Neither group experienced hypoglycemia.

Ideally, it is best to minimize the use of SSI orders. If SSI is used, a single standardized regimen should be used. The new *Subcutaneous Insulin Orders* should encourage broader use of basal and nutritional insulin regimens. SSI should be used only as a supplement to these superior regimens. Handwritten SSI orders will no longer be accepted after April 1, 2008.

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◆

QUOTABLE QUOTES

“Implementing a standardized subcutaneous insulin order set promoting the use of scheduled insulin therapy is a key intervention in the inpatient management of diabetes. These order sets should encourage basal replacement insulin therapy...and scheduled nutritional/prandial, short/rapid-acting insulin....This simple intervention will result in the subsequent substantial improvement in ward patients’ glycemic control and a significant reduction of hyperglycemic and hypoglycemic event rates...”

Umpierrez GE, Palacio A, Smiley D. Sliding scale insulin use: myth or insanity? *Am J Med* 2007;120:563-7.

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NEWS

Chantix® safety update

Varenicline (Chantix®) is a nicotine receptor partial agonist used as an aid in smoking cessation. Varenicline received priority review by the FDA due to potential benefit to public health and was granted approval in May 2006. Since approval, numerous neuropsychiatric adverse events have been reported via the manufacturer (Pfizer), the media, and FDA's voluntary reporting system MedWatch.

The adverse effects of a drug may not be fully appreciated until the drug has been used in the general population for a period of time. Rare adverse events are often not detected in clinical trials as usually no more than 3000 patients are exposed to a drug prior to it being marketed. This means that adverse events that occur in less than 0.1% of patients are very unlikely to be observed. Additionally, the patient population in clinical trials is much narrower than the population who will actually take the drug (ie, "real-life" patients often have comorbidities and take numerous other medications that may increase their chance of having an adverse event).

On November 20, 2007, FDA issued an "Early Communication About an Ongoing Safety Review" for Chantix®. This communication was in response to postmarketing cases of changes in behavior, agitation, depressed mood, suicidal ideation, and suicidal behavior associated with varenicline; a case of erratic behavior leading to the death of a patient has been reported. At the time of this communication, the role of Chantix® in these cases was not clear because smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms which has also been associated with the exacerbation of underlying psychiatric illness. Information about serious neuropsychiatric symptoms was added to the *POST-MARKETING EXPERIENCE* section of the prescribing information.

As FDA's review of this issue progressed, it appeared increasingly likely that there is an association between varenicline and serious neuropsychiatric symptoms. As a result, FDA requested that Pfizer elevate the

prominence of this safety information to the *WARNINGS* and *PRECAUTIONS* sections of the labeling. FDA is also working with Pfizer to finalize a Medication Guide for patients.

The FDA issued a Public Health Advisory on February 1, 2008, alerting healthcare providers, patients, and caregivers of the changes in the labeling. FDA emphasized the following safety information: Patients should tell their physician about any history of psychiatric illness prior to taking Chantix® and report any changes in mood or behavior during treatment. Chantix® may cause worsening of current psychiatric illness even if currently under control, or may cause an old psychiatric illness to reoccur. These symptoms can even develop following withdrawal of therapy.

By Russell McKelvey, PharmD

REFERENCE

FDA: Center for Drug Evaluation and Research. Varenicline (marketed as Chantix) Information. Created February 1, 2008. Available at: <http://www.fda.gov/CDER/drug/infopage/varenicline/default.htm>.