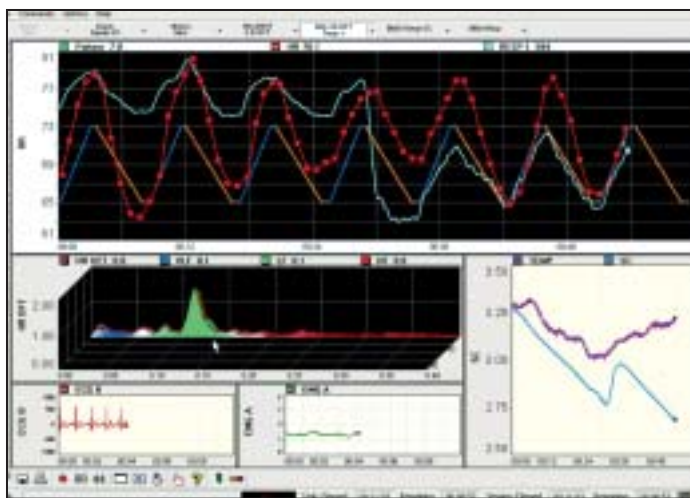


During each 1-hour session, the goal is to address various measures of autonomic nervous system functioning and the patient's response to stress.



COURTESY DR. ERIC SOWDER

## First-Line for Pediatric Pain?

Biofeedback from page 1

dren with recurrent abdominal pain to adapt their pain behavior. The technique addresses a proposed deficit in their autonomic nervous system response to stress. Also, biofeedback might help these patients counter an enhanced subjective response to pain.

To test these theories, pediatric gastroenterologists referred participants with recurrent abdominal pain. Patient ages ranged from 7 to 18 years, and 70% were female. Pain episodes per week were com-

pared before and after completion of biofeedback, and pain intensity was rated on a 1-10 visual analog scale.

Biofeedback significantly reduced the intensity and frequency of pain. Mean pain intensity ratings decreased from 6 to 2.5; mean number of pain episodes per week decreased from seven to three.

Researchers compared peak-to-valley differences in respiratory sinus arrhythmia (RSA) to reflect autonomic nervous system functioning.

The RSA during rest increased significantly, from 13.6 before biofeedback to 22.5 afterward. The RSA during slow-paced breathing likewise increased, from 22 to 32.5.

These findings suggest that biofeedback should be considered a first-line therapy for childhood recurrent abdominal pain,

**Following biofeedback, mean pain intensity ratings decreased from 6 to 2.5; the mean number of pain episodes per week decreased from seven to three.**

the researchers wrote. "We want to do more research and have a control group, and maybe compare this to hypnosis," Dr. Sowder said.

A second study demonstrated that "primary care and [emergency department] visits come down" with biofeedback, Dr. Sowder said. He, Dr. Shapiro, and a colleague demonstrated a significant reduction in health care utilization following biofeedback training of children with recurrent abdominal pain.

The researchers identified 39 children (mean age 13 years) who were diagnosed with recurrent abdominal pain and completed a mean of five biofeedback sessions. They compared health care utilization 2 years prior to biofeedback and 1 year afterward in a Kaiser Permanente database.

Biofeedback significantly reduced mean primary care visits from 10.3 to 3.8 per year; emergency department visits from 0.69 to 0.05; prescriptions from 8.8 to 4.5; and diagnostic tests from 0.77 to 0.08. The authors wrote, "Long-term studies need to be performed to see if this positive outcome effect persists into adulthood."

■

## Infliximab Approved For Ulcerative Colitis

Infliximab (Remicade), which blocks tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), is approved for maintaining clinical remission and mucosal healing in patients with moderately to severely active ulcerative colitis and who have had an inadequate response to conventional therapy. The approval is based primarily on a study that found patients on infliximab were twice as likely to be in remission at week 54, than those on placebo, according to Centocor (www.centocor.com).

Brief Summary of Prescribing Information April 2006

Rx Only

### LANTUS®

(insulin glargine [rDNA origin] injection)

LANTUS® must NOT be diluted or mixed with any other insulin or solution.

#### INDICATIONS AND USAGE

LANTUS is indicated for once-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

#### CONTRAINDICATIONS

LANTUS is contraindicated in patients hypersensitive to insulin glargine or the excipients.

#### WARNINGS

**Hypoglycemia is the most common adverse effect of insulin, including LANTUS. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.**

**Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, timing of dosing, manufacturer, type (e.g., regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetes treatment may need to be adjusted.**

#### PRECAUTIONS

##### General:

LANTUS is not intended for intravenous administration. The prolonged duration of activity of insulin glargine is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia.

**LANTUS must NOT be diluted or mixed with any other insulin or solution.** If LANTUS is diluted or mixed, the solution may become cloudy, and the pharmacokinetic/pharmacodynamic profile (e.g., onset of action, time to peak effect) of LANTUS and/or the mixed insulin may be altered in an unpredictable manner. When LANTUS and regular human insulin were mixed immediately before injection in dogs, a delayed onset of action and time to maximum effect for regular human insulin was observed. The total bioavailability of the mixture was also slightly decreased compared to separate injections of LANTUS and regular human insulin. The relevance of these observations in dogs to humans is not known.

As with all insulin preparations, the time course of LANTUS action may vary in different individuals or at different times in the same individual and the rate of absorption is dependent on blood supply, temperature, and physical activity. Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

##### Hypoglycemia:

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of LANTUS. Hypoglycemia is the most common adverse effect of insulins. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetes nerve disease, use of medications such as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of dosing is changed. Patients being switched from twice daily NPH insulin to once-daily LANTUS should have their initial LANTUS dose reduced by 20% from the previous total daily NPH dose to reduce the risk of hypoglycemia (see DOSAGE AND ADMINISTRATION, Changeover to LANTUS).

The prolonged effect of subcutaneous LANTUS may delay recovery from hypoglycemia. In a clinical study, symptoms of hypoglycemia or counterregulatory hormone responses were similar after intravenous insulin glargine and regular human insulin both in healthy subjects and patients with type 1 diabetes.

##### Renal Impairment:

Although studies have not been performed in patients with diabetes and renal impairment, LANTUS requirements may be diminished because of reduced insulin metabolism, similar to observations found with other insulins (see CLINICAL PHARMACOLOGY, Special Populations).

##### Hepatic Impairment:

Although studies have not been performed in patients with diabetes and hepatic impairment, LANTUS requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins (see CLINICAL PHARMACOLOGY, Special Populations).

##### Injection Site and Allergic Reactions:

As with all insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy include redness, pain, itching, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Reports of injection site pain were more frequent with LANTUS than NPH human insulin (2.7% insulin glargine versus 0.7% NPH). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy. Immediate-type allergic reactions are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalized skin reactions, angioedema, bronchospasm, hypotension, or shock and may be life threatening.

##### Intercurrent Conditions:

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or stress.

##### Information for Patients:

LANTUS must only be used if the solution is clear and colorless with no particles visible (see DOSAGE AND ADMINISTRATION, Preparation and Handling).

**Patients must be advised that LANTUS must NOT be diluted or mixed with any other insulin or solution (see PRECAUTIONS, General).**

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and hypoglycemia and hyperglycemia management. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the LANTUS "Patient Information" circular for additional information.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycemia or hyperglycemia.

Patients with diabetes should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy.

##### Drug Interactions:

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetes products, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.

The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g., olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

##### Carcinogenesis, Mutagenesis, Impairment of Fertility:

In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which is for the rat approximately 10 times and for the mouse approximately 5 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m<sup>2</sup>. The findings in female mice were not conclusive due to excessive mortality in all dose groups during the study. Histiocytomas were found at injection sites in male rats (statistically significant) and male mice (not statistically significant) in acid vehicle containing groups. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle. The relevance of these findings to humans is unknown.

Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames- and HGPRT-tests) and in tests for detection of chromosomal aberrations (cytogenetics in vitro in V79 cells and in vivo in Chinese hamsters).

In a combined fertility and prenatal and postnatal study in male and female rats at subcutaneous doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m<sup>2</sup>, maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH human insulin.

##### Pregnancy:

**Teratogenic Effects:** Pregnancy Category C. Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. The drug was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m<sup>2</sup>. In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m<sup>2</sup>, were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

There are no well-controlled clinical studies of the use of insulin glargine in pregnant women. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

##### Nursing Mothers:

It is unknown whether insulin glargine is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when LANTUS is administered to a nursing woman. Lactating women may require adjustments in insulin dose and diet.

##### Pediatric Use:

Safety and effectiveness of LANTUS have been established in the age group 6 to 15 years with type 1 diabetes.

##### Geriatric Use:

In controlled clinical studies comparing insulin glargine to NPH human insulin, 593 of 3890 patients with type 1 and type 2 diabetes were 65 years and older. The only difference in safety or effectiveness in this subpopulation compared to the entire study population was an expected higher incidence of cardiovascular events in both insulin glargine and NPH human insulin-treated patients.

In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly (see PRECAUTIONS, Hypoglycemia).

##### ADVERSE REACTIONS

The adverse events commonly associated with LANTUS include the following:

**Body as a whole:** allergic reactions (see PRECAUTIONS).

**Skin and appendages:** injection site reaction, lipodystrophy, pruritus, rash (see PRECAUTIONS).

**Other:** hypoglycemia (see WARNINGS and PRECAUTIONS).

In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy. Other treatment-emergent injection site reactions occurred at similar incidences with both insulin glargine and NPH human insulin.

Retinopathy was evaluated in the clinical studies by means of retinal adverse events reported and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH treatment groups were similar for patients with type 1 and type 2 diabetes. Progression of retinopathy was investigated by fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Study (ETDRS). In one clinical study involving patients with type 2 diabetes, a difference in the number of subjects with  $\geq 3$ -step progression in ETDRS scale over a 6-month period was noted by fundus photography (7.5% in LANTUS group versus 2.7% in NPH treated group). The overall relevance of this isolated finding cannot be determined due to the small number of patients involved, the short follow-up period, and the fact that this finding was not observed in other clinical studies.

##### OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes long-term and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

##### DOSAGE AND ADMINISTRATION

LANTUS is a recombinant human insulin analog. Its potency is approximately the same as human insulin. It exhibits a relatively constant glucose-lowering profile over 24 hours that permits once-daily dosing.

LANTUS may be administered at any time during the day. LANTUS should be administered subcutaneously once a day at the same time every day. For patients adjusting timing of dosing with LANTUS, see WARNINGS and PRECAUTIONS, Hypoglycemia. LANTUS is not intended for intravenous administration (see PRECAUTIONS). Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. The desired blood glucose levels as well as the doses and timing of antidiabetes medications must be determined individually. Blood glucose monitoring is recommended for all patients with diabetes. The prolonged duration of activity of LANTUS is dependent on injection into subcutaneous space. As with all insulins, injection sites within an injection area (abdomen, thigh, or deltoid) must be rotated from one injection to the next.

In clinical studies, there was no relevant difference in insulin glargine absorption after abdominal, deltoid, or thigh subcutaneous administration. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables.

LANTUS is not the insulin of choice for the treatment of diabetes ketoacidosis. Intravenous short-acting insulin is the preferred treatment.

##### Pediatric Use:

LANTUS can be safely administered to pediatric patients  $\geq 6$  years of age. Administration to pediatric patients <6 years has not been studied. Based on the results of a study in pediatric patients, the dose recommendation for changeover to LANTUS is the same as described for adults in DOSAGE AND ADMINISTRATION, Changeover to LANTUS.

##### Initiation of LANTUS Therapy:

In a clinical study with insulin-naïve patients with type 2 diabetes already treated with oral antidiabetes drugs, LANTUS was started at an average dose of 10 IU once daily, and subsequently adjusted according to the patient's need to a total daily dose ranging from 2 to 100 IU.

##### Changeover to LANTUS:

If changing from a treatment regimen with an intermediate- or long-acting insulin to a regimen with LANTUS, the amount and timing of short-acting insulin or fast-acting insulin analog or the dose of any oral antidiabetes drug may need to be adjusted. In clinical studies, when patients were transferred from once-daily NPH human insulin or ultralente human insulin to once-daily LANTUS, the initial dose was usually not changed. However, when patients were transferred from twice-daily NPH human insulin to LANTUS once daily, to reduce the risk of hypoglycemia, the initial dose (IU) was usually reduced by approximately 20% (compared to total daily IU of NPH human insulin) and then adjusted based on patient response (see PRECAUTIONS, Hypoglycemia).

A program of dose metabolic monitoring under medical supervision is recommended during transfer and in the initial weeks thereafter. The amount and timing of short-acting insulin or fast-acting insulin analog may need to be adjusted. This is particularly true for patients with acquired antibodies to human insulin needing high-insulin doses and occurs with all insulin analogs. Dose adjustment of LANTUS and other insulins or oral antidiabetes drugs may be required; for example, if the patient's timing of dosing, weight or lifestyle changes, or other circumstances arise that increase susceptibility to hypoglycemia or hyperglycemia (see PRECAUTIONS, Hypoglycemia).

The dose may also have to be adjusted during intercurrent illness (see PRECAUTIONS, Intercurrent Conditions).

Brief Summary of Prescribing Information April 2006

sanofi-aventis U.S. LLC  
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