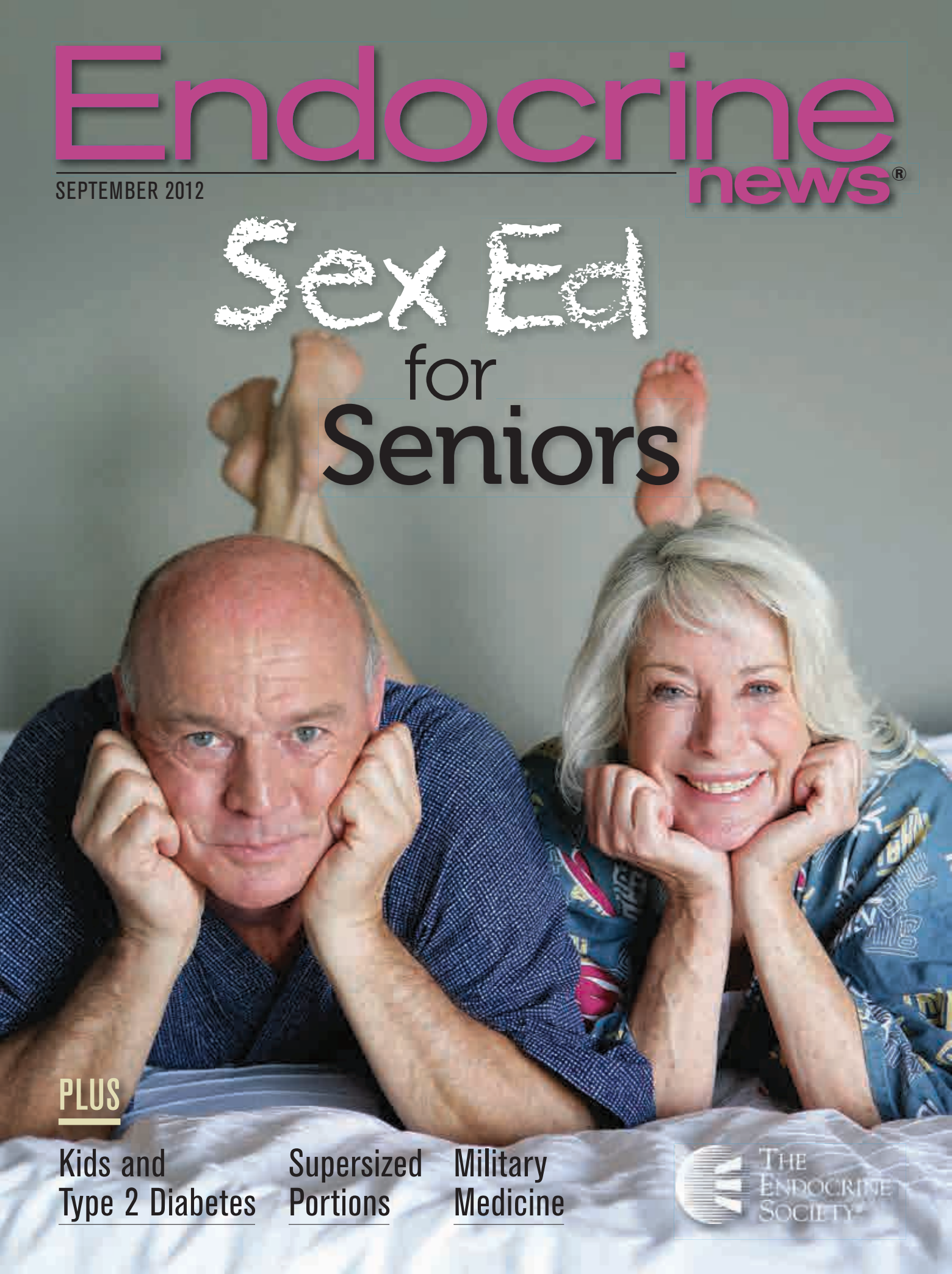
Endocrine news®
SEPTEMBER 2012

Sex Ed for Seniors



PLUS

Kids and Type 2 Diabetes

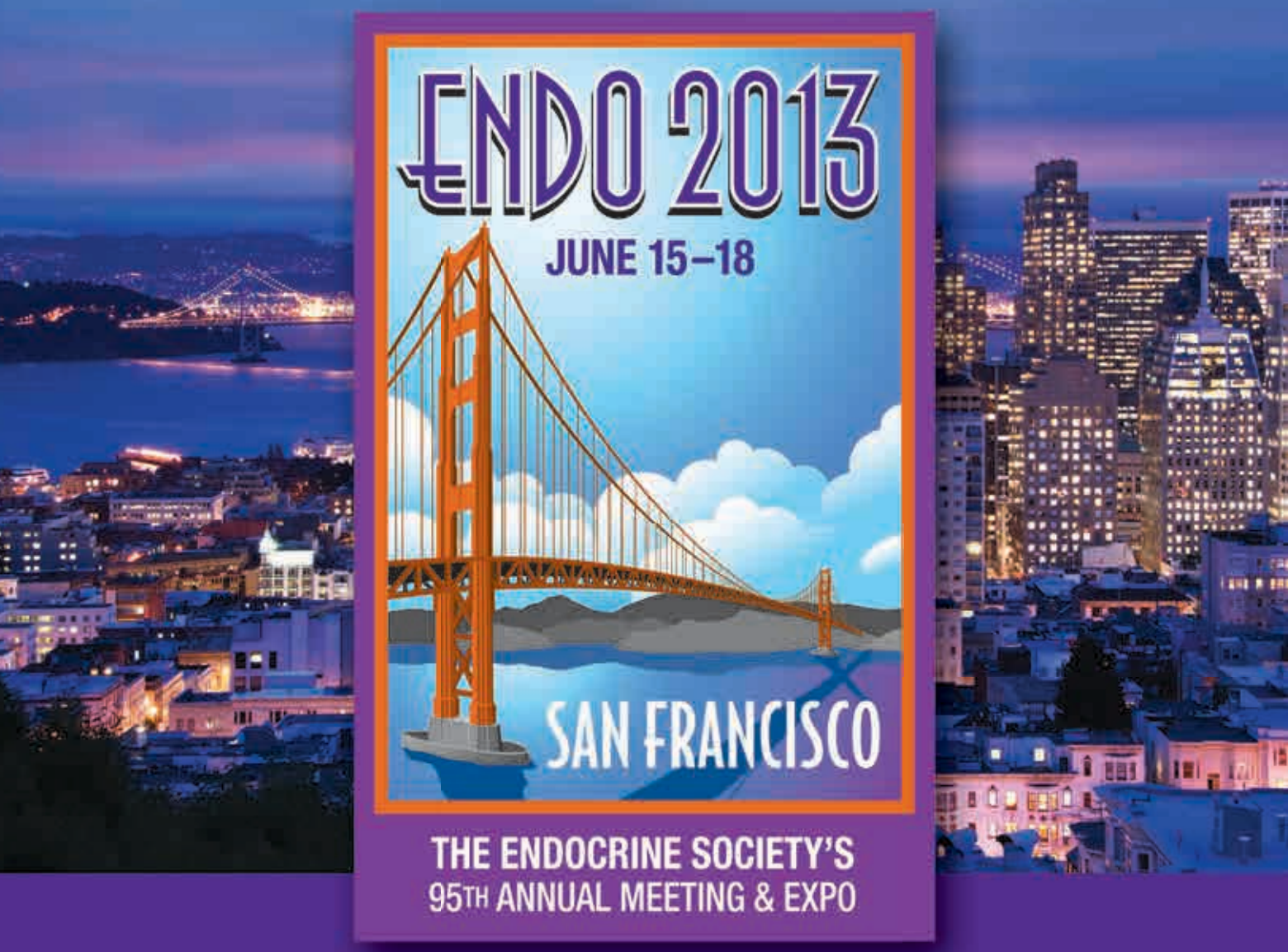
Supersized Portions

Military Medicine

The Endocrine Society

Save the Date for ENDO 2013

Join us for ENDO 2013, The Endocrine Society's 95th Annual Meeting & Expo, in the beautiful city by the bay.



Registration opens in the fall of 2012.

For more information, visit **www.endo-society.org/endo2013**

The Endocrine Society®

Choose Humalog and the MiniMed Paradigm® REAL-Time Revel™ Insulin Pump

For adult patients with type 1 diabetes ready to have a conversation about using an insulin pump

- Humalog® (100 units /mL) can be used in a Paradigm Revel Insulin Pump[1]

Indication for Humalog

- Humalog is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

Select Safety Information for Humalog

- Humalog is contraindicated during episodes of hypoglycemia and in patients who are hypersensitive to Humalog or any of its excipients.
- Closely monitor blood glucose in all patients treated with insulin. Change insulin regimens cautiously.
- Hypoglycemia is the most common adverse effect of Humalog therapy. The risk of hypoglycemia increases with tighter glycemic control. Severe hypoglycemia may be life threatening and can cause seizures or death.
- Humalog should be given within 15 minutes before or immediately after a meal.

Select Safety Information for Humalog, continued

- Humalog should not be diluted or mixed when used in an external insulin pump. Change Humalog in the reservoir at least every 7 days. Change the infusion set and insertion site at least every 3 days.
- Catheter occlusions and infusion-site reactions have been reported in patients receiving Humalog as a continuous subcutaneous infusion.

Reference
1. Paradigm® REAL-Time Revel™ User Guide. Starting on Insulin. ©2009 Medtronic MiniMed, Inc. 47.

Please see Important Safety Information on next page and Brief Summary of Full Prescribing Information for Humalog on following pages.

For more information about Humalog, please call The Lilly Answers Center at 1-800-LillyRx (1-800-545-5979), or visit www.Humalog.com. For more information about Paradigm® REAL-Time Revel™, please call Medtronic at 1-888-350-3199, or visit www.medtronicdiabetes.com.

Humalog®

insulin lispro injection, USP (rDNA origin)

Paradigm REAL-Time Revel™ MiniMed

Medtronic

Lilly

Important Safety Information for Humalog

Contraindications

- Humalog® is contraindicated during episodes of hypoglycemia and in patients who are hypersensitive to Humalog or any of its excipients.

Warnings and Precautions

- **Dose Adjustment and Monitoring:** Closely monitor blood glucose in all patients treated with insulin. Change insulin regimens cautiously. Concomitant oral antidiabetic treatment may need to be adjusted.

  The time course of action for Humalog may vary in different individuals or at different times in the same individual and is dependent on many conditions, including delivery site, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require insulin dose adjustment.

- **Hypoglycemia:** Hypoglycemia is the most common adverse effect of Humalog. The risk of hypoglycemia increases with tighter glycemic control. Educate patients to recognize and manage hypoglycemia. Hypoglycemia can happen suddenly and symptoms may vary for each person and may change over time. Early warning symptoms of hypoglycemia may be different or less pronounced under conditions such as long-standing diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. These situations may result in severe hypoglycemia and possibly loss of consciousness prior to the patient's awareness of hypoglycemia. Severe hypoglycemia may be life threatening and can cause seizures or death.

  Use caution in patients with hypoglycemia unawareness and who may be predisposed to hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value.

  Timing of hypoglycemia usually reflects the time-action profile of administered insulins. Other factors such as changes in food intake, injection site, exercise, and concomitant medications may alter the risk of hypoglycemia.

- **Allergic Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with Humalog.

- **Hypokalemia:** Humalog can cause hypokalemia, which, if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (eg, patients using potassium-lowering medications or medications sensitive to serum potassium concentrations).

Important Safety Information for Humalog, continued

Warnings and Precautions, continued

- **Renal or Hepatic Impairment:** Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

- **Mixing of Insulins:** Humalog for subcutaneous injection should not be mixed with insulins other than NPH insulin. If Humalog is mixed with NPH insulin, Humalog should be drawn into the syringe first. Injection should occur immediately after mixing.

- **Subcutaneous Insulin Infusion Pump:** Humalog should not be diluted or mixed when used in an external insulin pump. Change Humalog in the reservoir at least every 7 days. Change the infusion set and insertion site at least every 3 days.

  Malfunction of the insulin pump or infusion set or insulin degradation can rapidly lead to hyperglycemia and ketosis. Prompt correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with Humalog may be required. Train patients using an insulin pump to administer insulin by injection and to have alternate insulin therapy available in case of pump failure.

- **Drug Interactions:** Some medications may alter glucose metabolism, insulin requirements, and the risk for hypoglycemia or hyperglycemia. Signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs. Particularly close monitoring may be required.

Adverse Reactions

- Adverse reactions associated with Humalog include hypoglycemia, hypokalemia, allergic reactions, injection-site reactions, lipodystrophy, pruritus, rash, weight gain, and peripheral edema.

Use in Specific Populations

- **Pediatrics:** Humalog has not been studied in children with type 1 diabetes less than 3 years of age or in children with type 2 diabetes.

Dosage and Administration

- Humalog should be given within 15 minutes before or immediately after a meal.

Please see following pages for Brief Summary of Full Prescribing Information for Humalog.

HI HCP ISI 08JUN2011

Humalog®

insulin lispro injection, USP (rDNA origin)

Paradigm REAL-Time Revel™ MiniMed

MiniMed Paradigm® REAL-Time Revel™ Insulin Pump Indications for Use

Pump

- The Paradigm Revel insulin pump is indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin.

MiniMed Paradigm REAL-Time Revel Insulin Pump Important Safety Information

Contraindications

- Pump therapy is not recommended for people who are unwilling or unable to perform a minimum of four blood glucose tests per day and to maintain contact with their healthcare professional. Successful insulin pump therapy requires sufficient vision or hearing to allow recognition of the pump signals and alarms.

Warnings

- The pump is not suitable for use in the presence of a flammable anesthetic mixture with air, oxygen, or nitrous oxide.
- Standard Luer sets are not compatible with the Medtronic MiniMed Paradigm pump. Medtronic Paradigm reservoirs and Paradigm-compatible infusion sets are specifically designed for use with the pump.
- Do not modify your Paradigm reservoir or Paradigm-compatible infusion set.
- Do not put any other drugs/medications inside your reservoir to use with this pump. Only insulin that has been prescribed by your physician can be used in this pump.
- Do not use pump cases that have a magnetic clasp.
- Do not expose your insulin pump to MRI equipment or other devices that generate very strong magnetic fields. The magnetic fields in the immediate vicinity of these devices can damage the part of the pump's motor that regulates insulin delivery, possibly resulting in over-delivery and severe hypoglycemia. Your pump must be removed and kept outside the room during magnetic resonance imaging (MRI) procedures.
- If your pump is inadvertently exposed to a strong magnetic field, discontinue use and contact our 24-Hour HelpLine for further assistance.

Please visit http://www.medtronicdiabetes.com/about/safety.html for complete safety information.

The MiniMed Paradigm Revel Insulin Pump is Continuous Glucose Monitoring (CGM) ready. Optional glucose sensor and MiniLink® REAL-Time transmitter are available separately from Medtronic.

For information on the MiniMed Paradigm Revel Insulin Pump integrated with CGM, please contact your Medtronic representative.

Please see Important Safety Information for Humalog on opposite page.

Medtronic

Lilly

Humalog®

(insulin lispro injection, USP [rDNA origin])

Brief Summary: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE

HUMALOG is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

CONTRAINDICATIONS

HUMALOG is contraindicated:

- during episodes of hypoglycemia
- in patients who are hypersensitive to HUMALOG or to any of its excipients.

WARNINGS AND PRECAUTIONS

Dose Adjustment and Monitoring—Glucose monitoring is essential for patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose. Concomitant oral antidiabetic treatment may need to be adjusted.

As with all insulin preparations, the time course of action for HUMALOG may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages.

Hypoglycemia—Hypoglycemia is the most common adverse effect associated with insulins, including HUMALOG. The risk of hypoglycemia increases with tighter glycemic control. Patients must be educated to recognize and manage hypoglycemia. Hypoglycemia can happen suddenly and symptoms may be different for each person and may change from time to time. Severe hypoglycemia can cause seizures and may be life-threatening or cause death.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia *[see Drug Interactions]*.

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers *[see Drug Interactions]*, or intensified diabetes control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.

Hypersensitivity and Allergic Reactions—Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including HUMALOG *[see Adverse Reactions]*.

Hypokalemia—All insulin products, including HUMALOG, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

Renal or Hepatic Impairment—Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

Mixing of Insulins—HUMALOG for subcutaneous injection should not be mixed with insulin preparations other than NPH insulin. If HUMALOG is mixed with NPH insulin, HUMALOG should be drawn into the syringe first. Injection should occur immediately after mixing.

Do not mix HUMALOG with other insulins for use in an external subcutaneous infusion pump.

Subcutaneous Insulin Infusion Pumps—When used in an external insulin pump for subcutaneous infusion, HUMALOG should not be diluted or mixed with any other insulin. Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days. HUMALOG should not be exposed to temperatures greater than 98.6°F (37°C).

Malfunction of the insulin pump or infusion set or insulin degradation can rapidly lead to hyperglycemia and ketosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with HUMALOG may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure *[see Dosage and Administration and How Supplied/ Storage and Handling]*.

Drug Interactions—Some medications may alter insulin requirements and the risk for hypoglycemia or hyperglycemia *[see Drug Interactions]*.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia *[see Warnings and Precautions]*.
- Hypokalemia *[see Warnings and Precautions]*.

Clinical Trial Experience—Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared with those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of Treatment-Emergent Adverse Events during HUMALOG clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (adverse events with frequency ≥5%)

Events, n (%)	Lispro (n=81)	Regular human insulin (n=86)	Total (n=167)
Flu syndrome	28 (34.6)	28 (32.6)	56 (33.5)
Pharyngitis	27 (33.3)	29 (33.7)	56 (33.5)
Rhinitis	20 (24.7)	25 (29.1)	45 (26.9)
Headache	24 (29.6)	19 (22.1)	43 (25.7)
Pain	16 (19.8)	14 (16.3)	30 (18.0)
Cough increased	14 (17.3)	15 (17.4)	29 (17.4)
Infection	11 (13.6)	18 (20.9)	29 (17.4)
Nausea	5 (6.2)	13 (15.1)	18 (10.8)
Accidental injury	7 (8.6)	10 (11.6)	17 (10.2)
Surgical procedure	5 (6.2)	12 (14.0)	17 (10.2)
Fever	5 (6.2)	10 (11.6)	15 (9.0)
Abdominal pain	6 (7.4)	7 (8.1)	13 (7.8)
Asthenia	6 (7.4)	7 (8.1)	13 (7.8)
Bronchitis	6 (7.4)	6 (7.0)	12 (7.2)
Diarrhea	7 (8.6)	5 (5.8)	12 (7.2)
Dysmenorrhea	5 (6.2)	6 (7.0)	11 (6.6)
Myalgia	6 (7.4)	5 (5.8)	11 (6.6)
Urinary tract infection	5 (6.2)	4 (4.7)	9 (5.4)

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (adverse events with frequency ≥5%)

Events, n (%)	Lispro (n=714)	Regular human insulin (n=709)	Total (n=1423)
Headache	63 (11.6)	66 (9.3)	149 (10.5)
Pain	77 (10.8)	71 (10.0)	148 (10.4)
Infection	72 (10.1)	54 (7.6)	126 (8.9)
Pharyngitis	47 (6.6)	58 (8.2)	105 (7.4)
Rhinitis	58 (8.1)	47 (6.6)	105 (7.4)
Flu syndrome	44 (6.2)	58 (8.2)	102 (7.2)
Surgical procedure	53 (7.4)	48 (6.8)	101 (7.1)

Insulin initiation and intensification of glucose control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Lipodystrophy

Long-term use of insulin, including HUMALOG, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy [see Dosage and Administration].

Weight gain

Weight gain can occur with insulin therapy, including HUMALOG, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

Peripheral Edema

Insulin, including HUMALOG, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Adverse Reactions with Continuous Subcutaneous Insulin Infusion (CSII)

In a 12-week, randomized, crossover study in adult patients with type 1 diabetes (n=39), the rates of catheter occlusions and infusion site reactions were similar for HUMALOG and regular human insulin treated patients (see Table 3).

Table 3: Catheter Occlusions and Infusion Site Reactions

	HUMALOG (n=38)	Regular human insulin (n=39)
Catheter occlusions/month	0.09	0.10
Infusion site reactions	2.6% (1/38)	2.6% (1/39)

In a randomized, 16-week, open-label, parallel design study of children and adolescents with type 1 diabetes, adverse event reports related to infusion-site reactions were similar for insulin lispro and insulin aspart (21% of 100 patients versus 17% of 198 patients, respectively). In both groups, the most frequently reported infusion site adverse events were infusion site erythema and infusion site reaction.

Allergic Reactions

Local Allergy — As with any insulin therapy, patients taking HUMALOG may experience redness, swelling, or itching at the site of the injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of HUMALOG. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy — Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin, including HUMALOG. Generalized allergy to insulin may cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis.

In controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving regular human insulin (n=2969) and 30 patients receiving HUMALOG (n=2944).

Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in HUMALOG *[see Contraindications]*.

Antibody Production

In large clinical trials with patients with type 1 (n=509) and type 2 (n=262) diabetes mellitus, anti-insulin antibody (insulin lispro-specific antibodies, insulin-specific antibodies, cross-reactive antibodies) formation was evaluated in patients receiving both regular human insulin and HUMALOG (including patients previously treated with human insulin and naive patients). As expected, the largest increase in the antibody levels occurred in patients new to insulin therapy. The antibody levels peaked by 12 months and declined over the remaining years of the study. These antibodies do not appear to cause deterioration in glycemic control or necessitate an increase in insulin dose. There was no statistically significant relationship between the change in the total daily insulin dose and the change in percent antibody binding for any of the antibody types.

Postmarketing Experience—The following additional adverse reactions have been identified during post-approval use of HUMALOG. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Medication errors in which other insulins have been accidentally substituted for HUMALOG have been identified during postapproval use.

DRUG INTERACTIONS

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

Following are some of the examples:

- **Drugs That May Increase the Blood-Glucose-Lowering Effect of HUMALOG and Susceptibility to Hypoglycemia:** Oral antidiabetic agents, salicylates, sulfonamide antibiotics, monoamine oxidase inhibitors, fluoxetine, pramlintide, disopyramide, fibrates, propoxyphene, pentoxifylline, ACE inhibitors, angiotensin II receptor blocking agents, and somatostatin analogs (e.g., octreotide).
- **Drugs That May Reduce the Blood-Glucose-Lowering Effect of HUMALOG:** corticosteroids, isoniazid, niacin, estrogens, oral contraceptives, phenothiazines, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), somatropin, atypical antipsychotics, glucagon, protease inhibitors, and thyroid hormones.
- **Drugs That May Increase or Reduce the Blood-Glucose-Lowering Effect of HUMALOG:** beta-blockers, clonidine, lithium salts, and alcohol. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
- **Drugs That May Reduce the Signs of Hypoglycemia:** beta-blockers, clonidine, guanethidine, and reserpine.

USE IN SPECIFIC POPULATIONS

Pregnancy—Pregnancy Category B. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes 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 these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking HUMALOG.

Although there are limited clinical studies of the use of HUMALOG in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome.

In a combined fertility and embryo-fetal development study, female rats were given subcutaneous insulin lispro injections of 5 and 20 units/kg/day (0.8 and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) from 2 weeks prior to cohabitation through Gestation Day 19. There were no adverse effects on female fertility, implantation, or fetal viability and morphology. However, fetal growth retardation was produced at the 20 units/kg/day-dose as indicated by decreased fetal weight and an increased incidence of fetal runts/litter.

In an embryo-fetal development study in pregnant rabbits, insulin lispro doses of 0.1, 0.25, and 0.75 unit/kg/day (0.03, 0.08, and 0.24 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) were injected subcutaneously on Gestation days 7 through 19. There were no adverse effects on fetal viability, weight, and morphology at any dose.

Nursing Mothers—It is unknown whether insulin lispro is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HUMALOG is administered to a nursing woman. Use of HUMALOG is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

Pediatric Use—HUMALOG is approved for use in children for subcutaneous daily injections and for subcutaneous continuous infusion by external insulin pump. HUMALOG has not been studied in pediatric patients younger than 3 years of age. HUMALOG has not been studied in pediatric patients with type 2 diabetes.

As in adults, the dosage of HUMALOG must be individualized in pediatric patients based on metabolic needs and results of frequent monitoring of blood glucose.

Geriatric Use—Of the total number of subjects (n=2834) in eight clinical studies of HUMALOG, twelve percent (n=338) were 65 years of age or over. The majority of these had type 2 diabetes. HbA1c values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of HUMALOG action have not been performed.

OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. 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. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

DOSAGE AND ADMINISTRATION

Dosage Considerations—When given subcutaneously, HUMALOG has a more rapid onset of action and a shorter duration of action than regular human insulin.

The dosage of HUMALOG must be individualized. Blood glucose monitoring is essential in all patients receiving insulin therapy.

The total daily insulin requirement may vary and is usually between 0.5 to 1 unit/kg/day. Insulin requirements may be altered during stress, major illness, or with changes in exercise, meal patterns, or coadministered drugs.

Subcutaneous Administration—HUMALOG should be given within 15 minutes before a meal or immediately after a meal.

HUMALOG given by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin.

HUMALOG administered by subcutaneous injection should be given in the abdominal wall, thigh, upper arm, or buttocks. Injection sites should be rotated within the same region (abdomen, thigh, upper arm, or buttocks) from one injection to the next to reduce the risk of lipodystrophy *[see Adverse Reactions]*.

Continuous Subcutaneous Infusion (Insulin Pump)—HUMALOG may be administered by continuous subcutaneous infusion by an external insulin pump. Do not use diluted or mixed insulins in external insulin pumps. Infusion sites should be rotated within the same region to reduce the risk of lipodystrophy *[see Adverse Reactions]*. Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days.

The initial programming of the external insulin infusion pump should be based on the total daily insulin dose of the previous regimen. Although there is significant variability among patients, approximately 50% of the total dose is usually given as meal-related boluses of HUMALOG and the remainder is given as a basal infusion. HUMALOG is recommended for use in pump systems suitable for insulin infusion such as MiniMed, Disetronic, and other equivalent pumps.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

HUMALOG 100 units per mL (U-100) is available as:

10 mL vials	NDC 0002-7510-01 (VL-7510)
3 mL vials	NDC 0002-7510-17 (VL-7533)
5 x 3 mL cartridges[1]	NDC 0002-7516-59 (VL-7516)
5 x 3 mL prefilled pen	NDC 0002-8725-59 (HP-8725)
5 x 3 mL Humalog KwikPen (prefilled)	NDC 0002-8799-59 (HP-8799)

Storage

Do not use after the expiration date.

Unopened HUMALOG should be stored in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use HUMALOG if it has been frozen. In-use HUMALOG vials, cartridges, pens, and HUMALOG KwikPen® should be stored at room temperature,

below 86°F (30°C) and must be used within 28 days or be discarded, even if they still contain HUMALOG. Protect from direct heat and light. See table below:

	Not In-Use (Unopened) Room Temperature (Below 86°F [30°C])	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature, (Below 86°F [30°C])
10 mL vial	28 days	Until expiration date	28 days, refrigerated/ room temperature.
3 mL vial	28 days	Until expiration date	28 days, refrigerated/ room temperature.
3 mL cartridge	28 days	Until expiration date	28 days, **Do not refrigerate.**
3 mL prefilled pen	28 days	Until expiration date	28 days, **Do not refrigerate.**
3 mL Humalog KwikPen (prefilled)	28 days	Until expiration date	28 days, **Do not refrigerate.**

Use in an External Insulin Pump — Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days or after exposure to temperatures that exceed 98.6°F (37°C). A HUMALOG 3 mL cartridge used in the D-Tron® pumps should be discarded after 7 days, even if it still contains HUMALOG. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion set insertion site should be selected at least every 3 days.

Diluted HUMALOG for Subcutaneous Injection — Diluted HUMALOG may remain in patient use for 28 days when stored at 41°F (5°C) and for 14 days when stored at 86°F (30°C). Do not dilute HUMALOG contained in a cartridge or HUMALOG used in an external insulin pump.

Preparation and Handling

Diluted HUMALOG for Subcutaneous Injection — HUMALOG may be diluted with Sterile Diluent for HUMALOG for subcutaneous injection. Diluting one part HUMALOG to nine parts diluent will yield a concentration one-tenth that of HUMALOG (equivalent to U-10). Diluting one part HUMALOG to one part diluent will yield a concentration one-half that of HUMALOG (equivalent to U-50).

PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling and Patient Counseling Information section of the Full Prescribing Information.

---

† 3 mL cartridge is for use in Eli Lilly and Company's HumaPen® Memoir™ and HumaPen® Luxura™ HD insulin delivery devices, Owen Mumford, Ltd.'s Autopen® 3-mL insulin delivery device and Disetronic D-TRON® and D-TRON® Plus pumps.

Lilly

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

Additional information can be found at www.humalog.com.

HI HCP BS 31AUG2011 PV5533

contents

NEWS & INSIGHTS FOR THE ENDOCRINE COMMUNITY

THE ENDOCRINE SOCIETY®
WWW.ENDO-SOCIETY.ORG

Features

Departments

Need Tips on How to Lose Weight?
Read the Hormone Health Network's fact sheet on Proven Weight Loss Methods (pages 37,38)

Scan this QR code with your smartphone/mobile device for ***Endocrine News*** *Online.*

Support For Young Professionals

William F. Young, Jr. M.D., M.Sc.

Dear Colleagues:

The Endocrine Society continues its strong commitment to preparing future endocrine leaders by creating career development programming that has substantial impact on young professionals pursuing careers in endocrinology. The Society has a trainee membership of nearly 3,000 and provides a strong portfolio of programs aimed at supporting trainees' work at the cutting edge of research and practice. The portfolio of career development programming has been enhanced by including curricula to address critical issues for junior faculty and mid-career professionals.

Programming for Early- and Mid-Career Professionals at ENDO 2012

ENDO 2012, held in Houston, was highlighted by dynamic programming for young professionals in our field. The *6th Annual Endocrine Trainee Day Workshop*, co-sponsored by Women in Endocrinology, hosted more than 230 trainees who attended interactive sessions in clinical and basic science tracks. These sessions were hosted by preeminent leaders in the field and began a series of activities specifically designed to meet the needs of trainees.

The very popular Career Development Workshops featured new sessions this year, including the half-day workshop, "How to Secure Promotion and Tenure for Junior Faculty and Mid-Career Professionals," and the "Writing a Successful R01 and Other Independent Research Grant Applications: Tips for the Mid-Career Professional" evening session.

Trainee posters were identified for special consideration in the *Presidential Poster Competition*. Many trainees met with old friends and made new connections at the Trainee Reception and used the *Trainee Career Center* to continue networking with leaders and one another. A new networking event added this year included the *Mentor Connection Breakfast*, where volunteer mentors who participate in the Society's *Mentor Exchange* were available to meet one-on-one with early career professionals seeking advice and mentorship.

2012 Early Investigators Workshop

The Early Investigators Workshop will be held on September 28–29, 2012, in San Francisco. This event will provide an intensive introduction on what it takes to create a successful career in endocrine research for as many as 50 young basic research and clinical trainees. The workshop will offer joint sessions that cover general and translational topics and breakout sessions on topics of specific interest to each track. Session topics will include practical guidance for pursuing NIH funding, how to establish an effective mentor relationship, balancing career and family life, and more. In addition, fellows will receive guidance from Society experts who are on hand to provide constructive feedback on the fellows' research projects. More details of this workshop are presented in the Trainees and Students section of the Society's Web site (*www.endo-society.org/awards/eiw*).

Career Advancement

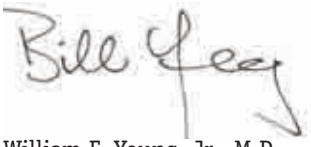
The Society continues to offer the *Mentor Exchange*, an online portal for endocrinologists of all experience levels to mentor students, fellows in training, and other members. Society mentors offer a variety of perspectives on the diverse opportunities an endocrinology career affords. More than 110 members have volunteered to be mentors and are available to connect with early-career professionals. Details on becoming a mentor or finding a mentor are on the Mentor Exchange section of the Society's Web site at *www.endo-society.org/mentor*. You may also find great tips and career advice on the revamped *EndoCareers*® Web site at *www.endocareers.org*. Finally, the new *EndoGrants Central*™ is a database of funding opportunities of particular interest to the endocrine community. Members may search for grants or post opportunities at *www.endo-society.org/awards/EndoGrants/*.

In the coming months, the Society will begin the 2013 awards season with calls for applications for the numerous Society awards and travel grants for trainees and early-career professionals. I encourage all those who are eligible to apply.

As you can see, many exciting opportunities exist within The Endocrine Society to promote the development of early-career professionals while building a community where young endocrinologists will thrive.

Most importantly, your opinions and ideas are essential in helping us create quality programming, and I invite you to submit any comments or suggestions to me c/o *president@endo-society.org*. ■

Sincerely,



William F. Young, Jr., M.D.
President, The Endocrine Society

Dear Readers,

The people who brought us the sexual revolution of the 1960s are now senior citizens. Many are still going strong—enjoying careers, traveling, playing sports, and, yes, having sex. Although no longer concerned about unwanted pregnancies, this population often needs a refresher course in sex education to deal with today's sexual issues, Melissa Mapes writes in our cover story. Like the sex and aging seminars cropping up across the country, her story offers a frank discussion of sex among seniors (page 22).

We used to call type 2 diabetes "adult onset," but the increasing incidence among American youth has widened the scope of the chronic condition and raised awareness of an evolving health problem. How best to treat children with the diseases is a matter of debate and research, free-lancer Eric Seaborg writes (page 32). Because obesity and type 2 diabetes are linked, prevention through exercise and diet is a highly favored strategy. Healthy eating, however, is a daunting challenge, as our story on portion sizes attests. Writer Kelly Horvath reports that some servings are five times larger than they were in 1970. Health advocates offer tips for portion control (page 36).

War brings casualties. The National Museum of Health and Medicine, a repository of military medical history near Washington, D.C., is a reminder of the extraordinary efforts medical personnel make to save lives and care for the wounded. The museum's history and ongoing service, the focus of our Back Story this month, are well worth exploring (page 54). ■

Sincerely,

Marian Smith Holmes
Managing Editor
Endocrine News

ENDOCRINE NEWS ONLINE EXCLUSIVES

The following articles are housed online only. See ***Endocrine News*** *Online* to read them and find related links *(www.endo-society.org/endo_news).*

Social Network for Diabetes

A new trial shows that young teens with Type 1 diabetes may benefit from Internet programs.

Caffeine and Pregnancy

The commonly consumed stimulant in coffee, chocolate, and other foods may inhibit a successful pregnancy, research suggests.

No Weigh!

A new study finds that Americans typically underestimate the number of pounds they've gained.

THE ENDOCRINE SOCIETY℠

Endocrine News® *is a registered trademark owned by The Endocrine Society.*

Endocrine news

Endocrine News® is published 12 times a year by The Endocrine Society, 8401 Connecticut Ave., Suite 900, Chevy Chase, MD 20815
Phone 301-941-0200 • Fax 301-941-0259
www.endo-society.org.

Print ISSN 2157-2089 Online ISSN 2157-2097

Boxers or Briefs and Other Male Fertility Factors

➤ Boxers or briefs? A light-hearted question often asked of celebrities and politicians may be a critical decision in regards to a man's fertility. Research from the Universities of Manchester and Sheffield in England, recently published in ***Human Reproduction*** [*humrep.oxfordjournals.org*], shows boxers are better for fertility, but surprisingly, several other lifestyle choices seem to have little effect on sperm motility.

Men unsuccessfully attempting conception for 12 months were recruited through United Kingdom fertility clinics and assessed for job histories, lifestyle, and health factors. Those with medical conditions or treatments known to cause infertility were excluded. Those chosen to participate were interviewed about clothing choices, recreational drug use, and fertility history.

Wearing boxers was associated with higher motile sperm concentration (MSC). Previous studies have suggested that tight underwear such as briefs may elevate the temperature of the testicles and slow down production of sperm.

Low (MSC) occurred in men with previous testicular surgery, possibly due to similar factors found in undescended testicles that reduce fertility. Men doing manual work also had low MSC, and this can be explained, in part, by exposure to toxicants. Students and the unemployed are at a similarly high risk with little explanation as to why.

MSC was not lowered, however, by smoking, alcohol, or recreational drug use, the study concluded. Although direct changes to sperm were either insignificant or undetected in this study, these habits may affect fertility through other means. ■

Dan Kelly

Quality of Life of Pediatric Cancer Patients Better than Expected

➤ It's hard to hear of a child with a rare disease but surely harder to live as one. Quality of life (QOL) can suffer from even the stress of diagnosis and treatment. Pediatric differentiated thyroid cancer (DTC) spreads to the cervical lymph nodes in 40–90 percent of patients and metastasizes distantly in 20–30 percent. Despite the aggressiveness of this rare disease, QOL has gone mostly unstudied.

Researchers at the Hospital for Sick Children in Toronto predicted pediatric DTC patients to have low QOL and high anxiety. Their study, lead by Asaf Oren and to be published in ***The Journal of Clinical Endocrinology & Metabolism*** [*jcem.endojournals.org*], found the opposite. Neither age, length of time since diagnosis or therapeutic factors altered anxiety levels and QOL beyond norms in the control group or healthy population.

Assessed through 3 questionnaires, 16 DTC patients aged 10–18 years measured QOL scores and anxiety levels similar to 16 adolescents with autoimmune hypothyroidism receiving L-thyroxine (L-T4) therapy. L-T4 has been found to increase anxiety during administration with only a slight decrease during withdrawal. None of the 16 DTC patients were experiencing withdrawal at the time of the study, and their free T4 levels did not correlate to their scores.

Recombinant human thyroid stimulating hormone (rhTSH) and L-T4 withdrawal are typically used in follow-up of DTC and use of rhTSH in adult patients has been linked to improved QOL. In this study, no difference was found between the QOL scores of adolescents who received rhTSH and those managed with use of withdrawal L-T4.

Following up through an endocrinology clinic instead of an oncology clinic might influence these scores, as might discussions of "excellent prognosis." However, QOL in other long-term pediatric cancer survivors improves from diagnosis to levels similar to those in the healthy population. Compared to healthy siblings, long-term pediatric cancer survivors have scored lower only on assessment of physical well-being. It may well be the ability of children to adapt easily and accentuate the positive that gives adolescent cancer patients a better self-perceived QOL. ■

Dan Kelly

Number of β-Cells Set by Age 5

➤ Type-2 diabetes is sometimes linked to a patient's low level of pancreatic β-cells, which control insulin. A new study investigates why some patients have lower pancreatic β-cells than others and whether the differences are genetic or environmental. A team of scientists led by Brigid Gregg, M.D., of Kovler Diabetes Center, University of Chicago, explored whether there is a baseline number of β-cells in humans. They also analyzed if this number is established by birth or if it can change later in life.

The researchers performed immunofluorescence examinations on pancreatic tissue samples from 40 human cadavers between the ages of 23 weeks premature and 72 years. None of the subjects had a personal or family history of diabetes and none were obese. Cell counts and islet size were done on at least 25 sample images from each subject's pancreatic section.

The study, published in ***The Journal of Clinical Endocrinology & Metabolism*** [*jcem.endojournals.org*], found that the highest rate of β-cell creation occurred preterm and up to about 2 years of age. Afterward, the rate of β-cell proliferation dropped to about 0.5 percent.

In the article, the researchers conclude that baseline β-cell population and its link with other islet cell types are established in humans before 5 years of age. They write that genetic factors and the maternal intrauterine environment could influence the degree of human pancreatic islet formation and the size of baseline β-cell mass. If this is small, they report, then a likelihood of developing diabetes can be set very early on in life. ■

Glenda Fauntleroy

Exercise Increases sRAGE, Benefits Diabetes Patients

➤ Scientists have known for some time that advanced glycation end products (AGEs) and their receptor (RAGE) play an important role in the development of atherosclerosis in patients with type 2 diabetes. New research now reveals that low levels of the soluble form of RAGE (sRAGE)—a critical risk factor for cardiovascular disease—may be improved with exercise.

Exercise helps protect against atherosclerosis by reducing or preventing oxidative stress and systemic inflammation, symptoms exacerbated by AGEs. A team of Korean researchers, led by Kyung Mook Choi, M.D., Ph.D., from the Division of Endocrinology and Metabolism in the College of Medicine at Korea University, Seoul, explored how exercise would affect the levels of sRAGE and its impact on cardiometabolic risk factors.

In their study soon to be published in ***The Journal of Clinical Endocrinology & Metabolism*** [*jcem.endojournals.org*], 75 Asian women with T2DM were randomized either into a control or aerobic exercise groups. The patients' average age was 54.4 years, average body mass index 26.8, and all had a sedentary lifestyle. While the control group continued their normal routines, the exercise group was instructed to walk at a moderate pace for an hour five days per week for 12 weeks. Exercise sessions were monitored every two weeks by a multi-record accelerometer.

After 12 weeks, the exercisers showed significant improvements in many cardiometabolic risk factors, including an increase in aerobic capacity and decreased body weight, waist size, blood pressure, cholesterol levels, glucose levels, and visceral fat area. The exercise group also had increases in sRAGE levels and decreases in high sensitive C-reactive protein levels, another cardiovascular disease risk factor. These decreases were not found in the control group.

The researchers show that sRAGE is a potential mechanism underlying the benefits of exercise in type 2 diabetes patients. ■

Glenda Fauntleroy

Continued on page 18

Start a smart partnership

For patients not at goal on insulin glargine, adding BYETTA® can deliver a complementary approach to glycemic control

Indication and usage

BYETTA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

- Not a substitute for insulin and should not be used in patients with type 1 diabetes or diabetic ketoacidosis.
- Concurrent use with prandial insulin cannot be recommended.
- Has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYETTA; consider other antidiabetic therapies for these patients.

Important Safety Information

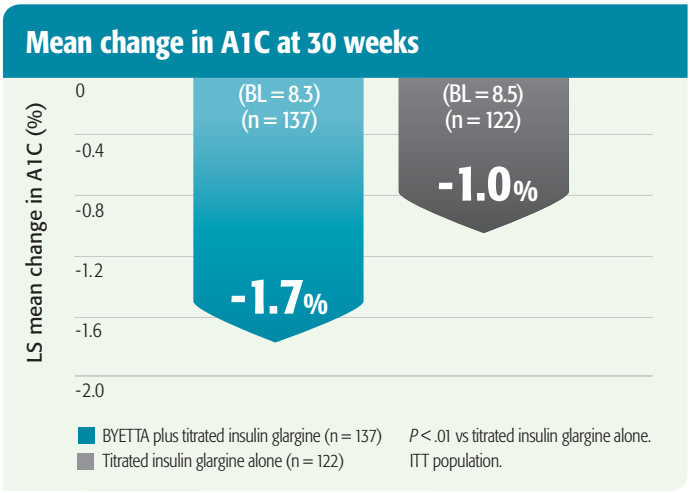
Contraindications

- BYETTA is contraindicated in patients with prior severe hypersensitivity reactions to exenatide or to any of the product components.

Warnings and precautions

- **Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation and dose increases of BYETTA, observe patients carefully for pancreatitis (persistent severe abdominal pain, sometimes radiating to the back, with or without vomiting). If pancreatitis is suspected, BYETTA should be discontinued promptly. BYETTA should not be restarted if pancreatitis is confirmed.**
- Increased risk of hypoglycemia when used in combination with glucose-independent insulin secretagogues (eg, sulfonylureas); reduction of the sulfonylurea dose may be needed. When used with insulin, evaluate and consider reducing the insulin dose in patients at increased risk of hypoglycemia.
- Postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure, and acute renal failure, sometimes requiring hemodialysis and kidney transplantation. BYETTA should not be used in patients with severe renal impairment or end-stage renal disease. Use with caution in patients with renal transplantation or when initiating or escalating the dose in patients with moderate renal failure.
- Not recommended in patients with severe gastrointestinal disease (eg, gastroparesis).
- Patients may develop antibodies to exenatide. In 3 registration trials, antibody levels were measured in 90% of patients, with up to 4% of patients having high-titer antibodies and attenuated glycemic response. If worsening of or failure to achieve adequate glycemic control occurs, consider alternative antidiabetic therapy.
- Postmarketing reports of serious hypersensitivity reactions (eg, anaphylaxis and angioedema). If this occurs, patients should discontinue BYETTA and other suspect medications and promptly seek medical advice.

BYETTA added to titrated insulin glargine achieved a significantly greater A1C reduction vs titrated insulin glargine alone



Abbreviations: LS, least squares; BL, baseline; ITT, intent to treat.

Patients with type 2 diabetes on insulin glargine alone or in combination with oral agents (metformin, thiazolidinedione, or both) were enrolled in a 30-week, randomized, double-blind, placebo-controlled clinical study to receive either BYETTA (5 mcg BID for 4 weeks then 10 mcg BID) or placebo in addition to titrated insulin glargine. In both arms, under investigator guidance, insulin was titrated to achieve a targeted fasting glucose level of <100 mg/dL using the Treat-to-Target algorithm.

- BYETTA did not increase the risk of hypoglycemia over that seen with insulin glargine alone and provided the potential benefit of weight loss (on average, 4.0 lb over 30 weeks).* Consider reducing the dose of insulin glargine in patients at increased risk for hypoglycemia.

***BYETTA is not indicated for the management of obesity, and weight change was a secondary endpoint.**

Warnings and precautions (cont'd)

- No clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug.

Adverse reactions

- Most common adverse reactions in registration trials associated with BYETTA vs placebo (PBO): nausea (44% vs 18%), vomiting (13% vs 4%), and diarrhea (13% vs 6%). Other adverse reactions ≥5% and more than PBO: feeling jittery, dizziness, headache, and dyspepsia. With a thiazolidinedione (TZD), adverse reactions were similar; as monotherapy, most common was nausea (8% vs 0%). With insulin glargine: nausea (41% vs 8%), vomiting (18% vs 4%), diarrhea (18% vs 8%), headache (14% vs 4%), constipation (10% vs 2%), dyspepsia (7% vs 2%), asthenia (5% vs 1%).
- Hypoglycemia incidence, BYETTA vs PBO, with metformin (MET): 5.3% (10 mcg) and 4.5% (5 mcg) vs 5.3%; with SFU, 35.7% (10 mcg) and 14.4% (5 mcg) vs 3.3%; with MET + SFU, 27.8% (10 mcg) and 19.2% (5 mcg) vs 12.6%; with TZD, 10.7% (10 mcg) vs 7.1%; as monotherapy, 3.8% (10 mcg) and 5.2% (5 mcg) vs 1.3%; with insulin glargine, 24.8% (10 mcg) vs 29.5%.
- Withdrawals: as monotherapy, 2 of 155 BYETTA patients withdrew due to headache and nausea vs 0 PBO; with MET and/or SFU vs PBO, nausea (3% vs <1%) and vomiting (1% vs 0); with TZD ± MET, nausea (9%) and vomiting (5%), with <1% of PBO patients withdrawing due to nausea; with insulin glargine vs PBO, nausea (5.1% vs 0), vomiting (2.9% vs 0).

Drug interactions

- BYETTA slows gastric emptying and can reduce the extent and rate of absorption of orally administered drugs. Use with caution with medications that have a narrow therapeutic index or require rapid gastrointestinal absorption. Medications dependent on threshold concentrations for efficacy should be taken at least 1 hour before BYETTA.
- Postmarketing reports of increased international normalized ratio (INR) sometimes associated with bleeding with concomitant use of warfarin. Monitor INR frequently until stable upon initiation or alteration of BYETTA.

Use in specific populations

- Based on animal data, BYETTA may cause fetal harm and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Caution should be exercised when administered to a nursing woman.
- Safety and effectiveness have not been established in pediatric patients.

To learn more, visit www.ByettaHCP.com.

For additional safety profile and other important prescribing considerations, please see the adjacent pages for Brief Summary of Prescribing Information.

†SDI data, December 2009.

Byetta® exenatide injection

AMYLIN

BYETTA® (exenatide) injection

Brief Summary: For complete details, please see full Prescribing Information.

INDICATIONS AND USAGE

Type 2 Diabetes Mellitus

BYETTA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important Limitations of Use

BYETTA is not a substitute for insulin. BYETTA should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis, as it would not be effective in these settings.

The concurrent use of BYETTA with prandial insulin has not been studied and cannot be recommended.

Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. BYETTA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYETTA. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

DOSAGE AND ADMINISTRATION

Recommended Dosing

Inject subcutaneously within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). Initiate at 5 mcg per dose twice daily; increase to 10 mcg twice daily after 1 month based on clinical response. Do not mix with insulin. Do not transfer BYETTA from the pen to a syringe or vial.

CONTRAINDICATIONS

Hypersensitivity

BYETTA is contraindicated in patients with prior severe hypersensitivity reactions to exenatide or to any of the product components.

WARNINGS AND PRECAUTIONS

Acute Pancreatitis

Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYETTA, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, BYETTA should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYETTA should not be restarted. Consider antidiabetic therapies other than BYETTA in patients with a history of pancreatitis.

Use with Medications Known to Cause Hypoglycemia

The risk of hypoglycemia is increased when BYETTA is used in combination with a sulfonylurea. Therefore, patients receiving BYETTA and a sulfonylurea may require a lower dose of the sulfonylurea to reduce the risk of hypoglycemia.

When BYETTA is used in combination with insulin, the dose of insulin should be evaluated. In patients at increased risk of hypoglycemia consider reducing the dose of insulin. The concurrent use of BYETTA with prandial insulin has not been studied and cannot be recommended. It is also possible that the use of BYETTA with other glucose-independent insulin secretagogues (e.g. meglitinides) could increase the risk of hypoglycemia.

Renal Impairment

BYETTA should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation. In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well-tolerated due to gastrointestinal side effects. Because BYETTA may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Caution should be applied when initiating or escalating doses of BYETTA from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min).

There have been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Some of these events occurred in patients receiving one or more pharmacologic agents known to affect renal function or hydration status, such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including BYETTA. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

Gastrointestinal Disease

BYETTA has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Because BYETTA is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhea, the use of BYETTA is not recommended in patients with severe gastrointestinal disease.

Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYETTA. Antibody levels were measured in 90% of subjects in the 30-week, 24-week and 16-week studies of BYETTA. In 3%, 4% and 1% of these patients, respectively, antibody formation was associated with an attenuated glycemic response. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered.

Hypersensitivity

There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with BYETTA. If a hypersensitivity reaction occurs, the patient should discontinue BYETTA and other suspect medications and promptly seek medical advice.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug.

ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Hypoglycemia

Table 1: Incidence (%) and Rate of Hypoglycemia When BYETTA was Used as Monotherapy or With Concomitant Antidiabetic Therapy in Six Placebo-Controlled Clinical Trials*

	BYETTA		
	Placebo twice daily	**5 mcg twice daily**	**10 mcg twice daily**
Monotherapy (24 Weeks)			
N	77	77	78
% Overall	1.3%	5.2%	3.8%
Rate (episodes/patient-year)	0.03	0.21	0.52
% Severe	0.0%	0.0%	0.0%
With Metformin (30 Weeks)			
N	113	110	113
% Overall	5.3%	4.5%	5.3%
Rate (episodes/patient-year)	0.12	0.13	0.12
% Severe	0.0%	0.0%	0.0%
With a Sulfonylurea (30 Weeks)			
N	123	125	129
% Overall	3.3%	14.4%	35.7%
Rate (episodes/patient-year)	0.07	0.64	1.61
% Severe	0.0%	0.0%	0.0%
With Metformin and a Sulfonylurea (30 Weeks)			
N	247	245	241
% Overall	12.6%	19.2%	27.8%
Rate (episodes/patient-year)	0.58	0.78	1.71
% Severe	0.0%	0.4%	0.0%
With a Thiazolidinedione (16 Weeks)			
N	112	not evaluated	121
% Overall	7.1%	not evaluated	10.7%
Rate (episodes/patient-years)	0.56	not evaluated	0.98
% Severe	0.0%	not evaluated	0.0%
With Insulin Glargine (30 Weeks) †			
N	122	not evaluated	137
% Overall	29.5%	not evaluated	24.8%
Rate (episodes/patient-years)	1.58	not evaluated	1.61
% Severe	0.8%	not evaluated	0.0%

* A hypoglycemic episode was recorded if a patient reported symptoms of hypoglycemia with or without a blood glucose value consistent with hypoglycemia. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose value consistent with hypoglycemia or prompt recovery after treatment for hypoglycemia.

† When BYETTA was initiated in combination with insulin glargine, the dose of insulin glargine was decreased by 20% in patients with an $HbA_{1c} \leq 8.0$ % to minimize the risk of hypoglycemia. See Table 9 for insulin dose titration algorithm.

N = The number of Intent-to-Treat subjects in each treatment group.

Immunogenicity

Antibodies were assessed in 90% of subjects in the 30-week, 24-week and 16-week studies of BYETTA. In the 30-week controlled trials of BYETTA add-on to metformin and/or sulfonylurea, antibodies were assessed at 2- to 6-week intervals. The mean antibody titer peaked at week 6 and was reduced by 55% by week 30. Three hundred and sixty patients (38%) had low titer antibodies (<625) to exenatide at 30 weeks. The level of glycemic control (HbA_{1c}) in these patients was generally comparable to that observed in the 534 patients (56%) without antibody titers. An additional 59 patients (6%) had higher titer antibodies (≥625) at 30 weeks. Of these patients, 32 (3% overall) had an attenuated glycemic response to BYETTA; the remaining 27 (3% overall) had a glycemic response comparable to that of patients without antibodies.

In the 16-week trial of BYETTA add-on to thiazolidinediones, with or without metformin, 36 patients (31%) had low titer antibodies to exenatide at 16 weeks. The level of glycemic control in these patients was generally comparable to that observed in the 69 patients (60%) without antibody titer. An additional 10 patients (9%) had higher titer antibodies at 16 weeks. Of these patients, 4 (4% overall) had an attenuated glycemic response to BYETTA; the remaining 6 (5% overall) had a glycemic response comparable to that of patients without antibodies.

In the 24-week trial of BYETTA used as monotherapy, 40 patients (28%) had low titer antibodies to exenatide at 24 weeks. The level of glycemic control in these patients was generally comparable to that observed in the 101 patients (70%) without antibody titers. An additional 3 patients (2%) had higher titer antibodies at 24 weeks. Of these patients, 1 (1% overall) had an attenuated glycemic response to BYETTA; the remaining 2 (1% overall) had a glycemic response comparable to that of patients without antibodies.

Antibodies to exenatide were not assessed in the 30-week trial of BYETTA used in combination with insulin glargine.

Two hundred and ten patients with antibodies to exenatide in the BYETTA clinical trials were tested for the presence of cross-reactive antibodies to GLP-1 and/or glucagon. No treatment-emergent cross reactive antibodies were observed across the range of titers.

Other Adverse Reactions

Monotherapy

Adverse reactions (excluding hypoglycemia) for the 24-week placebo-controlled study of BYETTA BID (N = 155) when used as a monotherapy, with an incidence ≥2% and occurring more frequently in BYETTA-treated patients versus placebo BID-treated patients (N = 77): nausea (8% vs 0%), vomiting (4% vs 0%), and dyspepsia (3% vs 0%).

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite, diarrhea, and dizziness. The most frequently reported adverse reaction associated with BYETTA, nausea, occurred in a dose-dependent fashion.

Two of the 155 patients treated with BYETTA withdrew due to adverse reactions of headache and nausea. No placebo-treated patients withdrew due to adverse reactions.

Combination Therapy

Add-on to metformin and/or sulfonylurea

Adverse reactions (excluding hypoglycemia) in the three 30-week controlled trials of BYETTA BID (N = 963) add-on to metformin and/or sulfonylurea, with an incidence ≥2% and occurring more frequently in BYETTA-treated patients versus placebo-treated patients (N = 483): nausea (44% vs 18%), vomiting (13% vs 4%), diarrhea (13% vs 6%), feeling jittery (9% vs 4%), dizziness (9% vs 6%), headache (9% vs 6%), dyspepsia (6% vs 3%), asthenia (4% vs 2%), gastroesophageal reflux disease (3% vs 1%), and hyperhydrosis (3% vs 1%).

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite. Nausea was the most frequently reported adverse reaction and occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased over time in most of the patients who initially experienced nausea. Patients in the long-term uncontrolled open-label extension studies at 52 weeks reported no new types of adverse reactions than those observed in the 30-week controlled trials.

The most common adverse reactions leading to withdrawal for BYETTA-treated patients were nausea (3% of patients) and vomiting (1%). For placebo-treated patients, <1% withdrew due to nausea and none due to vomiting.

Add-on to thiazolidinedione with or without metformin

Adverse reactions (excluding hypoglycemia) for the 16-week placebo-controlled study of BYETTA BID (N = 121) add-on to a thiazolidinedione, with or without metformin, with an incidence ≥2% and occurring more frequently in BYETTA-treated patients versus placebo-treated patients (N = 112): nausea (40% vs 15%), vomiting (13% vs 1%), dyspepsia (7% vs 1%), diarrhea (6% vs 3%), and gastroesophageal refiux disease (3% vs 0%).

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite. Chills (n = 4) and injection-site reactions (n = 2) occurred only in BYETTA-treated patients. The two patients who reported an injection-site reaction had high titers of antibodies to exenatide. Two serious adverse events (chest pain and chronic hypersensitivity pneumonitis) were reported in the BYETTA arm. No serious adverse events were reported in the placebo arm.

The most common adverse reactions leading to withdrawal for BYETTA-treated patients were nausea (9%) and vomiting (5%). For placebo-treated patients, <1% withdrew due to nausea.

Add-on to insulin glargine with or without metformin and/or thiazolidinedione

Adverse reactions (excluding hypoglycemia) for the 30-week placebo-controlled study of BYETTA BID (N = 137) as add-on to insulin glargine with or without oral antihyperglycemic medications with an incidence ≥2% and occurring more frequently in BYETTA-treated patients versus placebo-treated patients (N = 122): nausea (41% vs 8%), vomiting (18% vs 4%), diarrhea (18% vs 8%), headache (14% vs 4%), constipation (10% vs 2%), dyspepsia (7% vs 2%), asthenia (5% vs 1%), abdominal distension (4% vs 1%), decreased appetite (3% vs 0%), flatulence (2% vs 1%), gastroesophageal reflux disease (2% vs 1%).

The most frequently reported adverse reactions leading to withdrawal for BYETTA-treated patients were nausea (5.1%) and vomiting (2.9%). No placebo-treated patients withdrew due to nausea or vomiting.

Post-Marketing Experience

The following additional adverse reactions have been reported during post-approval use of BYETTA. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergy/Hypersensitivity: injection-site reactions, generalized pruritus and/or urticaria, macular or papular rash, angioedema, anaphylactic reaction.

Drug Interactions: International normalized ratio (INR) increased with concomitant warfarin use sometimes associated with bleeding.

Gastrointestinal: nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death.

Neurologic: dysgeusia; somnolence

Renal and Urinary Disorders: altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure or acute renal failure (sometimes requiring hemodialysis), kidney transplant and kidney transplant dysfunction.

Skin and Subcutaneous Tissue Disorders: alopecia

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of BYETTA use in pregnant women. In animal studies, exenatide caused cleft palate, irregular skeletal ossification and an increased number of neonatal deaths. BYETTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Female mice given SC doses of 6, 68, or 760 mcg/kg/day beginning 2 weeks prior to and throughout mating until gestation day 7 had no adverse fetal effects. At the maximal dose, 760 mcg/kg/day, systemic exposures were up to 390 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

In developmental toxicity studies, pregnant animals received exenatide subcutaneously during organogenesis. Specifically, fetuses from pregnant rabbits given SC doses of 0.2, 2, 22, 156, or 260 mcg/kg/day from gestation day 6 through 18 experienced irregular skeletal ossifications from exposures 12 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC. Moreover, fetuses from pregnant mice given SC doses of 6, 68, 460, or 760 mcg/kg/day from gestation day 6 through 15 demonstrated reduced fetal and neonatal growth, cleft palate and skeletal effects at systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

Lactating mice given SC doses of 6, 68, or 760 mcg/kg/day from gestation day 6 through lactation day 20 (weaning), experienced an increased number of neonatal deaths. Deaths were observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

Pregnancy Registry

Amylin Pharmaceuticals, Inc. maintains a Pregnancy Registry to monitor pregnancy outcomes of women exposed to exenatide during pregnancy. Physicians are encouraged to register patients by calling 1-800-633-9081.

Nursing Mothers

It is not known whether exenatide is excreted in human milk. However, exenatide is present at low concentrations (less than or equal to 2.5% of the concentration in maternal plasma following subcutaneous dosing) in the milk of lactating mice. Many drugs are excreted in human milk and because of the potential for clinically significant adverse reactions in nursing infants from exenatide, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account these potential risks against the glycemic benefits to the lactating woman. Caution should be exercised when BYETTA is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of BYETTA have not been established in pediatric patients.

Geriatric Use

Population pharmacokinetic analysis of patients ranging from 22 to 73 years of age suggests that age does not influence the pharmacokinetic properties of exenatide. BYETTA was studied in 282 patients 65 years of age or older and in 16 patients 75 years of age or older. No differences in safety or effectiveness were observed between these patients and younger patients. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function.

OVERDOSAGE

In a clinical study of BYETTA, three patients with type 2 diabetes each experienced a single overdose of 100 mcg SC (10 times the maximum recommended dose). Effects of the overdoses included severe nausea, severe vomiting, and rapidly declining blood glucose concentrations. One of the three patients experienced severe hypoglycemia requiring parenteral glucose administration. The three patients recovered without complication. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

Manufactured for Amylin Pharmaceuticals, Inc., San Diego, CA 92121

This product and its use are covered by US Patent Nos. 5,424,286, 6,858,576, 6,872,700, 6,902,744, 6,956,026, 7,297,761, 7,521,423, 7,741,269, and other patents pending.

1-800-868-1190

http://www.BYETTA.com

Literature Revised December 2011

822017-AA
02-09-9300-E

Continued from page 13

Slug's Potential for Prostate Cancer Treatment

➤ Like its namesake, Slug, the most recently identified member of the zinc finger transcription factor family Snail, is sticky—it binds to the androgen receptor (AR) regardless of the presence of androgen. This finding could be useful in patients with castration-resistant prostate cancer (CRPC), a deadly cancer that contains cells with altered and increased AR levels.

Led by Jer-Tsong Hsieh, Ph.D. at UT Southwestern Medical Center at Dallas, and Dalin He, M.D., at First Affiliated Hospital, Medical School of Xi'an Jiaotong University, in China, scientists stained and analyzed 400 human prostate cancer tissue specimens, categorized by hormone therapy status, Gleason score, and primary or end-stage status, to show the concurrent elevation of Slug and AR. The study also shows both Slug and AR interacting with each other, thereby forming a complex. Significantly, in the presence of Slug, AR does not need androgen to become active. Researchers backed up these observations with at least two CDNA microarrays that examined gene expression in prostate cancer tissues. In their paper, to be published soon in ***Molecular Endocrinology*** [*mend.endojournals.org*], the researchers report that the Slug–AR reciprocal relationship hyperactivates transcriptional activity of AR, which contributes to the progression of CRPC—that is, the androgen-independent form.

The researchers conclude that due to its key role in CRPC, Slug has potential in both prostate cancer prognosis as a marker and in therapy as a drug target. ■

Kelly Horvath

STATS

Limiting daily sitting to

< 3 hours

increases U.S. life expectancy by 2 years.

Source: Katzmarzyk PT, Lee I-M. Sedentary behavior and life expectancy in the USA: A cause-deleted life table analysis. *BMJ Open*, 2012, 2:e000828. doi:10.1136/bmjopen-2012-000828.

Bariatric Surgery Raises Risks of Alcoholism

➤ Patients who have gastric bypass surgery are 30 percent more likely to have problems with alcohol, according to a new prospective study.

Spurred by anecdotal reports linking bariatric surgery to an increased risk of alcohol abuse disorders, researchers led by Wendy C. King, Ph.D., of the University of Pittsburgh, designed a multicenter study to compare 1,945 patients' experiences before and after Roux-en-Y gastric bypass (RYGB) and laparoscopic adjustable gastric banding (LAGB) surgery.

Participants completed pre- and postoperative assessments on their experience with alcohol use disorders, such as alcohol abuse and dependence. The prevalence of symptoms did not differ from the year before surgery to the first year after, but was significantly higher in the second year, going from 7.6 percent before surgery, to 7.3 percent the year after, to 9.6 percent in the second year. The increase was almost entirely among the RYGB patients, who made up 70 percent of the study group, with virtually no increase in the LAGB patients.

In an article published in *JAMA* [*jama.jamanetwork.com*], the researchers noted evidence that some bariatric procedures, including RYGB and sleeve gastrectomy, alter the pharmacokinetics of alcohol. These patients feel the effects of alcohol more quickly and reach a higher peak alcohol level.

The researchers identified several risk factors that increase the likelihood of alcohol problems: male sex, younger age, regular alcohol consumption, recreational drug use, and less interpersonal support. They recommend that alcohol screening and referral be offered to patients both before and after the surgery. ■

Eric Seaborg

Growth Hormone Linked to Healthy Aging

➤ If a baby continued growing at the rate she does the first year of life (about 10 inches in length), by the time she turned 60, she would be 600 inches or 50 feet tall! Luckily by 2 years of age, a baby's height growth stabilizes at a steady rate of 2.5 inches per year until adolescence.

Growth hormone (GH) parallels this downward spiral, in that its secretion naturally declines after adolescence at a rate of 14 percent each decade. Elderly people and patients with adult onset GH deficiency have similar body compositions with reduced muscle and bone and increased fat. The converse is also true—increased adiposity reduces GH secretion. These findings have led researchers to believe that impaired GH may contribute to the development of metabolic maladies such as obesity.

Seeking to find out what happens to GH secretion in young adults with dietary-induced weight gain, Lili Huang, M.D., Frederick J. Steyn, Ph.D., and a team of scientists led by Chen Chen, M.D., Ph.D., at the School of Biomedical Sciences, University of Queensland in Brisbane, Australia, fed wild-type mice either a standard or high-fat diet until the mice reached early adulthood (~11 weeks). Blood sample analysis revealed lower serum GH levels between ages 12 and 16 weeks in the high fat-fed mice compared to those on regular chow. In their paper, to be published soon in ***Endocrinology*** [*endojournals.org*], the researchers report increased adiposity in high-fat diet mice, with adipose tissue also found in the liver, and decreased levels of insulin-like growth factor I (IGF-I), which works in concert with GH to maintain healthy aging and phenotype. IGF-I attrition is also characteristic of obesity.

The researchers conclude that weight gain speeds up GH secretion decline, which may yield gigantic health problems throughout the lifespan, including increased risk for hyperinsulinemia, obesity, and impaired liver function. ■

Kelly Horvath

Irregular Menstrual Cycles as Markers for Health Risks

➤ Much of a woman's health centers on her menstrual cycle. Exposure to endogenous hormones factors into both reproductive development and risk of various cancers and diseases. Menstrual cycles are typically used to measure these risks rather than the hormones directly, but how hormone concentrations and cycle length interact is largely unknown.

Assessing 259 regularly menstruating women age 18–44 years, researchers at the National Institutes of Health and the University at Buffalo found marked differences between hormone levels of long and short cycles. Follicular phase estradiol had a late rise during longer cycles, with follicle stimulating hormone (FSH) and luteinizing hormone (LH) also peaking later. LH concentrations remained high across the cycle, which may actually delay FSH and rising estradiol production and follicular development.

Women with short cycles show concentrations of FSH higher in early follicular and late luteal phases. Follicular phase estradiol was also higher. Short cycles themselves and short follicular phases specifically are conjectured to be due to early rises in FSH and faster follicular development.

An early rise of estradiol may mean per-cycle exposure is low, but a greater number of cycles experienced over a lifetime may increase exposure to levels above even regular cycles. Early follicular phase concentrations of FSH and estradiol with low luteal phase progesterone are a classic pattern of reproductive aging.

Both short and long cycles were associated with an increased risk of anovulation as compared to regular cycles. These findings, to be published in ***The Journal of Clinical Endocrinology & Metabolism*** [*jcem.endojournals.org*], add strength to using cycle length in measuring anovulation risk and hormone exposure in normally cycling women. "[It's] a potentially valuable tool," writes article author Sunni Mumford, Ph.D., "for measuring a woman's lifetime exposure to hormones and in understanding associations with health outcomes." ■

Dan Kelly

Vitamin D Dietary Supplements No Help in Normal Calcium Absorption

➤ Calcitriol, the vitamin D active metabolite, is known to mediate calcium absorption in the gut. It is dependent on an adequate substrate of serum 25OHD. Also well documented is the age-related decline in the efficiency of this mechanism and a concomitant decrease in endogenous calcitriol production. Due to the high incidence of calcium deficiency–related disorders such as osteoporosis among older adult women, health care providers have long advised dietary supplements of calcium plus vitamin D in this population. A recent cross-sectional study postulated that there was a threshold of serum 25OHD of 30 ng/mL (75 nmol/L) at which point increasing supplementary vitamin D became more effective for increasing calcium absorption.

Scientists led by Chris Gallagher, M.D., at the Creighton University Medical Center in Omaha, Nebraska, tested where this threshold lies by analyzing data from the ViDOS (Vitamin D supplementation in Older Subjects) trial, in which 143 postmenopausal women were given dietary supplements of 200 mg calcium plus one of seven levels of vitamin D supplement ranging from 400–4,800 IU or placebo daily for one year to measure calcium absorption across a range of resulting serum 25OHD levels, from 10 to 66 ng/mL (25–165 nmol/L).

In their paper, to be published soon in ***The Journal of Clinical Endocrinology & Metabolism*** [*jcem.endojournals.org*], the researchers report that in this longitudinal study, the threshold for normal calcium absorption occurred at a very low level of serum 25OHD, less than 5–10 ng/mL (12.5–25 nmol/L) —this being the 25OHD level at which serum 1,25(OH)2D fell—much lower than previously reported.

The researchers conclude that vitamin D supplementation may not be useful in older women unless they have severe vitamin D deficiency (< 5–10 ng/mL). This population can achieve the desired level of calcium absorption by drinking an extra 100 ml of milk or with a 100-mg calcium supplement, they add. ■

Kelly Horvath

Building a Better Diabetes Drug

➤ Fibroblast growth factor 21 (FGF21), a novel hormone involved in glucose and energy homeostasis, shows promise in treating obesity and diabetes. In rodents and primates, it has been shown to normalize blood sugar and lipid levels and decrease weight. The only catch is its short life. FGF21 stays in the body for only one to two hours. To get the desired effects, researchers would have to give multiple injections, thus failing to avoid the same complication that most insulin users already face.

In hopes of developing a longer-acting alternative, researchers, led by Jing Xu, Ph.D. and Murielle M. Véniant, Ph.D., of Amgen, Inc., in Thousand Oaks, California, fused the hormone containing two engineered mutations with an Fc fragment to generate a molecule they called Fc-FGF21(RG). They then compared the efficacy of their new creation with that of hrFGF21 in diet-induced obese mice and obese rhesus monkeys.

The diet-induced obese mice treated with either compound showed several metabolic improvements: decreased body weight; decreased glucose, insulin, cholesterol, and triglyceride levels; and improved glucose tolerance. The obese rhesus monkeys showed similar results in these measures, with the Fc-FGF21(RG) having greater effects than the hrFGF21. An important difference: Both species were treated with the Fc-FGF21(RG) only once every five to seven days, compared with daily administration of hrFGF21.

In an article awaiting publication in ***Endocrinology*** [*endo.endojournals.org*], the researchers note that finding in two species that weekly Fc-FGF21(RG) showed efficacy similar to or greater than daily hrFGF21 offers a promising avenue to explore for new therapeutic options. ■

Eric Seaborg

Fructose Transporter Becomes Latest Obesity Drug Target

➤ One factor in the increased obesity epidemic is the overindulgence in dietary sugars such as high-fructose corn syrup (HFCS). Researchers are honing in on how fructose is involved in fat cell formation. Data from the U.S. National Health and Nutrition Examination Survey (NHANES) suggest that about 15 percent of Americans consume greater than 25 percent of their energy from added sugars such as HFCS. Research in rhesus monkeys has shown that when these animals are fed about 30 percent of their energy intake as fructose, they develop features of metabolic syndrome such as abdominal obesity, dyslipidemia, and inflammation.

To gain greater insight into how fructose promotes fat, Anthony Heaney, M.D., and his research group from the University of California, Los Angeles, examined a mouse pre-adipocyte cell line, 3T3-L1 and mice that lacked a glucose/fructose transporter, GluT5. Their results are discussed in an upcoming issue of ***Molecular Endocrinology*** [*mend.endojournals.org*].

Preadipocytes that were incubated in fructose had a greater propensity toward differentiation into full-fledged fat cells than those on regular cell culture medium. When these cells were hit with a specific GluT5 inhibitor, differentiation decreased. Similarly, *GluT5 -/-* mice had less white adipose tissue compared with wild-type mice and were resistant to diet-induced obesity.

These findings suggest a new target for weight loss drugs, suggested the authors. ■

Jacqueline Ruttimann

Gonadotropins Not Linked to Higher IVF Failures

➤ Although it has become a popular option for women seeking treatment for infertility, the rates of in vitro fertilization (IVF) resulting in a viable pregnancy still remain low, mostly due to the high numbers of embryos produced with chromosomal abnormalities.

Researchers from the University of Valencia in Spain, led by Elena Labarta, M.D., explored whether the high chromosomal abnormality rates, as compared with the rates in embryos produced from natural fertilization, could be traced to the use of gonadotropins to stimulate the ovaries during IVF.

The study took place in a private infertility clinic over a four-year period. Researchers recruited healthy, fertile oocyte and sperm donors between the ages of 18 and 34. An unstimulated IVF cycle was first conducted on 51 oocyte donors, which resulted in 35.3 percent of the embryos having chromosomal abnormalities. Of those 51 women, 46 later completed a second stimulated cycle—taking about 10 days of a combination dose of 150 IU follicle-stimulating hormone and 75 IU of highly purified human menopausal gonadotropin. The same sperm donor was used for both cycles.

In the women who completed both cycles, 34.8 percent of the embryos showed chromosomal abnormalities in the unstimulated cycle compared with 40.6 percent in the stimulated cycle. The study found no differences between the unstimulated and stimulated cycles in embryo quality and type of chromosomal abnormalities.

The researchers conclude in their upcoming article in ***The Journal of Clinical Endocrinology & Metabolism*** [*jcem.endojournals.org*] that the use of moderate doses of gonadotropins for ovarian stimulation during an IVF cycle does not significantly increase the abnormality rate in young women with normal ovulation. ■

Glenda Fauntleroy

Sexed for Seniors

By Melissa Mapes

Sex reigns king over all taboo topics. Parents dread the infamous birds and bees conversation almost as much as their children do. Although sex education remains an awkward but important step for adolescents, recent studies indicate that an important demographic is due for a refresher course: grandparents. The risk of sexually transmitted diseases (STDs) in seniors is growing faster than in teens. Younger groups are still at a much greater overall risk of infection, but the U.S. Centers for Disease Control and Prevention (CDC) has reported skyrocketing rates of STDs in people more than 50 years of age during the past decade. Cases of syphilis and chlamydia alone have nearly tripled.

People often assume that sexual activity ceases after a certain age, when sex hormones and vitality begin to diminish. The truth is quite the opposite. The elderly may not talk much about sex, but that does not mean they are not engaging in it. More than 80 percent of people 50 years and older reported regular sexual activity in one British study, which included participants up to 90 years of age. A comparable study in the United States found 73 percent of those ages 57–64 years, 53 percent of those ages 65–74 years, and 26 percent of those ages 75–85 years to be sexually active. Sex can be good for general health if practiced safely. Unfortunately, seniors are less likely to use protection.

A 2009 AARP survey found that only 12 percent of single and dating men and 32 percent of single and dating women 45 years of age and older consistently used protection during sex. As a result, research from the British journal *Sexually Transmitted Infections* indicates that STD rates among those in this age group have doubled in one decade. Without fear of pregnancy, some seniors forgo condoms during sex. One theory is that older populations are hesitant to discuss sex and assume that STDs rarely occur in their age group. The hard truth is that 17 percent of all new HIV diagnoses and 23 percent of all new AIDS diagnoses in the United States in 2009 were in patients 50 years and older, according to the CDC.

The Benefits of Oxytocin

Studies show that human contact is good for all of us, seniors included. The hormone oxytocin, which is released during orgasm in men and women, plays a role in social bonding and our overall sense of well-being. Elders who live relatively isolated lives often lack opportunities for intimacy, which can promote mental and physical health. It is not unusual for people living in senior communities or nursing homes to turn to their peers for physical contact, even if suffering from a degenerative mental condition like dementia. A recent Australian study published in the *Journal of Medical Ethics* showed that patients still pursue sexual relationships during the earlier stages of such illnesses.

The study also discusses claims that some health care workers in institutions prohibited sex among patients based on the staff's personal beliefs or safety concerns for patients. The question of when sex should be allowed or denied in nursing homes falls into a gray area that has not received much attention. Some nursing homes work to combat the touch deficit by bringing in pets for patients. The therapeutic effects of petting and cuddling with animals have been shown

to increase oxytocin levels among older people who may be deficient in the hormone.

Although the benefits of touch and sexual activity are clearly documented, providing comprehensive information to sexually active seniors has its challenges. Society's youth-oriented culture often results in a negative portrayal of physical intimacy among old people, which can make some of them less forthcoming about sexual problems. Diagnosing sexually transmitted diseases and infections in seniors can be difficult due to the confusing of aging and disease symptoms. Patients may chalk up frequent urination and other mild aches and pains as a natural progression into the golden years. By the time an STD is caught and treated, it might have already spread to other sexual partners.

Physical effects of aging also catalyze the spread of diseases during sex. Vaginal atrophy, a thinning of vaginal membranes after menopause and a decline in estrogen, puts women at risk for tearing during sex and for transmission of sexual diseases. "There is an argument that changes to the vaginal mucosa postmenopause may make the tissues more friable and create microabrasions, which enhance transmission of sexually transmitted infections," said Rachel Von Simson, a final year medical student at the King's College in London and co-author of a recent editorial called "Sexual Health and the Older Adult" in the *Student BMJ*. "Vaginal pH is higher postmenopause, and in younger adults a higher vaginal pH has been associated with an increased risk of STDs."

Research has not definitely explained why STD rates are increasing among older women, however, even though a higher pH has always been the norm among them, nor can it explain why the rates are increasing in older men. Erectile dysfunction (ED) drugs like Viagra provide one of the connections. A study published in the *Annals of Medicine* tested the hypothesis that older men using ED drugs were more likely to contract STDs than those who did not request these drugs from their physician. By reviewing thousands of insurance claims, Anupam B. Jena, M.D., Ph.D., an assistant professor of health care policy at Harvard Medical School and a physician at Massachusetts General Hospital, found that men more than 40 years of age using ED drugs were 2–3 times more likely to contract an STD than other men in the same age group. Although taking ED medications cannot be said to directly increase a patients' risk of infection, Jena said, "the introduction of these medications allowed them to either have sex or to have sex more frequently, and by definition having sex more often one would expect that STD rates would go up."

Safe Sex Campaigns

Longer lives and higher divorce rates have also been pinpointed as factors in the spread of STDs among older adults. With good health lasting longer into life, people are more likely to remain sexually active after retirement. This factor, combined with an uptick in divorces, many later in life, increases the likelihood of having a greater number of sexual partners over a lifetime. Von Simson explained that the STD trend has led to the inclusion of elders in the National Survey of Sexual Health and Behavior, started by Dr. Alfred Kinsey in the 1940s. A similar report, "NATSAL [National Survey of Sexual Attitudes and Lifestyles], is expanding to include older adults, but this will only give us a snapshot of now, not of how behaviors may have changed," Von Simson said. The lack of historical evidence on the sexual behavior of seniors presents a challenge for researchers seeking the source of increasing STD infections. She believes that many opportunities remain for research in this field.

> Society's negative portrayal of physical intimacy among old people can make some of them less forthcoming about sexual problems.

Because contracting STDs is still far more common among young adults, the primary focus of the medical community has

been on the adolescent cohort. But the changing tides of sex-related issues in elders has inspired a new wave of safe sex campaigns and seminars in several cities, from New York to San Jose. In May 2012, *SaferSex4Seniors.org* released a risqué public service announcement in the form of a YouTube video. The 30-second video shows fully-clothed seniors demonstrating various sexual positions in rapid succession. The clip ends with the statistic that STD rates among seniors in Florida have risen 71 percent. The tagline encourages seniors to "Do it. Safely."

Advising Older Patients

Experts agree that rising STD rates do not mean seniors should be pressed into abstinence. A study presented at **The Endocrine Society's 94th Annual Meeting, ENDO 2012,** in Houston, Texas, found that testosterone levels remain high in healthy sexually active men between the ages of 35 and 80 years, especially in those who are married. Healthy levels of this hormone promote important bodily functions and help keep muscle-to-fat ratios in check. Physical intimacy and touch set off a complex chain of hormonal responses that have been shown to enhance quality of life at any age. When it comes to sex, a number of studies show that overall health is much more critical that one's calendar age. From a scientific point of view it is perfectly fine for seniors to "do it."

The conclusive cause of increasing STD rates in older populations many continue to elude researchers for a while. The answer may be too complex and multifaceted to pinpoint cause, but Jena suspects the trend is simply linked to a change in social norms. "It's not like there were massive advertising campaigns or things like Facebook that only applied to older folks," Jena said. Experts say doctors should be prepared to advise their older patients about how to carry on a healthy sex life even as they age, and to remind them of the basic safety tip they learned years ago in high school: Always use a condom. ■

Mapes is a freelance writer in Washington, D.C.

ENDO LINKS For additional links related to this feature, please visit *Endocrine News Online* at *www.endo-society.org/endo_news*.

$50/MONTH CO-PAY*

HER FIRST OSTEOPOROTIC FRACTURE COULD LEAD TO ANOTHER

INDICATIONS AND USAGE

- FORTEO® (teriparatide [rDNA origin] injection) is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, and for the treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture
- High risk for fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy

FORTEO is administered as a 20 microgram once daily dose and is available in a 2.4 mL prefilled delivery device for subcutaneous injection over 28 days.

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

See the Important Safety Information for Complete Boxed Warning.

- **In rats, teriparatide caused an increase in the incidence of osteosarcoma, a malignant bone tumor.**
- **Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO only for patients for whom potential benefits outweigh potential risk.**
- **FORTEO should not be prescribed for patients at increased baseline risk for osteosarcoma (eg, those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).**

Find out how FORTEO helps form new bone at www.FORTEOhcp.com

FORTEO™

teriparatide (rDNA origin) injection

ANABOLIC ACTION FOR NEW BONE

NOW IS THE TIME FOR ANABOLIC ACTION

FORTEO CONNECT OFFERS PERSONALIZED SUPPORT TO HELP PATIENTS THROUGHOUT THEIR TREATMENT

- Patients can choose to sign up for an insurance investigation, injection training, and/or ongoing support for up to 24 months
- Now with the FORTEO Co-pay Card, eligible commercially insured patients will pay no more than a **$50/month** co-pay*

*This offer may be terminated, rescinded, revoked, or amended by Lilly USA, LLC at any time without notice. Patient should provide the card to his/her pharmacist, along with a valid prescription from the physician.

FORTEO SELECT SAFETY INFORMATION

Prescribe FORTEO only for patients for whom the potential benefits are considered to outweigh the potential risks. FORTEO should not be prescribed for patients at increased baseline risk for osteosarcoma, including those with Paget's disease of bone, unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy. Additionally, patients with bone metastases or a history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or pre-existing hypercalcemia should not receive FORTEO.

Use of FORTEO for more than 2 years during a patient's lifetime is not recommended.

Please see Important Safety Information, including Boxed Warning regarding osteosarcoma, and Brief Summary on following pages. See Full User Manual that accompanies the delivery device.

Lilly

INDICATIONS AND USAGE

- FORTEO® (teriparatide [rDNA origin] injection) is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, and for the treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture
- High risk for fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy

FORTEO is administered as a 20 microgram once daily dose and is available in a 2.4 mL prefilled delivery device for subcutaneous injection over 28 days.

IMPORTANT SAFETY INFORMATION

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® (teriparatide [rDNA origin] injection) only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).

CONTRAINDICATIONS

Hypersensitivity to teriparatide or to any of its excipients. Reactions have included angioedema and anaphylaxis.

WARNINGS AND PRECAUTIONS

The following categories of patients have increased baseline risk of osteosarcoma and therefore should not be treated with FORTEO: Paget's disease of bone, pediatric populations and young adults with open epiphyses, or prior external beam or implant radiation therapy.

Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org.

Osteosarcoma occurs in about 4 out of every million older adults each year. Cases of bone tumor and osteosarcoma have been reported rarely in people taking FORTEO in the post-marketing period. The causality to FORTEO use is unclear.

Use of FORTEO for more than 2 years during a patient's lifetime is not recommended.

Patients with the following conditions also should not receive FORTEO: bone metastases or a history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or hypercalcemic disorders.

FORTEO may increase serum calcium, urinary calcium, and serum uric acid.

Use with caution in patients with active or recent urolithiasis because of risk of exacerbation. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered.

Transient orthostatic hypotension may occur with initial doses of FORTEO. In short-term clinical pharmacology studies, transient episodes of symptomatic orthostatic hypotension were observed in 5% of patients. FORTEO should be administered initially under circumstances where the patient can sit or lie down if symptoms of orthostatic hypotension occur.

Patients receiving digoxin should use FORTEO with caution because FORTEO may transiently increase serum calcium and hypercalcemia may predispose patients to digitalis toxicity.

ADVERSE REACTIONS

The most common adverse reactions in clinical trials include: arthralgia (10.1 FORTEO vs. 8.4 placebo), pain (21.3 FORTEO vs. 20.5 placebo), and nausea (8.5 FORTEO vs. 6.7 placebo). Other adverse reactions include: dizziness, leg cramps, joint aches, and injection site reactions.

USE IN PREGNANCY/NURSING MOTHERS

FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on animal studies, FORTEO may cause fetal harm.

It is not known whether teriparatide is excreted in human milk. Breastfeeding mothers should discontinue nursing or FORTEO, taking into account the importance of treatment to the mother.

INSTRUCTIONS FOR FORTEO USE

FORTEO is provided as a fixed-dose, prefilled delivery device that can be used for up to 28 days, including the first injection. The delivery device contains 28 daily doses of 20 mcg each. Do not transfer the contents of the delivery device into a syringe. The FORTEO Delivery Device should be stored under refrigeration at 36° to 46° F (2° to 8° C) at all times. Do not use FORTEO if it has been frozen.

For more safety information, please see Brief Summary of Prescribing Information, including Boxed Warning regarding osteosarcoma, on following pages. See Full User Manual that accompanies the delivery device.

TE HCP ISI 07Apr2011

FORTEO™
teriparatide (rDNA origin) injection
ANABOLIC ACTION FOR NEW BONE

Lilly

FORTEO® (teriparatide [rDNA origin] 20 mcg for injection)

Brief Summary Consult the package insert for complete prescribing information.

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).

INDICATIONS AND USAGE

FORTEO is indicated: for the treatment of postmenopausal women with osteoporosis at high risk for fracture; to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; for the treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy at high risk for fracture. High risk for fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

CONTRAINDICATIONS

Do not use FORTEO in patients with Hypersensitivity to teriparatide or to any of its excipients. Reactions have included angioedema and anaphylaxis.

WARNINGS AND PRECAUTIONS

Osteosarcoma In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. FORTEO should not be prescribed for patients at increased baseline risk of osteosarcoma. These include Paget's disease of bone (unexplained elevations of alkaline phosphatase may indicate Paget's disease of bone); pediatric and young adult patients with open epiphyses; prior external beam or implant radiation therapy involving the skeleton. Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org. **Treatment Duration** The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years during a patients' lifetime is not recommended. **Bone Metastases and Skeletal Malignancies** Patients with bone metastases or a history of skeletal malignancies should not be treated with FORTEO. **Metabolic Bone Diseases** Patients with metabolic bone diseases other than osteoporosis should not be treated with FORTEO. **Hypercalcemia and Hypercalcemic Disorders** FORTEO has not been studied in patients with pre-existing hypercalcemia. These patients should not be treated with FORTEO because of the possibility of exacerbating hypercalcemia. Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with FORTEO. **Urolithiasis or Pre-existing Hypercalciuria** In clinical trials, the frequency of urolithiasis was similar in patients treated with FORTEO and placebo. However, FORTEO has not been studied in patients with active urolithiasis. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered. FORTEO should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition. **Orthostatic Hypotension** FORTEO should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur. In short-term clinical pharmacology studies with teriparatide, transient episodes of symptomatic orthostatic hypotension were observed in 5% of patients. Typically, an event began within 4 hours of dosing and spontaneously resolved within a few minutes to a few hours. When transient orthostatic hypotension occurred, it happened within the first several doses, it was relieved by placing the person in a reclining position, and it did not preclude continued treatment. **Drug Interactions** Hypercalcemia may predispose patients to digitalis toxicity. Because FORTEO transiently increases serum calcium, patients receiving digoxin should use FORTEO with caution.

ADVERSE REACTIONS

Clinical Trials Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. *Treatment of Osteoporosis in Men and Postmenopausal Women* The safety of FORTEO in the treatment of osteoporosis in men and postmenopausal women was assessed in two randomized, double-blind, placebo controlled trials of 1382 patients (21% men, 79% women) aged 28 to 86 years (mean 67 years). The median durations of the trials were 11 months for men and 19 months for women, with 691 patients exposed to FORTEO and 691 patients to placebo. All patients received 1000 mg of calcium plus at least 400 IU of vitamin D supplementation per day. The incidence of all cause mortality was 1% in the FORTEO group and 1% in the placebo group. The incidence of serious adverse events was 16% in FORTEO patients and 19% in placebo patients. Early discontinuation due to adverse events occurred in 7% of FORTEO patients and 6% of placebo patients. **Percentage of Patients with Adverse Events Reported by at Least 2% of FORTEO-Treated Patients and in More FORTEO-Treated Patients than Placebo-Treated Patients from the Two Principal Osteoporosis Trials in Women and Men Adverse Events are Shown Without Attribution of Causality(FORTEO, N=691, Placebo, N=691):** *Body as a Whole:* Pain (21.3%, 20.5%), Headache (7.5%, 7.4%), Asthenia (8.7%, 6.8%), Neck Pain (3.0%, 2.7%); *Cardiovascular:* Hypertension (7.1%, 6.8%), Angina Pectoris (2.5%, 1.6%), Syncope (2.6%, 1.4%); *Digestive System:* Nausea (8.5%, 6.7%), Constipation (5.4%, 4.5%), Diarrhea (5.1%, 4.6%), Dyspepsia (5.2%, 4.1%), Vomiting (3.0%, 2.3%), Gastrointestional disorder (2.3%, 2.0%), Tooth disorder (2.0%, 1.3%); *Musculoskeletal:* Arthralgia (10.1%, 8.4%), Leg cramps (2.6%, 1.3%); *Nervous System:* Dizziness (8.0%, 5.4%), Depression (4.1%, 2.7%) Insomnia (4.3%, 3.6%), Vertigo (3.8%, 2.7%); *Respiratory System:* Rhinitis (9.6%, 8.8%), Cough increased (6.4%, 5.5%), Pharyngitis (5.5%, 4.8%), Dyspepsia (3.6%, 2.6%), Pneumonia (3.9%, 3.3%); *Skin and Appendages:* Rash (4.9%, 4.5%), Sweating (2.2%, 1.7%). Immunogenicity In the clinical trial, antibodies that cross-reacted with teriparatide were detected in 3% of women (15/541) receiving FORTEO. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions or allergic reactions among these patients. Antibody formation did not appear to have effects on serum calcium, or on bone mineral density (BMD) response. *Laboratory Findings* **Serum Calcium:** FORTEO transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Serum calcium measured at least 16 hours post-dose was not different from pretreatment levels. In clinical trials, the frequency of at least 1 episode of transient hypercalcemia in the 4 to 6 hours after FORTEO administration was increased from 2% of women and none of the men treated with placebo to 11% of women and 6% of men treated with FORTEO. The number of patients treated with FORTEO whose transient hypercalcemia was verified on consecutive measurements was 3% of women and 1% of men. **Urinary Calcium:** FORTEO increased urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with FORTEO and placebo. **Serum Uric Acid:** FORTEO increased serum uric acid concentrations. In clinical trials, 3% of FORTEO patients had serum uric acid concentrations above the upper limit of normal compared with 1% of placebo patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis. **Renal Function:** No clinically important adverse renal effects were observed in clinical studies. Assessments included creatinine clearance; measurements of blood urea nitrogen (BUN), creatinine, and electrolytes in serum; urine specific gravity and pH; and examination of urine sediment. *Studies in Men and Women with Glucocorticoid-Induced Osteoporosis* The safety of FORTEO in the treatment of men and women with glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with $\geq$ 5mg per day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to FORTEO and 214 patients exposed to oral daily bisphosphonate (active control). All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day. The incidence of all cause mortality was 4% in the FORTEO group and 6% in the active

FORTEO® (teriparatide [rDNA origin] 20 mcg for injection) PA097FSAM01

control group. The incidence of serious adverse events was 21% in FORTEO patients and 18% in active control patients, and included pneumonia (3% FORTEO, 1% active control). Early discontinuation because of adverse events occurred in 15% of FORTEO patients and 12% of active control patients, and included dizziness (2% FORTEO, 0% active control). Adverse events reported at a higher incidence in the FORTEO group and with at least a 2% difference in FORTEO-treated patients compared with active control-treated patients were: nausea (14%, 7%), gastritis (7%, 3%), pneumonia (6%, 3%), dyspnea (6%, 3%), insomnia (5%, 1%), anxiety (4%, 1%), and herpes zoster (3%, 1%), respectively. **Postmarketing Experience:** The following adverse reactions have been identified during postapproval use of FORTEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **Osteosarcoma**: Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to FORTEO use is unclear. Long term osteosarcoma surveillance studies are ongoing. **Hypercalcemia**: Hypercalcemia greater than 13.0 mg/dL has been reported with FORTEO use. Adverse events reported since market introduction that were temporally (but not necessarily causally) related to FORTEO therapy include the following: *Allergic Reactions*: Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria; *Investigations:* Hyperuricemia; *Respiratory System*: Acute dyspnea, chest pain; *Musculoskeletal*: Muscle spasms of the leg or back; *Other*: Injection site reactions including injection site pain, swelling and bruising; oro-facial edema.

USE IN SPECIFIC POPULATIONS

Pregnancy Category C. There are no adequate and well-controlled studies of FORTEO in pregnant women. In animal studies, teriparatide increased skeletal deviations and variations in mouse offspring at doses more than 60 times the equivalent human dose and produced mild growth retardation and reduced motor activity in rat offspring at doses more than 120 times the equivalent human dose. FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In animal studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses 8 to 267 times the human dose. At doses $\geq$ 60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received subcutaneous teriparatide during organogenesis at doses 16 to 540 times the human dose, the fetuses showed no abnormal findings. In a perinatal/postnatal study, pregnant rats received subcutaneous teriparatide from organogenesis through lactation. Mild growth retardation in female offspring at doses $\geq$120 times the human dose (based on surface area, mcg/m2). Mild growth retardation in male offspring and reduced motor activity in both male and female offspring occurred at maternal doses 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively. Exposure multiples were normalized based on body surface area (mcg/m2). Actual animal doses: mice (30 to 1000 mcg/kg/day); rats (30 to 1000 mcg/kg/day). **Nursing Mothers:** It is not known whether teriparatide is excreted in human milk. Because of the potential for tumorigenicity shown for teriparatide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** The safety and efficacy of FORTEO have not been established in any pediatric population. FORTEO should not be prescribed in patients at an increased baseline risk of osteosarcoma which include pediatric and young adult patients with open epiphyses. Therefore, FORTEO is not indicated for use in pediatric or young adult patients with open epiphyses. **Geriatric Use:** Of the patients receiving FORTEO in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving FORTEO in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** No studies have been performed in patients with hepatic impairment. **Renal Impairment:** In 5 patients with severe renal impairment (CrCl<30 mL/min), the AUC and T1/2 of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased.

OVERDOSAGE

Incidents of overdose in humans have not been reported in clinical trials. Teriparatide has been administered in single doses of up to 100 mcg and in repeated doses of up to 60 mcg/day for 6 weeks. The effects of overdose that might be expected include a delayed hypercalcemic effect and risk of orthostatic hypotension. Nausea, vomiting, dizziness, and headache might also occur. In postmarketing spontaneous reports, there have been cases of medication errors in which the entire contents (up to 800 mcg) of the FORTEO delivery device (pen) have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. In some cases, no adverse events occurred as a result of the overdose. No fatalities associated with overdose have been reported. Overdose Management There is no specific antidote for teriparatide. Treatment of suspected overdose should include discontinuation of FORTEO, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration.

DOSAGE FORMS AND STRENGTHS

Multi-dose prefilled delivery device (pen) for subcutaneous injection containing 28 daily doses of 20 mcg.

PATIENT COUNSELING INFORMATION

Patients should read the FDA-approved *Medication Guide* and delivery device (pen) *User Manual* before starting therapy with FORTEO and re-read them each time the prescription is renewed. Patients need to understand and follow the instructions in the FORTEO delivery device *User Manual*. Failure to do so may result in inaccurate dosing.

06/15/2012

PLEASE SEE FULL PRESCRIBING INFORMATION OR WWW.FORTEOHCP.COM FOR ADDITIONAL INFORMATION.

Literature revised: March 21, 2012

Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA
www.forteo.com

PA097FSAM01

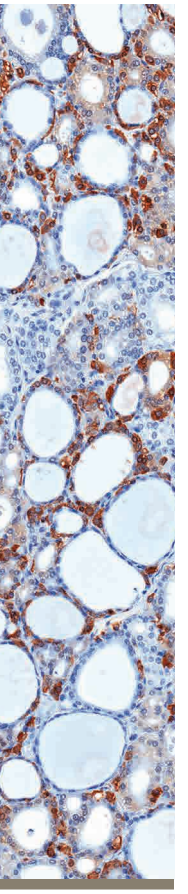
Rx only.

TE HCP BS 28JUN2012 PA097FSAM01

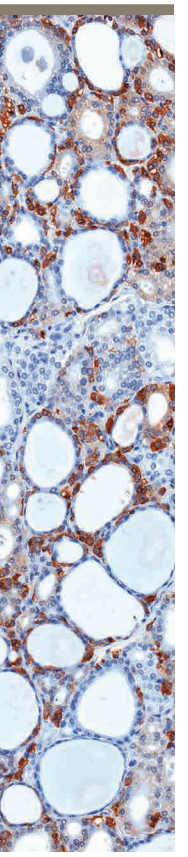
FORTEO® (teriparatide [rDNA origin] 20 mcg for injection) PA097FSAM01

Looking for MOC Points?

NOW AVAILABLE



THE EVALUATION OF THYROID NODULES
Practice Improvement Module (PIM)



The first endocrine-specific Practice Improvement Module (PIM), is a Web-based, self-evaluation tool designed to assist you in evaluating your care of patients with thyroid nodules. Using data from your practice, including patient charts, our PIM allows you to:

1) Evaluate your performance in evaluating thyroid nodules;
2) Compare your performance to ATA and AACE/AME/ETA clinical guidelines through personalized reports;
3) Create and implement an individualized improvement plan; and
4) Reassess the impact of that improvement plan on your practice.

Complete the PIM, either individually or as a part of a practice team, and earn 20 points toward the Self-Evaluation of Practice Performance (Part 4) requirement of Maintenance of Certification (MOC) and claim up to *20 AMA PRA Category 1 Credits*™.

Evaluation of Thyroid Nodules PIM Task Force
Erik Alexander, MD | Carol Greenlee, MD, FACP, FACE | Susan Mandel, MD, MPH

For more information visit endoselfassessment.org.

The Endocrine Society®

Treating Children with TYPE 2 DIABETES

By Eric Seaborg

The alarming increase in type 2 diabetes mellitus (T2DM) among children and adolescents has researchers scrambling for effective treatments. Amid growing evidence that the disease progresses more quickly in children than in adults, some doctors are advocating aggressive drug treatment, and nearly all experts are stressing prevention as a priority to combat the condition.

"The time to intervene with major lifestyle changes is not after diabetes has happened," said Kenneth Copeland, M.D., a pediatric endocrinologist at the University of Oklahoma. "Our focus needs to be on the kids who are at risk before they develop diabetes because effecting a major lifestyle change—enough to change the course of established diabetes in youth—is exceedingly difficult to do."

Copeland is a co-author of the recent study, "Treatment Options for type 2 Diabetes in Adolescents and Youth

(TODAY)," the first major trial to compare the effectiveness of three treatments for T2DM in young people. Results published in June in *The New England Journal of Medicine* showed that none of the treatments controlled glycemic levels in more than 61 percent of patients.

These findings are important, considering the increasing number of American youth with T2DM; from 2001 to 2009, the number of cases rose 21 percent. Some 3,700 children are diagnosed with the condition every year. Twenty years ago, T2DM was almost nonexistent among children, according to Philip Zeitler, M.D., Ph.D., a pediatric endocrinologist at Children's Hospital Colorado in Aurora and professor of pediatrics and clinical science at the University of Colorado School of Medicine. He is another co-author of the TODAY trial.

The incidence of the disease is likely to continue to grow because of the obesity epidemic. Seventeen percent of children between the ages of 2 and 19 are obese. This puts a large segment of the population at risk for developing high blood pressure, high cholesterol, and T2DM. Developing T2DM at a young age also increases the risk of heart disease, retinopathy, and kidney disease.

With such dire medical complications facing the nation's youth, TODAY researchers compared the efficacy of three treatments in maintaining glycemic control for a four-year period. One protocol used metformin, the standard treatment for children with T2DM; another treatment combined metformin with lifestyle intervention; and the third used metformin in combination with the insulin-sensitizing drug rosiglitazone. Failure of control was defined as the glycated hemoglobin, or A1C, level rising to 8 percent or more for six months.

Treatment with metformin alone failed 52 percent of the time, compared with a 47 percent failure rate for metformin plus lifestyle intervention and 39 percent for metformin and rosiglitazone combined. The researchers deemed the addition of lifestyle intervention not significantly different from metformin alone, but the two-drug combination led to a 25 percent improvement.

The 700 patients in the study were ages 10 to 17 years and had had T2DM for less than 2 years at study outset. Although the enrollment criteria specified that they have a body mass index (BMI) at or above the 85th percentile for age and sex, participants exceeded this requirement, with an average BMI in the mid-30s, putting them in the 98th percentile. After being weaned from any other diabetes medications, they were given a metformin dose of up to 1,000 mg twice daily to attain glycemic control, defined as a glycated hemoglobin level less than 8 percent for at least two months.

Because insulin sensitivity declines in all children during puberty and then improves at puberty's end, researchers wanted to test whether aggressive steps to maintain insulin sensitivity might offer patients a safe passage through this period, Zeitler said. But they found that the failure rate of metformin monotherapy was higher in the children than in adults.

Faster Progression of the Disease

One of the reasons for this lack of efficacy could be that T2DM seems to progress more quickly in young people than adults, the researchers said in a presentation at the American Diabetes Association's Scientific Sessions in June. By the end of the TODAY study, nearly one-third of the participants exhibited high blood pressure (compared with 12 percent at the beginning), 10 percent–30 percent had dyslipidemia, about 17 percent exhibited elevated urinary albumin levels (compared with 6 percent at the start), and 13 percent had retinopathy. These numbers represent a much faster progression of the complications of the disease than in adults.

> "It might be good to start with a more aggressive drug treatment approach," said Philip Zeitler, M.D.

In light of these results, "it might be good to start with a more aggressive drug treatment approach," Zeitler said. "The good news is nearly 50 percent of the kids did well on metformin therapy." Fortunately, patients who will respond well to metformin can be identified early on based on their A1C level, he said. "Those kids who had an A1C in the normal range did much better than those kids who got their A1C down but did not get a normal A1C. The kids you can get under control quickly and easily stay that way," Zeitler explained. The median time to a loss of glycemic control was less than a year. If the drug is not going work, physcians will know fairly quickly.

A question arises about where to turn when metformin, the only oral drug approved by the U.S. Food and Drug Administration (FDA) for treatment of children, fails to ameliorate T2DM. Rosiglitazone, used in the study's combination treatment, is not an option; in September

2010 the FDA imposed prescribing restrictions after studies linked it to a higher risk of heart attacks and stroke in adults. (Those concerns arose after the TODAY trial was designed and inaugurated, and the study was allowed to continue with careful monitoring of participants.) Whether other drugs in the thiazolidinedione family, such as pioglitazone, would be salutary without the risks of rosiglitazone requires more research. The fact remains that rosiglitazone still failed for many of these patients.

For now, the "only other well-studied option is combination with insulin," Zeitler said. The loss of insulin secretion was very rapid in the patients who lost glycemic control, and physicians may, therefore, want to move to insulin therapy quickly because the faster progression to comorbidities underscores the need to keep glycemic control in the adolescent age group.

Increase Efforts to Modify Lifestyle

The TODAY researchers and other experts agreed that the failure of the lifestyle modification efforts should not be seen as reason to abandon them, but instead to redouble their efforts to help children adopt healthier habits. The lifestyle intervention treatment model required assigning a behavioral interventionist called a "pal" to each participant. The pals held weekly meetings with the children, advised their families on being role models, chaperoned trips to the gym to exercise, and more.

In general, the results were similar to previous adolescent weight-loss efforts and T2DM development. "Although metformin plus lifestyle intervention significantly decreased percent overweight, this did not translate into sustained glycemic control, as compared with metformin monotherapy," the study said. Zeitler was surprised that the intervention was not able to budge the patients out of their overall environment of excess calories and a sedentary lifestyle enough to make a long-term difference.

"The key message wasn't so much about the need for add-on medications as it was about the need for prevention," said David Allen, M.D.

"The key message from this study wasn't so much about the need for add-on medications as it was about the need for prevention," David Allen, M.D., head of pediatric endocrinology at the University of Wisconsin School of Medicine, told ***Endocrine News.*** "By demonstrating that a large proportion of children were not retrievable by medical intervention, as well as the accelerated rate at which they deteriorated in spite of medical intervention, this study should add a tremendous impetus to focusing our energy on correcting the dangerous mismatch of calories consumed versus energy expended that these children experience." The focus on looking for more drug therapies could be a distraction from the need for prevention, he added.

Allen's call for prevention echoed The Endocrine Society's pediatric obesity clinical treatment guideline, which recommends physicians become much more active as community advocates for healthier school lunches, policies to ban advertising of unhealthful foods to children, and design of neighborhoods that emphasize walking instead of driving. School food programs are an important target because children who participate in the school lunch and breakfast programs consume one-third to one-fifth of their daily recommended caloric intake in school.

The Society's guidelines also note that pediatricians are lax in complying with the American Academy of Pediatricians guidelines on obesity. Clinicians in general should be more proactive in screening for obesity and become involved with the entire family in prescribing dietary, physical activity, and behavioral modifications in pursuit of a healthier lifestyle.

Allen compared the challenge of the obesity epidemic with that of coping with climate change. Both issues, he said, are "so complex, embedded in culture and economics, and intertwined with conflicts between individual freedom and societal health that solutions are difficult to envision." ■

Seaborg is a freelance writer in Charlottesville, Virginia.

ENO LINKS

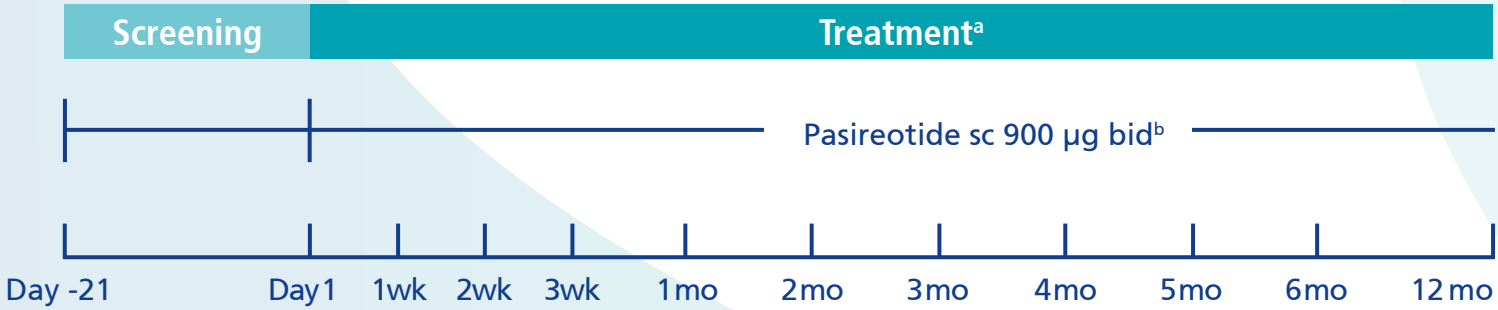
For additional links related to this feature, please visit *Endocrine News Online* at *www.endo-society.org/endo_news.*

CSOM230B2406 (Seascape): Investigating Pasireotide in the Treatment of Active Cushing's Disease

An open-label, multicenter, expanded-access study of pasireotide sc in patients with Cushing's disease

Enrolling now.

US health care professionals: please call (800) 340-6843 for more information. Health care professionals outside the US: please contact Novartis Oncology by visiting www.pasporttrials.com



[a]Patients will be followed at 12-week intervals between Months 6 and 12.
[b]Dose may be reduced to 600 µg bid and 300 µg bid upon sustained disease control, or in the case of tolerability concerns. The starting dose for patients with impaired glucose metabolism will be 600 µg bid.

ELIGIBLE PATIENTS:

- Adult patients with a confirmed diagnosis of Cushing's disease
  - Mean UFC >ULN
  - Morning plasma ACTH within or above the normal range
  - MRI confirmation of pituitary adenoma (≥0.6 cm) or positive inferior petrosal sinus gradient for patients with a microadenoma <0.6 cm
  - Histopathological confirmation of an ACTH-staining adenoma in postsurgical patients
- Patients with de novo Cushing's disease who are nonsurgical candidates

PRIMARY END POINT:

- The proportion of patients with drug-related grade 3 or 4 AEs or serious AEs

PASPORT

The PASPORT Research Program

PASireotide clinical trial PORTfolio: Evaluating pasireotide in patients with pituitary and gastroenteropancreatic neuroendocrine tumors

Pasireotide (SOM230) is an investigational new drug. Efficacy and safety have not been established. There is no guarantee that pasireotide will become commercially available.

Abbreviations: ACTH, adrenocorticotropic hormone; AEs, adverse events; bid, twice a day; MRI, magnetic resonance imaging; SC, subcutaneous; UFC, urinary free cortisol; ULN, upper limit of normal.

ClinicalTrials.gov Identifier: NCT01582061

Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936-1080

6/12
SOM-1045462

Downsizing Supersizes

By Kelly Horvath

If New York City Mayor Michael Bloomberg's proposal to ban sugary drinks larger than 16 ounces passes this month, health advocates hope obese New Yorkers and other Americans as well will get the push they need to go from supersized to healthy portions.

Since the 1970s, American waistlines have been steadily increasing in direct proportion with food portion sizes in restaurants, food stores, and homes. Many food items have increased two to five times in size. Outside the home, almost all food portion sizes have increased, some—such as sodas and cookies—up to eight times. These sizes also exceed U.S. Department of Agriculture (USDA) and U.S. Food and Drug Administration standard portions. Small wonder that 66 percent of Americans are now overweight or obese, compared to 47 percent 30 years ago.

Research supports Bloomberg's reasoning about portion control. Studies show that we tend to consume in units; if the food package is large, we consume the entire amount. We also tend to eat more when served more. "The more food you have in front of you, the more you are likely to eat," George A. Bray, M.D., chief of the Division of Clinical Obesity and Metabolism at Pennington Biomedical Research Center in Baton Rouge and a leading obesity researcher, told ***Endocrine News***. "This will be heightened if the foods are ones that you particularly like."

Outside the home, almost all food portion sizes have increased, some—such as cookies and sodas—up to eight times.

The psychology at work here contributes to overconsumption; people often don't realize they are eating more and they don't necessarily feel fuller. In a 2003 "bottomless bowl" study, 54 participants ate soup from either a normal bowl or a bowl rigged to inconspicuously and automatically refill. The refilling bowl subjects ate a whopping 73 percent more than those with the normal bowl. The researchers concluded that a large portion size sends a subliminal message to our brains that this is the accepted norm, making it appropriate, even expected, for us to consume that amount. Such visual cues also tend to reduce our reliance on our own self-monitoring systems. Importantly, this psychological mechanism affects most people, whether obese or not.

Knowing that our consumption patterns have a distinctly psychological nature in addition to the physiologic drive, has an upside. We can "trick" ourselves into eating less almost as easily as we succumb to overconsuming. Research presented in July at the Annual Meeting of the Society for the Study of Ingestive Behavior shows that cutting food into smaller pieces can reduce intake by creating the appearance of more food, which induces more rapid and increased satiety than single portions.

At the Hormone Health Network (*www.hormone.org*), health care providers offer a list of practical strategies for losing weight. A common theme among the items listed is changing what and how we eat, including eating less. Eating more slowly, for example, helps us eat less because it takes 20 minutes for the full signal from gut hormones, such as glucagon-like peptide-1 (GLP-1), cholecystokinin (CKK), and pancreatic polypeptide (PPY) among others, to reach the satiety center in the hypothalamus. Slowing down allows time for these hormones to do their work before those last forkfuls are taken.

In addition, said Caroline M. Apovian, M.D., director of the Nutrition and Weight Management Center at Boston Medical Center and professor of medicine at Boston University School of Medicine, "Eating slowly can increase the response of PYY and GLP-1 as compared to eating fast." It can also reduce levels of the so-called "hunger hormone" ghrelin. "Compared with 15 chews, 40 chews results in lower caloric intake, lower postprandial ghrelin concentrations, and higher GLP-1 and CCK concentrations," Apovian explained.

Other tips include getting adequate support, such as in a weight loss group, and keeping a food diary, both of which involve controlling portion size and, in turn, eating less.

Continued on page 38

Hormone Health NETWORK
Keep your body in balance

Proven Weight Loss Methods

WHAT CAN WEIGHT LOSS DO FOR YOU?

Losing weight can improve your health in a number of ways. It can lower your risk for type 2 diabetes, high blood pressure, stroke, and heart disease. Losing weight can also help you feel better.

There are proven ways to lose weight. You can find what works for you. Research has proven that **changing eating habits** and **increasing physical activity (exercising)** help people lose weight. Other strategies also can help. For example, you might find that rewarding yourself for exercising every day helps keep you motivated. Choose a non-food reward.

DID YOU KNOW?

Once you start eating, it takes 20 minutes for digestive hormones to tell your brain that you are full. For many people, eating slowly can help them eat less and still feel full.

THE DIABETES PREVENTION PROGRAM (DPP)

In this large study, researchers looked at what worked best for preventing type 2 diabetes. All of the people in the study were overweight. Results showed that people who lost a modest amount of weight through diet and exercise sharply lowered their risk for developing type 2 diabetes.

WHAT CHANGES IN EATING HABITS CAN HELP YOU LOSE WEIGHT?

Most people need to change **what** they eat and **how much** they eat in order to lose weight. Your health care provider can help you decide how to change your eating habits. Choices include

- Eating fewer calories than usual. This strategy helped people in the DPP study lose weight.
- Eating a low-carbohydrate diet.
- Eating less fat. People in the DPP study cut down on fat.
- Choosing more foods that aren't high in calories and low in nutrients. Eating foods such as non-starchy vegetables, some fruits, and broth soups help you feel full, even though you're eating fewer calories.
- Using meal replacements, such as shakes or bars. They control serving sizes, eliminate decisions about food choices, and are easy to keep on hand.

Other healthy diets, such as the low-sodium DASH diet, also can help. The DASH diet is designed to lower blood pressure but you can also use it to lose weight. It includes fruits, vegetables, whole grain foods, low-fat or non-fat dairy foods, nuts, seeds, and lean meats, poultry, and fish.

WHAT KINDS OF EXERCISE CAN HELP YOU LOSE WEIGHT?

In general, many kinds of exercise will help you lose weight, especially when you exercise daily or most days of the week. Walking briskly (for about 30 minutes a day) is a good way to exercise. To help you stick with your plan, you should choose a type of exercise you enjoy. People in the DPP study exercised a total of 150 minutes each week, or about 20 minutes each day.

However, exercise alone (without limiting calories) usually isn't enough to cause weight loss. But exercise plays an important part in helping people who have lost weight keep that weight off.

WHAT OTHER STRATEGIES CAN HELP YOU LOSE WEIGHT?

These actions also help:

- Weighing yourself every day
- Keeping daily food records of everything you eat and drink
- Eating breakfast every day
- Keeping the same eating patterns weekdays and weekends

Many people find that having support from other people helps them lose weight. You can get support by attending weekly group meetings or from weekly visits with a health care provider, such a registered dietitian.

CAN MEDICINES HELP WITH WEIGHT LOSS?

Studies show that anti-obesity medicines can help people lose more weight when combined with lifestyle changes (diet, exercise, and behavior change) than they can with lifestyle changes alone.

IS WEIGHT LOSS HARDER FOR PEOPLE WITH DIABETES?

Some studies show that weight loss is harder for people who have diabetes than for people who don't. But you can still lose weight, even if you have diabetes.

WHAT SHOULD YOU DO IF YOU WANT TO LOSE WEIGHT?

Tell your doctor, dietitian, or diabetes educator that you'd like to lose weight. Work with your provider to make a plan. Make sure you've included a way to change what you eat **and** a way to exercise. To get ready, choose a date to start. Decide how you'll reward yourself for doing what you've said you'll do.

Most importantly, focus on what you **can** control. You can control what you eat and whether you go for a walk. But you can't control how fast you lose weight. If you find that your plan isn't working, it doesn't mean you've failed. Instead, it means you should change your plan. Find a plan that works for you.

Questions to ask your doctor

- **What is a healthy weight for me?**
- **Can you recommend a diet plan for me?**
- **Should I see a registered dietitian?**
- **Should I see a diabetes educator?**
- **What kind of exercise is best for me?**
- **How long will it take to reach my weight goal?**

RESOURCES

- Find-an-Endocrinologist: *www.hormone.org* or call *1-800-HORMONE (1-800-467-6663)*
- Find a registered dietitian (Academy of Nutrition and Dietetics): *www.eatright.org/programs/rdfinder*
- Find a diabetes educator (American Association of Diabetes Educators): *www.diabeteseducator.org/DiabetesEducation/Find.html*
- Hormone Health Network information about hormones and obesity: *www.hormone.org/Other/upload/hormones-and-obesity-bilingual-042010.pdf*
- Mayo Clinic: *www.mayoclinic.com/health/weight-loss/NU00616*
- National Institutes of Health:
  - Weight-control Information Network: *www.win.niddk.nih.gov* or call (toll-free) *1-877-946-4627*
  - Diabetes Prevention Program (DPP): *diabetes.niddk.nih.gov/dm/pubs/preventionprogram*
  - DASH Diet: *www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf*

EDITORS

Caroline M. Apovian, MD
Judith Korner, MD, PhD

July 2012

The Hormone Health Network offers free, online resources based on the most advanced clinical and scientific knowledge from The Endocrine Society (*www.endo-society.org*). The Network's goal is to move patients from educated to engaged, from informed to active partners in their health care. This fact sheet is also available in Spanish at *www.hormone.org/Spanish*.

Hormone Health NETWORK
Keep your body in balance

www.hormone.org

Continued from page 36

Practice Resources

And, we can benefit from plain and simple education as well to remedy the all-too-common disconnect between portion size and serving size. Using vessels that show measurements is becoming a popular strategy to reduce intake. Measuring serving sizes and *seeing* what a cup, for example, really contains is an eye-opening experience for many people who previously estimated the capacity of a cup to be considerably larger.

The Portion Plate® demarcates a plate or placemat into appropriate serving sizes and pictorially compares serving sizes in many food categories to everyday items to facilitate remembering these sizes (for instance, 1.5 ounces of hard cheese = 3 dice.) *Web*MD offers downloadable template versions of a Portion Size Plate® in various sizes that can be carried in wallets or stuck to the front of the fridge. The USDA also provides similar services as part of their MyPlate program (*www.choosemyplate.gov/*).

A similar strategy involves repackaging foods into smaller-volume containers, as Bloomberg seeks to do. If the supersize soda ban proposal becomes law and Big Apple residents shrink their drinks and their waistlines, it will be an inspiration for people across the nation to mind their plates. ■

Hovarth is a free-lance writer and editor in Baltimore.

The Society Supports NIH's Workforce Diversity Effort

By Katie Moore, Ph.D.

As part of ongoing efforts to support a diverse and productive biomedical research workforce, The Endocrine Society recently contributed to a National Institutes of Health (NIH) initiative to increase support for underrepresented minorities in the biomedical research workforce.

NIH sought feedback from the scientific community after an August 2011 *Science* article titled, "Race, Ethnicity, and NIH Research Awards" raised concerns about opportunities for minorities. The article, which presents data correlating NIH R01 applicants' race or ethnicity and the probability of receiving an award, shows that underrepresented minorities—including African Americans, Hispanics, and Native Americans—with doctorates in science and engineering make up less than 9 percent of occupations in these fields. Compared to their white colleagues, Asian scientists are 4 percentage points less likely to receive R01 funding from NIH, the article said. For African-American scientists, the probability of receiving funding is even less likely, falling at 13 percentage points below whites (see *http://www.sciencemag.org/content/333/6045/1015*).

In response to the article the NIH Advisory Committee to the Director (ACD) created a working group to examine diversity in the biomedical research workforce. Acting on the working group's request, the Society sent a letter recommending specific actions that NIH can take to improve the participation and success of minorities in the field. Focusing on concepts that could enhance diversity throughout the biomedical research workforce pipeline, the Society suggested ways to bolster the success of minority grant applicants, including funding support for mentoring and career development programs. The Society also advocated for the development of a tracking system to monitor the progress of trainees throughout their careers. These recommendations are included in the working group's final report to NIH. In addition, the report encouraged NIH to establish an Office of Diversity and a new ACD working group to further examine methods for reducing disparities in research awards.

The Society has long been a proponent of programs to increase opportunities for minorities in the biomedical research workforce and maintains a broad array of career development activities and programs specifically for underrepresented groups. Student outreach and professional development programs, mentoring and networking activities, and comprehensive summer research training programs are a few examples of the Society's diversity portfolio.

A second NIH ACD working group was charged with recommending actions NIH could take to enhance training for all biomedical researchers—not just underrepresented minorities—while reducing overall training time. The Society's response to this working group highlighted the importance of recognizing scientific work outside of academia. The Society encouraged NIH to assist institutions in providing training and career development opportunities to prepare trainees for a variety of careers, specifically recommending the inclusion of training related to business management, mentoring, and teaching science.

These recommendations were included in the working group's final report to NIH, along with calls for the development of a more permanent research staffing model, for increases in the number of early career awards that NIH issues, and for limits on the amount of investigator, student, and postdoc salaries that can be charged to grants. The group also proposed that NIH undertake a closer examination of physician-scientist training.

The Society will continue to work with its members and the scientific community to advocate for equity in biomedical research and to develop programs and awards that support a sustainable, diverse biomedical research workforce. ■

Moore is the manager of science policy at The Endocrine Society.

BYDUREON:
the first and only once-weekly treatment for type 2 diabetes

To learn more about BYDUREON through our Professional Education Programs, please visit www.BYDUREONHCP.com/ProfEd

Indication and Usage

BYDUREON is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

- Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, prescribe only to patients for whom potential benefits are considered to outweigh potential risk.
- Not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
- Not a substitute for insulin, should not be used in patients with type 1 diabetes or diabetic ketoacidosis, and cannot be recommended for use with insulin.
- BYDUREON and BYETTA® (exenatide) injection both contain the same active ingredient, exenatide, and should not be used together.
- Exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, based on postmarketing data. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYDUREON; consider other antidiabetic therapies for these patients.

BOXED WARNING: RISK OF THYROID C-CELL TUMORS

Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether BYDUREON causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with BYDUREON. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

For additional safety profile and other important prescribing considerations, please see the adjacent pages for Brief Summary of Prescribing Information.

Once-weekly

BYDUREON®

exenatide extended-release for injectable suspension

AMYLIN

BYDUREON® (exenatide extended-release for injectable suspension)

Initial U.S. Approval: 2012

Brief Summary: For complete details, please see full Prescribing Information

WARNING: RISK OF THYROID C-CELL TUMORS

Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether BYDUREON causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with BYDUREON. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see *Contraindications* and *Warnings and Precautions*].

INDICATIONS AND USAGE

BYDUREON is an extended-release formulation of exenatide, administered as an injection once every seven days (weekly).

Type 2 Diabetes Mellitus

BYDUREON is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

Important Limitations of Use

Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, prescribe BYDUREON only to patients for whom the potential benefits are considered to outweigh the potential risk.

BYDUREON is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

BYDUREON is not a substitute for insulin. BYDUREON should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

The concurrent use of BYDUREON with insulin has not been studied and cannot be recommended.

BYDUREON and BYETTA® (exenatide) injection both contain the same active ingredient, exenatide, and therefore should not be used together.

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. BYDUREON has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYDUREON. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

CONTRAINDICATIONS

Medullary Thyroid Carcinoma

BYDUREON is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Hypersensitivity

BYDUREON is contraindicated in patients with a prior serious hypersensitivity reaction to exenatide or to any of the product components.

WARNINGS AND PRECAUTIONS

Risk of Thyroid C-cell Tumors

In both genders of rats, exenatide extended-release caused a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures compared to controls. A statistically significant increase in malignant thyroid C-cell carcinomas was observed in female rats receiving exenatide extended-release at 25-times clinical exposure compared to controls and higher incidences were noted in males above controls in all treated groups at ≥2-times clinical exposure. The potential of exenatide extended-release to induce C-cell tumors in mice has not been evaluated. Other GLP-1 receptor agonists have also induced thyroid C-cell adenomas and carcinomas in male and female mice and rats at clinically relevant exposures. It is unknown whether BYDUREON will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies. Serum calcitonin was not assessed in the clinical trials supporting the approval of BYDUREON [see *Boxed Warning*].

Serum calcitonin is a biological marker of MTC. Patients with MTC usually have calcitonin values >50 ng/L. Patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation. Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with BYDUREON. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin testing for MTC and a high background incidence of thyroid disease. If serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

Acute Pancreatitis

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYDUREON, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, BYDUREON should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYDUREON should not be restarted. Consider antidiabetic therapies other than BYDUREON in patients with a history of pancreatitis.

Hypoglycemia

The risk of hypoglycemia is increased when exenatide is used in combination with a sulfonylurea. Therefore, patients receiving BYDUREON and a sulfonylurea may require a lower dose of the sulfonylurea to minimize the risk of hypoglycemia. It is also possible that the use of BYDUREON with other glucose-independent insulin secretagogues (e.g. meglitinides) could increase the risk of hypoglycemia.

Renal Impairment

BYDUREON should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation. In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well tolerated due to gastrointestinal side effects. Because BYDUREON may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Use BYDUREON with caution in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min). BYDUREON has not been studied in patients with end-stage renal disease or severe renal impairment.

There have been postmarketing reports of altered renal function with exenatide, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Some of these events occurred in patients receiving one or more pharmacologic agents known to affect renal function or hydration status such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including exenatide. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

Gastrointestinal Disease

Exenatide has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Because exenatide is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhea, the use of BYDUREON is not recommended in patients with severe gastrointestinal disease.

Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYDUREON. Anti-exenatide antibodies were measured in all BYDUREON-treated patients in the five comparator-controlled 24-30 week studies of BYDUREON. In 6% of BYDUREON-treated patients, antibody formation was associated with an attenuated glycemic response. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered.

Hypersensitivity

There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with exenatide. If a hypersensitivity reaction occurs, the patient should discontinue BYDUREON and other suspect medications and promptly seek medical advice.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYDUREON or any other antidiabetic drug.

ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of BYDUREON was assessed in five comparator-controlled trials, in patients who entered the studies not achieving adequate glycemic control on their current therapy. In a double-blind 26 week trial, patients on diet and exercise were treated with BYDUREON 2 mg once every seven days (weekly), sitagliptin 100 mg daily, pioglitazone 45 mg daily, or metformin 2000 mg daily. In a double-blind 26 week trial, patients on metformin were treated with BYDUREON 2 mg once every seven days (weekly), sitagliptin 100 mg daily, or pioglitazone 45 mg daily. In an open-label 26 week trial, patients on metformin or metformin plus sulfonylurea were treated with BYDUREON 2 mg once every seven days (weekly) or optimized insulin glargine. In two open-label 24 to 30 week studies, patients on diet and exercise or metformin, a sulfonylurea, a thiazolidinedione or combination of oral agents were treated with BYDUREON 2 mg once every seven days (weekly) or BYETTA 10 mcg twice daily.

Withdrawals

The incidence of withdrawal due to adverse events was 4.9% (N=45) for BYDUREON-treated patients, 4.9% (N=13) for BYETTA-treated patients and 2.0% (N=23) for other comparator-treated patients in the five comparator-controlled 24-30 week trials. The most common adverse reactions leading to withdrawal for BYDUREON-treated patients were nausea 0.5% (N=5) versus 1.5% (N=4) for BYETTA and 0.3% (N=3) for other comparators, injection site nodule 0.5% (N=5) versus 0.0% for BYETTA and 0.0% for other comparators, diarrhea 0.3% (N=3) versus 0.4% (N=1) for BYETTA and 0.3% (N=3) for other comparators, injection site reaction 0.2% (N=2) versus 0.0% for BYETTA and 0.0% for other comparators and headache 0.2% (N=2) versus 0.0% for BYETTA and 0.0% for other comparators.

Hypoglycemia

The incidence (% of subjects) and rate (episodes/subject year) of minor hypoglycemia in the five comparator-controlled 24-30 week trials of BYDUREON used as monotherapy or as add-on to metformin, a sulfonylurea, a thiazolidinedione or combination of these oral antidiabetic agents were as follows. In these trials, an event was classified as minor hypoglycemia if there were symptoms of hypoglycemia with a concomitant glucose <54 mg/dL and the patient was able to self-treat.

In the 26-week monotherapy trial: BYDUREON, 2.0% (0.05) [N = 248]; sitagliptin, 0.0% (0.00) [N = 163]; pioglitazone, 0.0% (0.00) [N = 163]; and metformin, 0.0% (0.00) [N = 246]. In the 26-week add-on to metformin trial: BYDUREON, 1.3% (0.03) [N = 160]; sitagliptin, 3.0% (0.12) [N = 166]; and pioglitazone, 1.2% (0.03) [N = 165]. In the 26-week add-on to metformin or metformin plus sulfonylurea trial: with concomitant sulfonylurea, BYDUREON, 20.0% (1.11) [N = 70] and titrated insulin glargine, 43.9% (2.87) [N = 66]; without concomitant sulfonylurea, BYDUREON, 3.7% (0.11) [N =163] and titrated insulin glargine, 19.1% (0.64) [N = 157]. Insulin glargine was dosed to a target fasting glucose concentration of 72 to 100 mg/dL. The mean dose of insulin glargine was 10 Units/day at baseline and 31 Units/day at endpoint.

In the 24-30 week trials of BYDUREON as monotherapy or add-on to metformin, sulfonylurea, thiazolidinedione or any combination of these oral agents, incidence (% of subjects) and rate (episodes/subject year) of minor hypoglycemia were as follows. In the 24-week trial: with concomitant sulfonylurea, BYDUREON, 12.5% (0.72) [N = 40] and BYETTA, 11.8% (0.31) [N = 34]; without concomitant sulfonylurea, BYDUREON, 0.0% (0.00) [N = 89] and BYETTA, 0.0% (0.00) [N = 89]. In the 30-week trial: with concomitant sulfonylurea, BYDUREON, 14.5% (0.55) [N =55] and BYETTA, 15.4% (0.37) [N = 52]; without concomitant sulfonylurea, BYDUREON, 0.0% (0.00) [N = 93] and BYETTA, 1.1% (0.02) [N = 93].

There were no reported events of major hypoglycemia in these five comparator-controlled 24-30 week trials. Major hypoglycemia was defined as loss of consciousness, seizure or coma (or other mental status change consistent with neuroglycopenia in the judgment of the investigator or physician) which resolved after administration of glucagon or glucose or required third party assistance to resolve because of severe impairment in consciousness or behavior. Patients were to have a concomitant glucose <54 mg/dL.

Immunogenicity

Anti-exenatide antibodies were measured at prespecified intervals (4-14 weeks) in all BYDUREON-treated patients (N=918) in the five comparator-controlled studies of BYDUREON. In these five trials, 452 BYDUREON-treated patients (49%) had low titer antibodies (≤125) to exenatide at any time during the trials and 405 BYDUREON-treated patients (45%) had low titer antibodies to exenatide at study endpoint (24-30 weeks). The level of glycemic control in these patients was generally comparable to that observed in the 379 BYDUREON-treated patients (43%) without antibody titers. An additional 107 BYDUREON-treated patients (12%) had higher titer antibodies at endpoint. Of these patients, 50 (6% overall) had an attenuated glycemic response to BYDUREON (<0.7% reduction in HbA_{1c}); the remaining 57 (6% overall) had a glycemic response comparable to that of patients without antibodies. In the 30-week trial in which anti-exenatide antibody assessments were performed at baseline and at 4-week intervals from week 6 to week 30, the mean anti-exenatide antibody titer in the BYDUREON-treated patients peaked at week 6 then declined by 56% from this peak by week 30.

DID YOU KNOW?

You can post your CV, post an open position or look for your next career opportunity in the targeted **EndoCareers™** site.

www.endocareers.org

THE ENDOCRINE SOCIETY®

NEW! Endo Pubs App

The Endocrine Society's Full-Text Multi Journal App

Available for both iOS and Android platforms

Now you can read your Endocrine Society journals anywhere, anytime with the Endo Pubs App. Get instant access to these features and many more:

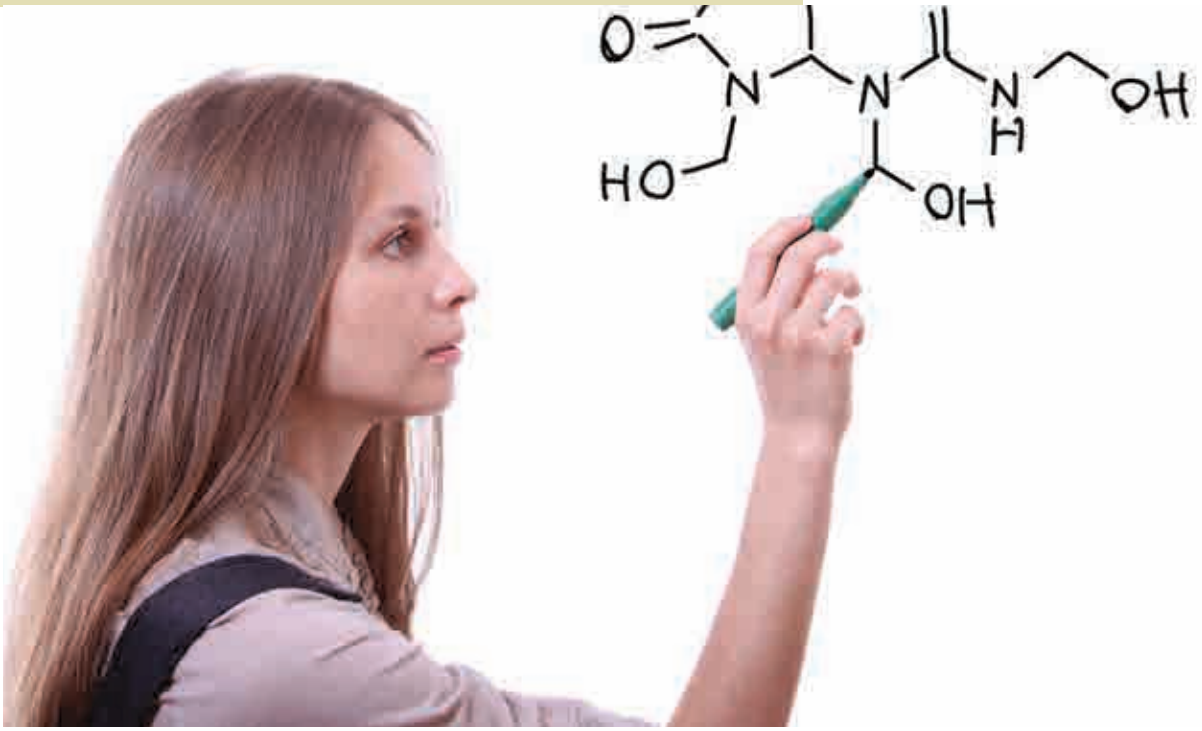
- Download, search, view, and save abstracts and full-text articles
- Full-text search on abstracts, title, authors, and keywords
- Social sharing: Facebook and Twitter posts
- Access supplemental material

Available at Apple App Store and Android Market.

THE ENDOCRINE SOCIETY®

www.endo-society.org

TRAINEE CORNER



Teaching Experience Can Expand Your Career Options

By Robert K. Dearth

For many doctoral candidates and postdoctoral trainees, securing a tenure-track faculty position at a college or university is essential. The reality is that you will be competing for an ever-decreasing number of faculty positions. Having prior college teaching experience is one way to gain a competitive advantage. Yet acquiring teaching experience is not always accommodated in doctoral and postdoctoral programs where the priority must be given to mastering the skill-set needed to become a successful independent researcher. After all, that is why you spend countless hours in the lab, living off caffeine or energy drinks. College teaching experience, however, can set you apart and expand your career options.

At many, if not most, post-secondary institutions, entry-level tenure-track assistant professor positions expect faculty to teach, do research, and engage in service activities. This is especially true in the current climate of tight budgets and reduced state funding for public colleges and universities. Effective teaching may also provide an added level of career security in the competitive environment of acquiring external research funding.

Data from the U.S. Department of Education Integrated Postsecondary Education Data System (IPEDS; *www.nces.ed.gov/ipeds/datacenter*) show that of the 4,371 new tenure track hires from 2006–2010, 75 percent (3,285) of the new hires were at "teaching universities" with 1,086 new tenure track hires at "research universities." At "research universities," your research experience and success will make you a desirable hire. At "teaching universities," research may still be an important component, but a strong emphasis will be placed on your ability to teach. Many of these universities will not give serious attention to candidates without prior college teaching experience. Clearly, adding teaching experience to your basic science training will make you more competitive in your quest for a faculty position.

As a science trainee your primary focus should remain on science and research. Acquiring teaching experience can be accomplished at the same time. Teaching should serve to strengthen your training portfolio and create more career opportunities. Teaching can also provide you with insight and knowledge that can advance your research.

Attend ENDO's Trainee Day

The most opportune time to gain valuable teaching experience is probably during your graduate training. One of the easiest ways to learn how teaching can impact your career is to attend the Endocrine Trainee Day at The Endocrine Society's Annual Meeting. ENDO's Trainee Day provides valuable informational sessions about teaching and research in academia. For individuals who are in graduate studies at undergraduate degree–granting universities, being a teaching assistant (TA) for a defined length of time (at least a semester) is a great way to gain experience and might be a requirement for the degree. Being a TA can also help support your graduate studies.

For individuals in a graduate pro-

gram at institutions that don't have an undergraduate program (such as medical schools and health science schools) getting in front of the class can be a little more difficult. My best advice, if teaching is not a part of your program, is to talk to your mentor and other professors about your desire to assist in a course, perhaps as a guest lecturer. Getting some level of classroom experience can help you decide if this is a desirable aspect of your training. Furthermore, some undergraduate universities and colleges will hire recently granted Ph.D.s with little or no postdoctoral training if they have had teaching experience as a graduate student. Understand that if you do accept a primary teaching position, with little or no research requirement, you must be sure that you want a career with a focus on teaching. The longer you are away from the bench, the more difficult it is to transition back into research.

It becomes increasingly difficult to gain valuable teaching experience as you progress in your training. If you are looking for a postdoctoral position and have decided that you want some level of classroom teaching, you should try to get teaching experience before accepting the position. Being honest and upfront with your potential mentor will be beneficial to both of you.

Adjunct Teaching Opportunities

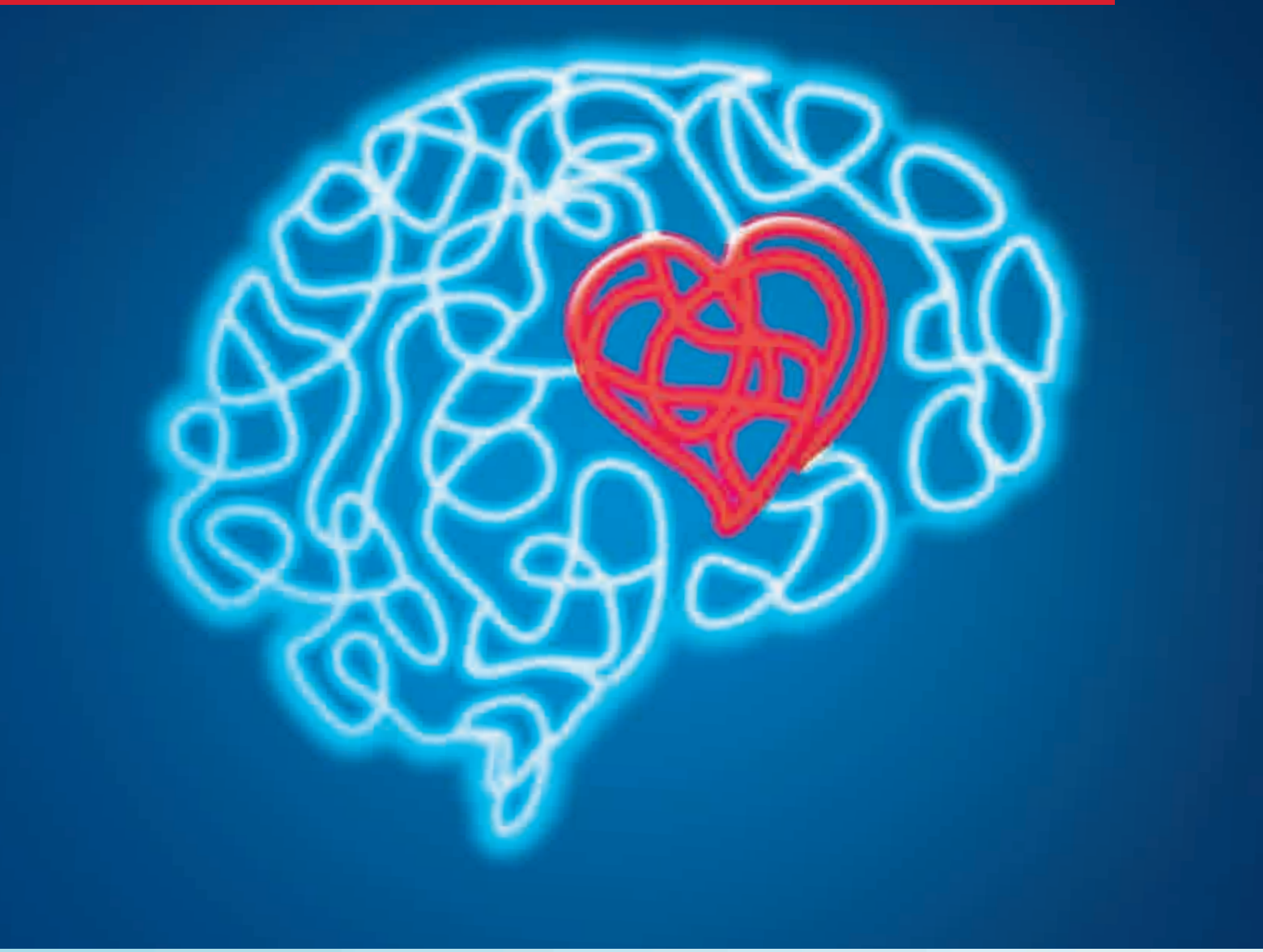
Several institutions now offer postdoctoral training programs specifically for basic scientists that include classroom teaching. These programs include adjunct teaching positions at area universities and community colleges and are the best training program for individuals wishing to obtain a tenure track position that requires a heavy teaching load.

If you are a current postdoctoral fellow and chose the position based on the research opportunity, remember your mentor is there to facilitate your desire to become a researcher and it is not his or her responsibility, nor the institution's, to help you gain teaching experience. My advice is first to establish yourself in the lab, stay committed to your research, mentor students, continue to publish, and seek funding. Once you are comfortable with your research progress, talk to your mentor about your desire to take on a teaching load and assure him it will not detract from your responsibilities in the lab.

Overall, adding teaching to your training portfolio will make you a more rounded potential hire. Better yet, you may actually discover that one of your biggest contributions to science is teaching future scientists. ■

Robert K. Dearth, Ph.D., is an assistant professor of biology at the University of Texas-Pan American in Edinburg, Texas.

CYCLOSET®: First-in-class therapy for type 2 diabetes in adults



Important Safety Information

CYCLOSET is contraindicated in patients with hypersensitivity to ergot-related drugs, bromocriptine, or any of the excipients in CYCLOSET. Do not use in patients with syncopal migraines. It may precipitate hypotension. Do not use in nursing women. It may inhibit lactation. There are postmarketing reports of stroke in this patient population.

CYCLOSET can cause orthostatic hypotension and syncope, particularly upon initiation or dose escalation. Use with caution in patients taking antihypertensive medications. CYCLOSET may exacerbate psychotic disorders or reduce the effectiveness of drugs that treat psychosis. Use in patients with severe psychotic disorders is not recommended. CYCLOSET may cause somnolence. Advise patients not to operate heavy machinery if symptoms of somnolence occur. Concomitant use with dopamine antagonists such as neuroleptic agents is not recommended.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with CYCLOSET or any other antidiabetic drug. CYCLOSET does not increase the risk of macrovascular events.

In controlled clinical trials, adverse reactions reported in ≥5% of patients treated with CYCLOSET, and reported more commonly than in patients treated with placebo, included nausea, fatigue, dizziness, vomiting, and headache.

Safety and effectiveness have not been established in pediatric patients.

CYCLOSET is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

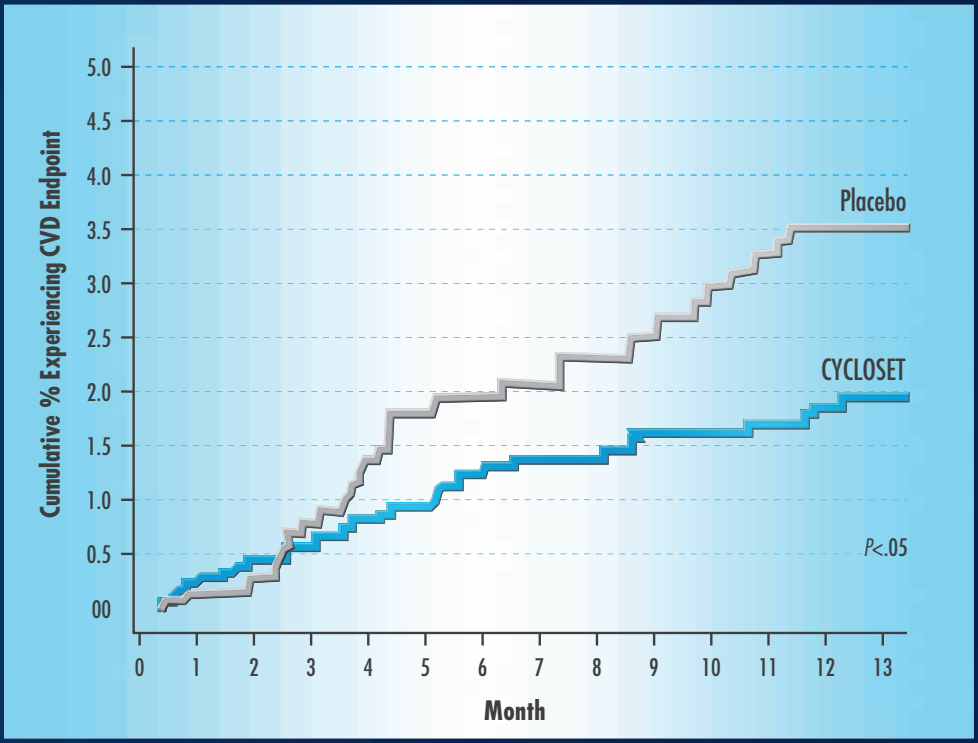
Please see adjacent Brief Summary of Prescribing Information.
Full Prescribing Information available at www.cycloset.com.

Improved glycemic control*

- **0.6% to 0.9% A1C reductions** seen when added to other oral agents†

Demonstrated CV safety profile‡

- 42% relative risk reduction for composite CVD endpoint§ vs placebo. Hazard ratio=0.58 (95% CI, 0.35-0.96); *P*<.05



CYCLOSET is a dopamine receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

*Preclinical studies suggest that appropriately timed daily administration of bromocriptine, the active ingredient of CYCLOSET, may positively affect hypothalamic activities associated with insulin resistance and glucose intolerance. In clinical studies, morning administration of CYCLOSET improved glycemic control in adults with type 2 diabetes without increasing plasma insulin concentrations. The precise mechanism of action of CYCLOSET is unknown.

†Findings from a 52-week, randomized controlled trial to evaluate the safety and efficacy of CYCLOSET. Data shown are from a prospective 24-week assessment for treatment differences in the change from baseline to Week 24 in A1C among subjects with a baseline A1C ≥7.5% (average baseline A1C of 8.3%), taking 1 or 2 OADs, and completing 24 weeks of therapy. In the intent-to-treat, LOCF population, A1C reductions in the CYCLOSET arm vs placebo were 0.5% for patients failing any OAD, 0.5% for patients failing metformin ± OAD, 0.5% for patients failing metformin + SU ± OAD, and 0.6% for patients failing TZD ± OAD.

‡In a 52-week, randomized clinical trial of 3,070 patients, CYCLOSET was not associated with an increased risk for adverse cardiovascular events.

§Prespecified composite CVD endpoint of time to first MI, stroke, coronary revascularization, hospitalization for unstable angina, or hospitalization for CHF.

Reference: Data on File. Santarus, Inc.

CV=cardiovascular; CVD=cardiovascular disease; OAD=oral antidiabetic therapy; LOCF=last observation carried forward; SU=sulfonylurea; TZD=thiazolidinedione; MI=myocardial infarction; CHF=congestive heart failure.

Manufactured for: VeroScience, LLC, Tiverton, RI.
Distributed and Marketed by: Santarus, Inc., San Diego, CA.
Please visit www.cycloset.com for more information.

 1-CYC12172 July 2012 Printed in the USA

SANTARUS, INC.®

CYCLOSET®
bromocriptine mesylate tablets

CYCLOSET®
bromocriptine mesylate tablets

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE
1.1 Type 2 Diabetes Mellitus
CYCLOSET is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

1.2 Important Limitations of Use
- CYCLOSET should not be used to treat type 1 diabetes or diabetic ketoacidosis.
- Limited efficacy data in combination with thiazolidinediones
- Efficacy has not been confirmed in combination with insulin.

4 CONTRAINDICATIONS
CYCLOSET is contraindicated in
- Patients with known hypersensitivity to bromocriptine, ergot-related drugs, or any of the excipients in CYCLOSET.
- Patients with syncopal migraine. Bromocriptine increases the likelihood of a hypotensive episode among patients with syncopal migraine. Loss of consciousness during a migraine may reflect dopamine receptor hypersensitivity. CYCLOSET is a dopamine receptor agonist, and may, therefore, potentiate the risk for syncope in these patients.
- Women who are nursing their children. CYCLOSET may inhibit lactation. There are postmarketing reports of stroke in this patient population although causality has not been proven *[See Nursing Mothers (8.3)]*.

5 WARNINGS AND PRECAUTIONS
5.1 Hypotension: Hypotension, including orthostatic hypotension, can occur, particularly upon initiation of CYCLOSET therapy and with dose escalation. In a 52-week, randomized clinical trial of 3070 patients, hypotension was reported in 2.2% of patients randomized to CYCLOSET compared to 0.8% of patients randomized to placebo. Among CYCLOSET-treated patients reporting symptomatic hypotension, 98% were on at least one blood pressure medication compared to 73% on such medication in the total study population. In this trial, six CYCLOSET-treated patients (0.3%) reported an adverse event of orthostatic hypotension compared to 2 (0.2%) placebo-treated patients. All six patients were taking anti-hypertensive medications. Hypotension can result in syncope. In this trial, syncope due to any cause was reported in 1.6% of CYCLOSET-treated patients and 0.7% of placebo-treated patients *[See Adverse Reactions (6.1)]*. As a precaution, assessment of orthostatic vital signs is recommended prior to initiation of CYCLOSET and periodically thereafter. During early treatment with CYCLOSET, patients should be advised to make slow postural changes and to avoid situations that could lead to serious injury if syncope was to occur. Use caution in patients taking anti-hypertensive medications.

5.2 Psychotic Disorders: In patients with severe psychotic disorders, treatment with a dopamine receptor agonist such as CYCLOSET may exacerbate the disorder or may diminish the effectiveness of drugs used to treat the disorder. Therefore, the use of CYCLOSET in patients with severe psychotic disorders is not recommended.

5.3 Somnolence: CYCLOSET may cause somnolence. In a 52-week, randomized clinical trial, 4.3% of CYCLOSET treated-patients and 1.3% of placebo-treated patients reported somnolence as an adverse event. None of these events were reported as serious and the majority of patients reported resolution of somnolence over time. Patients should be made aware of this potential side effect, particularly when initiating therapy with CYCLOSET. Patients experiencing somnolence should refrain from driving or operating heavy machinery.

5.4 Interaction with Dopamine Receptor Antagonists: Dopamine receptor antagonists, including neuroleptic agents that have dopamine D2 receptor antagonist properties (eg, Clozapine, Olanzapine, Ziprasidone), may reduce the effectiveness of CYCLOSET and CYCLOSET may reduce the effectiveness of these agents. CYCLOSET has not been studied in patients taking neuroleptic drugs. The concomitant use of CYCLOSET and dopamine receptor antagonists, including neuroleptic drugs, is not recommended.

5.5 Other Dopamine Receptor Agonists: Other dopamine receptor agonists are indicated for the treatment of Parkinson's disease, hyperprolactinemia, restless leg syndrome, acromegaly, and other disorders. The effectiveness and safety of CYCLOSET in patients who are already taking one of these other dopamine receptor agonists is unknown. Concomitant use is not recommended.

5.6 Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with CYCLOSET or any other anti-diabetic drug. In a 52-week, randomized clinical trial, CYCLOSET use was not associated with an increased risk for adverse cardiovascular events *[See Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

In the pooled CYCLOSET phase 3 clinical trials (CYCLOSET N = 2298; placebo N = 1266), adverse events leading to discontinuation occurred in 539 (24%) CYCLOSET-treated patients and 118 (9%) placebo-treated patients. This between-group difference was driven mostly by gastrointestinal adverse events, particularly nausea.

The CYCLOSET safety trial was a 52-week, placebo-controlled study that included patients treated only with diet therapy or with other anti-diabetic medications. A total of 3,070 patients were randomized to CYCLOSET (titrated to 1.6 to 4.8 mg daily, as tolerated) or placebo. The study population had a mean baseline age of 60 years (range 27-80) and 33% were 65 years of age or older. Approximately 43% of the patients were female, 68% were Caucasian, 17% were Black, 13% were Hispanic, and 1% were Asian. The mean baseline body mass index was 32 kg/m^2. The mean duration of diabetes at baseline was 8 years and the mean baseline HbA1c was 7.0% with a mean baseline fasting plasma glucose of 142 mg/dL. At baseline, 12% of patients were treated with diet only, 40% were treated with one oral anti-diabetic agent, 33% were treated with two oral anti-diabetic agents, and 16% were treated with insulin alone or insulin in combination with an oral anti-diabetic agent. At baseline, 76% of patients reported a history of hypercholesterolemia, 75% reported a history of hypertension, 11% reported a history of revascularization surgery, 10% reported a history of myocardial infarction, 10% reported a history of angina, and 5% reported a history of stroke. Forty-seven percent of the CYCLOSET-treated patients and 32% of the placebo-treated patients prematurely discontinued treatment. Adverse events leading to discontinuation of study drug occurred among 24% of the CYCLOSET-treated patients and 15% of the placebo-treated patients. This between-group difference was driven mostly by gastrointestinal adverse events, particularly nausea.

Table 1 summarizes the adverse events reported in ≥5% of patients treated with CYCLOSET in the phase 3 clinical trials regardless of investigator assessment of causality. The most commonly reported adverse events (nausea, fatigue, vomiting, headache, dizziness) lasted a median of 14 days and were more likely to occur during the initial titration of CYCLOSET. None of the reports of nausea or vomiting were described as serious. There were no differences in the pattern of common adverse events across race groups or age groups (<65 years old vs. >65 years old). In the 52-week CYCLOSET safety trial, 11.5% of CYCLOSET-treated women compared to 3.6% of placebo-treated women reported vomiting. In this same trial, 5.4% of CYCLOSET-treated men compared to 2.8% of placebo-treated men reported vomiting.

Table 1:
Adverse Events Reported in Phase 3 Clinical Trials of CYCLOSET (≥5% of Patients and Numerically More Frequent in CYCLOSET-Treated Patients than in Placebo-Treated Patients, Regardless of Investigator Assessment of Causality*)

Monotherapy	CYCLOSET 1.6 mg – 4.8 mg	Placebo
	N (%)	N (%)
N = 159	N = 80	N = 79
Nausea	26 (32.5)	6 (7.6)
Rhinitis	11 (13.8)	3 (3.8)
Headache	10 (12.5)	7 (8.9)
Asthenia	10 (12.5)	5 (6.3)
Dizziness	10 (12.5)	6 (7.6)
Constipation	9 (11.3)	3 (3.8)
Sinusitis	8 (10.0)	2 (2.5)
Diarrhea	7 (8.8)	4 (5.1)
Amblyopia	6 (7.5)	1 (1.3)
Dyspepsia	6 (7.5)	2 (2.5)
Vomiting	5 (6.3)	1 (1.3)
Infection	5 (6.3)	4 (5.1)
Anorexia	4 (5.0)	1 (1.3)
		continued

Table 1 *(continued)*
Adverse Events Reported in Phase 3 Clinical Trials of CYCLOSET (≥5% of Patients and Numerically More Frequent in CYCLOSET-Treated Patients than in Placebo-Treated Patients, Regardless of Investigator Assessment of Causality*)

Adjunct to Sulfonylurea (2 pooled 24 week studies)		
N = 494	N = 244	N = 250
Nausea	62 (25.4)	12 (4.8)
Asthenia	46 (18.9)	20 (8.0)
Headache	41 (16.8)	40 (16.0)
Flu syndrome	23 (9.4)	19 (7.6)
Constipation	24 (9.8)	11 (4.4)
Cold	20 (8.2)	20 (8.0)
Dizziness	29 (11.9)	14 (5.6)
Rhinitis	26 (10.7)	12 (4.8)
Sinusitis	18 (7.4)	16 (6.4)
Somnolence	16 (6.6)	5 (2.0)
Vomiting	13 (5.3)	8 (3.2)
Amblyopia	13 (5.3)	6 (2.4)
52-Week Safety Trial†		
N = 3070	N = 2054	N = 1016
Nausea	661 (32.2)	77 (7.6)
Dizziness	303 (14.8)	93 (9.2)
Fatigue	285 (13.9)	68 (6.7)
Headache	235 (11.4)	84 (8.3)
Vomiting	167 (8.1)	32 (3.1)
Diarrhea	167 (8.1)	81 (8.0)
Constipation	119 (5.8)	52 (5.1)

*All randomized subjects receiving at least one dose of study drug

†The Safety Trial enrolled patients treated with diet or no more than 2 anti-diabetic medications (metformin, insulin secretagogues such as a sulfonylurea, thiazolidinediones, alpha glucosidase inhibitors, and/or insulin)

Hypoglycemia
In the monotherapy trial, hypoglycemia was reported in 2 CYCLOSET-treated patients (3.7%) and 1 placebo-treated patient (1.3%). In the add-on to sulfonylurea trials, the incidence of hypoglycemia was 8.6% among the CYCLOSET-treated patients and 5.2% among the placebo-treated patients. In the CYCLOSET safety trial, hypoglycemia was defined as any of the following: 1) symptoms suggestive of hypoglycemia that promptly resolved with appropriate intervention, 2) symptoms with a measured glucose <60 mg/dL or 3) measured glucose below 49 mg/dL regardless of symptoms. In the 52-week safety trial, the incidence of hypoglycemia was 6.9% among the CYCLOSET-treated patients and 5.3% among the placebo-treated patients. In the safety trial, severe hypoglycemia was defined as an inability to self-treat neurological symptoms consistent with hypoglycemia that occurred in the setting of a measured blood glucose <50 mg/dl (or evidence of prompt resolution of these symptoms with administration of oral carbohydrates, subcutaneous glucagon, or intravenous glucose if blood glucose was not measured). In this trial, severe hypoglycemia was reported among 0.5% of CYCLOSET-treated patients and 1% of placebo-treated patients.

Syncope
In combined phase 2 and 3 clinical trials, syncope was reported in 1.4% of the 2,500 CYCLOSET-treated patients and 0.6% of the 1,454 placebo-treated patients. Among the 3,070 patients studied in the 52-week safety trial, 33 CYCLOSET-treated patients (1.6%) and 7 placebo-treated patients (0.7%) reported an adverse event of syncope. The cause of syncope is not known in all cases *[See Warnings and Precautions (5.1)]*. In this trial, electrocardiograms were not available at the time of these events, but an assessment of routine electrocardiograms obtained during the course of the trial did not identify arrhythmias or QTc interval prolongation among the CYCLOSET-treated patients reporting syncope.

Central Nervous System
In the 52-week safety trial, somnolence and hypoesthesia were the only adverse events within the nervous system organ class that were reported at a rate of < 5% and ≥ 1% and that occurred at a numerically greater frequency among CYCLOSET-treated patients (CYCLOSET 4.3% vs. Placebo 1.3% for somnolence; CYCLOSET 1.4% vs. Placebo 1.1% for hypoesthesia).

Serious Adverse Events and Cardiovascular Safety
The primary endpoint of the 52-week safety trial was the occurrence of all serious adverse events. A secondary endpoint was the occurrence of the composite of myocardial infarction, stroke, coronary revascularization, hospitalization for angina, and hospitalization for congestive heart failure.

All serious adverse events and cardiovascular endpoints were adjudicated by an independent event adjudication committee. Serious adverse events occurred in 176/2054 (8.5%) CYCLOSET-treated patients and 98/1016 (9.6%) placebo-treated patients. The hazard ratio comparing CYCLOSET to placebo for the time to first occurrence of a serious adverse event was 1.02 (upper bound of one-sided 96% confidence interval, 1.27). None of the serious adverse events grouped by System-Organ-Class occurred more than 0.3 percentage points higher with CYCLOSET than with placebo. The composite cardiovascular endpoint occurred in 31 (1.5%) CYCLOSET-treated patients and 30 (3.0%) placebo-treated patients. The hazard ratio comparing CYCLOSET to placebo for the time-to-first occurrence of the prespecified composite cardiovascular endpoint was 0.58 (two-sided 95% confidence interval, 0.35 – 0.96). Therefore, the incidence of this composite endpoint was not increased with CYCLOSET relative to placebo.

6.2 Postmarketing Experience
The active agent in CYCLOSET (bromocriptine mesylate) has been used in other formulations and often multiple times per day to treat hyperprolactinemia, acromegaly, and Parkinson's disease. The following adverse reactions have been identified during postapproval use of bromocriptine mesylate for these indications, generally at doses higher than those approved for the treatment of type 2 diabetes. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hallucinations
Hallucinations and mental confusion including delusions have been reported with bromocriptine. To date, there have been no reported cases of hallucinations or delusions among CYCLOSET-treated patients (n = 2500) in combined Phase 2 and 3 clinical trials of CYCLOSET.

Fibrotic - Related Complications
Fibrotic complications, including cases of retroperitoneal fibrosis, pulmonary fibrosis, pleural effusion, pleural thickening, pericarditis and pericardial effusions have been reported. These complications do not always resolve when bromocriptine is discontinued. Among several studies investigating a possible relation between bromocriptine exposure and cardiac valvulopathy, some events of cardiac valvulopathy have been reported, but no definitive association between bromocriptine mesylate use and clinically significant (moderate to severe) cardiac valvulopathy could be concluded.

To date, there have been no reported cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis or pericardial effusions among the CYCLOSET-treated patients (n=2500) in combined Phase 2 and 3 controlled clinical trials of CYCLOSET. There was one unconfirmed case (0.04% event rate) of an adverse event of pulmonary fibrosis classified as non-serious in a CYCLOSET-treated patient.

No cases of cardiac valvulopathy have been reported in any of the clinical studies to date with CYCLOSET.

Psychotic and Psychiatric Disorders
Psychotic disorders have been reported with bromocriptine. Additionally, pathological gambling has been reported with bromocriptine used to treat patients with Parkinson's disease. To date, there have been no reported cases of psychoses or pathological gambling among the CYCLOSET-treated patients (N=2500) in combined Phase 2 and 3 controlled clinical trials of CYCLOSET.

Stroke
The indication for use of bromocriptine for inhibition of postpartum lactation was withdrawn based on postmarketing reports of stroke. Causality of bromocriptine use and the occurrence of stroke in this patient population has not been proven. Based on the CYCLOSET clinical trials, there is no evidence of increased risk for stroke when CYCLOSET is used to treat type 2 diabetes.

Neuroleptic - like Malignant Syndrome
A neuroleptic-like malignant syndrome (manifested by high fever and increase in creatinine phosphokinase) has been reported upon cessation of bromocriptine treatment in patients with advanced Parkinson's disease or patients with secondary Parkinsonism. To date, there have been no reported cases of neuroleptic-like malignant syndrome in combined Phase 2 and 3 controlled clinical trials of CYCLOSET, including the Safety Trial (N = 2500). In the CYCLOSET Safety Trial, there were no reports of neuroleptic-like malignant syndrome during the 30 days of follow-up after cessation of CYCLOSET (N = 2054).

7 DRUG INTERACTIONS
The active ingredient in CYCLOSET, bromocriptine mesylate, is highly bound to serum proteins. Therefore, CYCLOSET may increase the unbound fraction of other concomitantly used highly protein-bound therapies (eg, salicylates, sulfonamides, chloramphenicol and probenecid), which may alter their effectiveness and risk for side effects.

CYCLOSET is a dopamine receptor agonist. Concomitant use of dopamine receptor antagonists, such as neuroleptics (eg, phenothiazines, butyrophenones, thioxanthenes), or metoclopramide may diminish the effectiveness of CYCLOSET and CYCLOSET may diminish the effectiveness of these other therapies. The concurrent use of CYCLOSET with these agents has not been studied in clinical trials and is not recommended *[see Warning and Precautions (5.4)]*.

CYCLOSET in combination with ergot-related drugs may cause an increase in the occurrence of ergot-related side effects such as nausea, vomiting, and fatigue, and may also reduce the effectiveness of these ergot therapies when used to treat migraine. The concurrent use of these ergot agents within 6 hours of CYCLOSET dosing is not recommended.

CYCLOSET is extensively metabolized by the liver via CYP3A4. Therefore, potent inhibitors or inducers of CYP3A4 may increase or reduce the circulating levels of CYCLOSET, respectively. Use caution when co-administering drugs that are strong inhibitors, inducers, or substrates of CYP3A4 (eg, azole antimycotics, HIV protease inhibitors) *[See Phamacokinetics (12.3)]*.

There are postmarketing reports of hypertension and tachycardia when bromocriptine was co-administered with sympathomimetic drugs (eg, phenylpropanolamine and isometheptene) in postpartum women. There are limited clinical trial data supporting the safety of co-administering sympathomimetic drugs and CYCLOSET for more than 10 days. Therefore, concomitant use of these agents with CYCLOSET for more than 10 days duration is not recommended. Also, there are limited clinical trial data supporting the safety of selective 5-hydroxytryptamine1B (5-HT1B) agonists (eg, sumatriptan) used concurrently with CYCLOSET and the concomitant use of these agents with CYCLOSET should be avoided.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category B
Two strains of pregnant rats were dosed orally with 3, 10, and 30 mg/kg/day (up to 72 times the human 4.8 mg daily dose, based on mg/m^2 comparison) from gestation day 6-15 and with a single dose of 10 mg/kg on gestation day 5. Implantation was inhibited at 10 and 30 mg/kg (24 and 72 times the human 4.8 mg daily dose, based on mg/m^2 comparison). When rats were dosed with 3, 10, and 30 mg/kg/day from gestation day 8-15 there was an increase in resorptions at 10 and 30 mg/kg. These effects were probably due to the dependence of implantation and the maintenance of gestation on prolactin in the rat and are not relevant for humans in which these events are not dependent on prolactin but on luteinizing hormone. There was no evidence of teratogenic effects in the rat.

In a small study in macaque monkeys given oral doses of 2 mg/kg/day (10 times the human 4.8 mg daily dose, based on mg/m^2 comparison) during organogenesis no embryotoxic or teratologic effects were observed.

When male rats given oral doses of 2, 10 or 50 mg/kg/day (up to 120 times the human 4.8 mg daily dose, based on mg/m^2 comparison) were mated with untreated females, there was a slight increase in pup loss in the 10 and 50 mg/kg/day groups (24-120 times the human 4.8 mg daily dose, based on mg/m^2 comparison).

In two strains of pregnant rabbits treated from gestation day 6-18 with oral doses of 3, 10, 30, 100, and 300 mg/kg/day (up to 1400 times the human 4.8 mg daily dose, based on mg/m^2 comparison) there was maternal toxicity and embryolethality at doses ≥10 mg/kg/day (48 times the human 4.8 mg daily dose, based on mg/m^2 comparison). Low incidences of fetal abnormalities were observed at maternally toxic doses of 100-300 mg/kg/day (480-1400 times the human 4.8 mg daily dose, based on mg/m^2 comparison). There were no treatment-related fetal abnormalities at doses ≤30 mg/kg/day (140 times the human 4.8 mg daily dose, based on mg/m^2 comparison). Implantation was not affected in rabbits treated from gestation day 1-6 with oral doses of 100-300 mg/kg/day (480-1400 times the human 4.8 mg daily dose, based on mg/m^2 comparison).

Studies in pregnant women have not shown that bromocriptine increases the risk of abnormalities when administered during pregnancy. Information concerning 1,276 pregnancies in women taking bromocriptine has been collected. In the majority of cases, bromocriptine was discontinued within the first 8 weeks of pregnancy (mean 29 days); however, 8 patients received the drug continuously throughout pregnancy. The mean daily dose for all patients was 5.8 mg (range 1-40 mg). Of these 1,276 pregnancies, there were 1,088 full-term deliveries (4 stillborn), 145 spontaneous abortions (11.4%), and 28 induced abortions (2.2%). Twelve extrauterine gravidities and 3 hydatidiform moles (twice in the same patient) caused early termination of pregnancy. These data compare favorably with the abortion rate (11-25%) cited for pregnancies induced by clomiphene citrate, menopausal gonadotropin, and chorionic gonadotropin. Although spontaneous abortions often go unreported, especially prior to 20 weeks of gestation, their frequency has been estimated to be 10-15% in the general population. The incidence of birth defects in the general population ranges from 2% to 4.5%. The incidence of birth defects in 1,109 live births from patients receiving bromocriptine was 3.3%. There is no suggestion that bromocriptine contributed to the type or incidence of birth defects in this group of infants.

A review of 4 different multicenter surveillance programs analyzed 2,351 pregnancies of 2,185 women treated with bromocriptine. In 583 children born of these women and followed for a minimum of 3-12 months, there was no suggestion of any adverse effect of intra-uterine exposure to bromocriptine on post-natal development. Most (≥75%) women had taken bromocriptine for 2-8 weeks and at 5-10 mg per day. Among 86 women having 93 pregnancies and treated with bromocriptine throughout pregnancy or from week 30 of pregnancy onwards (mostly for treatment of prolactinoma), there was only 1 spontaneous abortion. Similar results have been obtained in a Japanese hospital survey of 442 children born to 434 patients treated with bromocriptine during pregnancy and followed for at least one year.

Because the studies in humans cannot rule out the possibility of harm, CYCLOSET should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers
CYCLOSET is contraindicated in women who are nursing their children. CYCLOSET contains bromocriptine which inhibits lactation. The indication for use of bromocriptine for inhibition of postpartum lactation was withdrawn based on postmarketing reports of stroke in this setting *[See Contraindications (4) and Adverse Reactions (6.2)]*.

8.4 Pediatric Use
The safety and effectiveness of CYCLOSET in pediatric patients have not been established.

8.5 Geriatric Use
In the two clinical trials of CYCLOSET add-on to sulfonylurea therapy and in the monotherapy trial, a total of 54 patients randomized to CYCLOSET were ≥65 years old. In the 52-week safety trial, 601 of the 2,054 CYCLOSET-treated patients (29%) were ≥65 years old. No overall differences in safety or effectiveness were observed between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. *[See Clinical Studies (14)]*.

10 OVERDOSAGE
With another formulation of bromocriptine mesylate, the most commonly reported signs and symptoms associated with acute overdose were nausea, vomiting, constipation, diaphoresis, dizziness, pallor, severe hypotension, malaise, confusion, lethargy, drowsiness, delusions, hallucinations, and repetitive yawning. The lethal dose has not been established.

Treatment of overdose consists of removal of the drug by emesis (if conscious), gastric lavage, activated charcoal, or saline catharsis. Careful supervision and recording of fluid intake and output is essential. Hypotension should be treated by placing the patient in the Trendelenburg position and administering intravenous fluids. If satisfactory relief of hypotension cannot be achieved by using the above measures to their fullest extent, vasopressors should be considered.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
In a 74-week dietary study in mice at doses up to 50 mg/kg/day (56 times the human 4.8 mg daily dose, based on mg/m^2 comparison) there was no evidence of tumorigenicity.

In a 100-week dietary carcinogenicity study in rats at doses of 1.8, 9.9 and 44.5 mg/kg/day (up to 106 times the human 4.8 mg daily dose, based on mg/m^2 comparison) there was a significant increase in the incidence of malignant uterine neoplasms in the mid- and high dose groups (24-106 times the human 4.8 mg daily dose, based on mg/m^2 comparison). The increase in uterine neoplasms was probably due to the inhibition of prolactin-stimulated progesterone secretion resulting in estrogen domination and endometrial stimulation in the aging rat. Because prolactin does not play a role in human progesterone production this finding is unlikely to be clinically relevant.

Mutagenicity
Bromocriptine was not mutagenic in the in vitro Ames bacterial mutation assay, the V79 Chinese hamster fibroblast mutagenity test, the in vivo bone marrow micronucleus test in mice and the in vivo Chinese hamster bone marrow chromosomal aberration test.

Impairment of Fertility
In female rats treated with oral doses of 1 and 3 mg/kg (2 to 7 times the human 4.8 mg daily dose, based on mg/m^2 comparison) from 2 weeks prior to mating through 2 weeks post mating or throughout lactation there was no effect on fertility. Postnatal pup weight gain was reduced dose-dependently in treated groups probably due to lactation inhibition.

In male rats treated with oral doses of 2, 10, and 50 mg/kg/day (up to 120 times the human 4.8 mg daily dose, based on mg/m^2 comparison) there was no effect on mating or fertility.

Manufactured for: VeroScience, LLC, Tiverton, RI.
Distributed and Marketed by: Santarus, Inc., San Diego, CA.

RESEARCH BRIEFS

➤ The following studies will be published in Endocrine Society journals. Before print, they are edited and posted online in each journal's Early Release section. You can access the journals via *www.endo-society.org*.

Endocrinology

➤ **Males with familial hypertrophic cardiomyopathy should avoid phytoestrogens.**
Haines CD, Harvey PA, Luczak ED, et al. *Estrogenic compounds are not always cardioprotective and can be lethal in males with genetic heart disease.*

➤ **This new stem cell methodology could provide future therapies for patients with adrenal insufficiency.**
Sonoyama T, Sone M, Honda, et al. *Differentiation of human embryonic stem cells and human induced pluripotent stem cells into steroid-producing cells.*

➤ **AMH knock-down may have therapeutic value in infertile women who respond poorly to ovarian stimulation.**
Campbell BK, Clinton M, Webb R. *The role of anti-müllerian hormone (AMH) during follicle development in a monovulatory species (sheep).*

➤ **PPARγ expression in pancreatic β-cells is unlikely to be directly essential for normal β-cell function or the insulin-sensitizing actions of rosiglitazone.**
Welters HJ, El Ouaamari A, Kawamori D, et al. *Rosiglitazone promotes PPARγ-dependent and independent alterations in gene expression in mouse islets.*

➤ **TH signaling in tadpoles is active even before thyroid formation, suggesting an early sensitivity to endocrine-disrupting chemicals.**
Fini JB, Le Mével S, Palmier K. *Thyroid hormone signaling in the* Xenopus laevis *embryo is functional and susceptible to endocrine disruption.*

The Journal of Clinical Endocrinology & Metabolism

➤ **Sedation and anesthesia can induce a significant rise in cortisol in children.**
Hsu AA, von Elten K, Chan D. *Characterization of the cortisol stress response to sedation and anesthesia in children.*

➤ **The need for hormone replacement therapy should be re-evaluated three months after surgical correction of NPH because most endocrine dysfunctions are reversed in this time.**
Moin T, Bergsneider M, Vespa P, Heaney A. *Pituitary function in patients with normal pressure hydrocephalus before and after neurosurgical correction.*

➤ **Runt-related transcription factor 2 potentiates the migration and invasive capacity of thyroid tumor cells.**
Sancisi V, Borettini G, Maramotti S, et al. *Runx2 isoform I controls a panel of pro-invasive genes driving aggressiveness of papillary thyroid carcinomas.*

➤ **Circulating myostatin levels in men are associated with seasonal changes, age, body mass index, fat mass, smoking, and 25-hydroxycholecalciferol levels.**
Szulc P, Schoppet M, Goettsch C, et al. *Endocrine and clinical correlates of myostatin serum concentration in men—the STRAMBO study.*

➤ **Physical activity promotes favorable estrogen metabolism that could lead to prevention of chronic diseases such as breast cancer and osteoporosis.**
Matthews CE, Fortner RT, Xu X, Hankinson SE, Eliassen AH, Ziegler RG. *Association between physical activity and urinary estrogens and estrogen metabolites in premenopausal women.*

Molecular Endocrinology

➤ **Using small molecules or IGF-I/IGF-II antibodies might aid in avoiding anti-IGF-IR resistance in EWS patients.**
Garofalo C, Mancarella C, Grilli A, et al. *Identification of common and distinctive mechanisms of resistance to different anti-IGF-1R agents in Ewing's sarcoma.*

➤ **New molecular mechanisms are suggested for the functional withdrawal of progesterone at term labor.**
Xie N, Liu L, Li Y, et al. *Expression and function of myometrial PSF suggest a role in progesterone withdrawal and initiation of labor.*

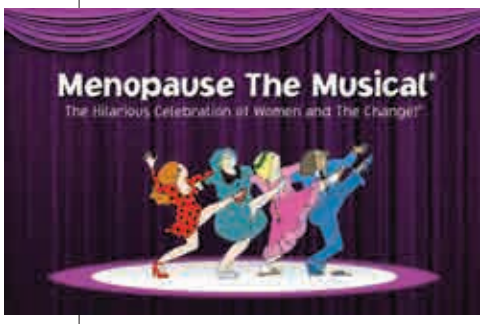
➤ **Lung cancer incidence and treatment approach could be predicted by NR expression.**
Jeong Y, Xie Y, Lee W, et al. *Diagnostic and therapeutic potential of nuclear receptor expression in lung cancer.*

Hormones and Cancer

➤ **Endometrial cancer risk is not associated with migraine history and NSAID use.**
Phipps AI, Anderson GL, Cochrane BB, et al. *Migraine history, nonsteroidal anti-inflammatory drug use, and risk of postmenopausal endometrial cancer.* ■

ENDOCRINE Society update

HHN Joins Forces with Menopause the Musical®



For women going through the "change of life," managing menopausal symptoms is no laughing matter: A recent national survey by the Hormone Health Network found that 72 percent of women experiencing troublesome symptoms have not received treatment, and another 60 percent are not discussing treatment options with their doctor. To help bridge this conversation gap, the Network teamed up with Menopause the Musical®, a light-hearted look at four women coping with their menopausal symptoms, at the Warner Theater in August to introduce the Menopause Map to its Washington, D.C., audience. Attendees had the opportunity to complete the online, interactive Map on-site, and received the Networks' patient fact sheets on menopause.

Third Annual Endocrine Summit in India

On September 30, The Endocrine Society will present the third Annual Endocrine Summit in India. This program, held in Mumbai, will bring together more than 200 of India's endocrinologists for an interactive platform that provides a comprehensive review of best practices and evidence-based strategies in the field of endocrinology. Attendees will gain insight into the evaluation and management of patients with endocrine disorders and diseases. Presented by world-renowned faculty, the 2012 program will include female reproduction and pituitary, thyroid, and adrenal disorders. The faculty is comprised of Past President Janet Hall, M.D., past Annual Meeting Steering Committee Chair Lynnette Nieman, M.D., David Cooper, M.D., and David Clemmons, M.D.

FLARE Ignites Careers of Young Professionals

The Endocrine Society is pleased to announce the launch of the Future Leaders Advancing Research in Endocrinology (FLARE) program, which will provide leadership development training to senior graduate students and postdoctoral and clinical fellows from underrepresented communities. The FLARE program is funded by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases. More information can be found at *www.endo-society.org/FLARE*.

Endocrine Education in Your Backyard

The Endocrine Society brings top-quality clinical updates to your area with **Endocrine Essential Live**. This new regional series features two programs designed for both professional endocrinologists and for primary care physicians treating endocrine-related diseases.

Endocrine Essentials Pro, chaired by Lisa Fish, M.D., is designed for endocrinologists and focuses on metabolic bone disease and adrenal disorders.

Endocrine Essentials for Primary Care, chaired by Rocio Pereira, M.D., is a diabetes program for internists, general practitioners, diabetes educators, and other primary care providers.

These programs are scheduled for the following towns and dates: Minneapolis on September 29, Kansas City, Missouri, on October 20, Indianapolis on October 27, and New York City on November 10.

These concurrent half-day programs provide state-of-the-art updates on current practice challenges from expert faculty. More information and registration is available online at *www.endo-society.org/eelive*. ■

calendar

SEPT 11–15: MIAMI
Endocrine Board Review and Clinical Endocrinology Update
www.endo-society.org/miami

SEPT 19–23: QUEBEC CITY, CANADA
American Thyroid Association 82st Annual Meeting
www.thyroid.org/ann_mtg/index.html

SEPT 20–24: SAN ANTONIO
The Obesity Society's 30th Annual Scientific Meeting
www.obesity.org/meetings-and events/annual-meeting.htm

OCT 13–17: NEW ORLEANS
Society for Neuroscience 42nd Annual Meeting
www.sfn.org/am2012

OCT 17–19: PHILADELPHIA
American Academy of Family Physicians (AAFP)
www.aafp.org/online/en/home/cme/aafpcourses/conferences/assembly.html

See more events at *www.endosociety.org*, on the Worldwide Endocrine Events Calendar.

Classifieds

If you are interested in submitting classified advertising to **Endocrine News**, *please contact Christine Whorton at* endocareers@endo-society.org *or 800-361-3906.*

Endocrinologist Needed in Growing Philadelphia Suburb

Gateway Medical Endocrinology Associates is seeking a BC/BE Endocrinologist to join well-established group. Join three endocrinologists, one diabetologist, two nurse practitioners, and a diabetes educator. This respected practice is located in West Chester Pennsylvania, an outstanding place to live and work. Allscripts EMR. Competitive Salary! Email CV to *mdyson@gatewaydoctors.com.*

Endocrinologist

The Strelitz Diabetes Center and Division of Endocrinology and Metabolism, at the Eastern Virginia Medical School are seeking an Endocrinologist at the Assistant or Associate Professor rank (tenure track). The candidate will participate in clinical and educational activities of the division, and will have completed an endocrinology fellowship and be BC/BE in Internal Medicine and Endocrinology. Opportunities for program development include diabetes education, inpatient glucometrics and thyroid cancer management. We are seeking an individual to join our group with interests in quality and the development of innovative clinical programs focusing on early intervention. The successful candidate will become an integral part of a system of care, working with our primary care network and multiple specialties to enhance diabetes care. The position includes a faculty appointment, teaching opportunities and a competitive salary and benefit package. Previous experience with thyroid ultrasound preferred. The search committee will also consider applicants with an active research program focused on aspects related to diabetes or thyroid disease. There are excellent laboratory facilities available and possible start up package. The historic port city of Norfolk is centrally located in the 1.8 million person Hampton Roads area on the Chesapeake Bay, a short drive from the Virginia Beach oceanfront. Forward CV to: HRapps@evms.edu. EVMS is an Equal Opportunity/Affirmative Action Employer/M/F/D/V and a Drug and Tobacco Free workplace. ■

Nemours. Alfred I. duPont Hospital for Children

DIVISION CHIEF OF PEDIATRIC ENDOCRINOLOGY

The Nemours/Alfred I. DuPont Hospital for Children in Wilmington, Delaware seeks a Division Chief of Endocrinology to join their team. Interested candidates must be board certified in Pediatric Endocrinology, be ranked at the Associate Professor level, and have a track record of federal funding. Management and prevention of pediatric obesity is a major area of investigation.

Nemours is one of the nation's premier pediatric health care systems. The Nemours/Alfred I. DuPont Hospital for Children offers intensive and acute inpatient and outpatient services covering more than 30 pediatric specialties. They care for approximately a quarter of a million children annually and have done so for more than 70 years.

Position offers a competitive income along with a full and comprehensive benefits package.

To learn more visit: Nemours.org

Nemours is a registered trademark of the Nemours Foundation. Nemours is an Equal Opportunity Employer.

To learn more, please contact either

Danise Cooper
800-678-7858 x63006
dcooper@cejkasearch.com

Beth Briggs
800-678-7858 x64454
ebriggs@cejkasearch.com

ID#139877A15 cejkasearch.com

THE Bluegrass IS CALLING.

Lexington Clinic is seeking a full-time BC/BE Endocrinologist to join a thriving practice.

- 100% clinical endocrinology
- Outpatient only with limited office call
- Large internal/external referral base
- Favorable payer mix

Lexington Clinic is the largest and oldest private multi-specialty group practice in the Commonwealth of Kentucky, consisting of primary care physicians, surgical specialists and allied health professionals. We offer a competitive salary, plus bonus; excellent benefits; CME and relocation allotment. *Partnership available after one year.*

Interested candidates please contact:
Audra Davidson
Manager, Physician Services and Recruitment
adavi@lexclin.com
p. 859.258.4135
c. 859.230.4417
LexingtonClinic.com

Lexington Clinic is an Equal Opportunity Employer.

ENDOCRINOLOGIST

OCHSNER HEALTH SYSTEM in New Orleans is searching for a BC/BE **ENDOCRINOLOGIST to join our staff at Ochsner Baptist Medical Center.** Candidates with experience or directly from training are welcomed to apply. Areas of interest should include general endocrine disorders, diabetes, and endocrine disorders as related to pregnancy. This position is mainly outpatient-based but will serve a large Ob/Gyn group with significant inpatient consultation. Salary is competitive and commensurate with experience and training.

Ochsner Baptist Medical Center, with a deep-rooted history in Uptown New Orleans, is a fully accredited, full-service hospital staffed by more than 390 physicians. We have all private rooms, an ICU, thirteen operating rooms, and a state-of-the art imaging center. We are proud to be distinguished by our excellence in specialty care and high patient satisfaction scores. Our newly renovated 24-hour full-service emergency department is staffed by a team of board-certified ER physicians.

Ochsner™ Health System

The Ochsner Health System is comprised of 8 hospitals and more than 38 clinics across southeast Louisiana which sees over 1.5 million clinic patient visits annually. Ochsner is a major provider of graduate medical education with 23 ACGME accredited residency and fellowship programs including our Endocrinology fellowship program.

New Orleans is a cosmopolitan, historic city with a pleasant climate, unique architecture, multiple medical schools and academic centers, professional sports teams, world-class dining and cultural interests, and world-renowned live entertainment and music.

Please email CV to: ochsnerphysiciancv@gmail.com Ref. # ABENDO1 or call 800-488-2240 for more information. EOE.

Sorry, no J-1 visa opportunities available.

Division Director, Division of Endocrinology
Department of Internal Medicine
The Ohio State University

Wexner Medical Center

The Department of Internal Medicine of the Ohio State University College of Medicine seeks to recruit a Director for the Division of Endocrinology, Diabetes and Metabolism. The ideal candidate will be a visionary leader interested in building upon the division's strengths to expand its tripartite mission in clinical care, medical education and research excellence. The new Division Director would be expected to lead the division in achieving its vision of translating knowledge to improved care of endocrine and metabolic disease, mentoring faculty to support their career success, and collaborating across divisions, departments, centers and colleges at one of the nation's most comprehensive universities and one of the largest academic health sciences campuses.

The Department is interested in strong candidates who have demonstrated commitment to excellence by providing leadership in teaching, research, and clinical service. Experience in building and/or supporting innovative clinical programs would be a strength. Applicants with mature research programs in basic, clinical or translational research are encouraged to apply. A track record of mentoring trainees for successful academic careers or supporting the career development of faculty is desirable as recruitment of additional faculty aligned with research, clinical and educational missions is anticipated.

The Division currently consists of 15 faculty whose clinical expertise spans a broad scope of general endocrinology and diabetes while supporting individuals focusing in diabetes, obesity, thyroid cancer, adrenal disorders, and bone health. Areas of research excellence include strong multidisciplinary research programs in thyroid cancer, diabetes, neuroendocrine tumors and women's musculoskeletal health. In addition, Ohio State offers many unique opportunities for collaboration including the Comprehensive Cancer Center, The Center of Clinical and Translational Science, The Davis Heart and Lung Research Institute, Transplant Medicine and Bariatric Surgery among others. High quality clinical care is maintained through focused quality improvements, optimized electronic health records, cross-disciplinary teams and support staff. Post-graduate training includes a GME accredited fellowship program, and rotating residents in outpatient clinics and inpatient consultative services. The division is active in Ohio State's innovative Lead.Serve.Inspire Curriculum for the medical students. The division is currently ranked in the top 20 by the U.S. News & World Report.

Candidates should be eligible for Associate Professor rank or above. To apply for the Division Director for the Division of Endocrinology at the Ohio State University Wexner Medical Center, submit a confidential inquiry, nomination, referral, or application to:

Dan Dolan, Director of Senior Leader Recruitment for the OSU Medical Center
660 Ackerman Road, P.O. Box 183100, Columbus, OH 43218-3100.
Dan.Dolan@osumc.edu 614-293-4513

To build a diverse workforce, the Ohio State University Wexner Medical Center encourages applications from individuals with disabilities, minorities, veterans, and women. Ohio State is an EEO/AA Employer.

A Second Look at the Military Medical Museum

By Marian Smith Holmes

Weird. Quirky. Eeew! Such are the knee-jerk assessments people often make when they hear about the National Museum of Health and Medicine (NMHM). Yes, the exhibitions include a massive human hair ball, a huge elephantiasis leg and diverse organs preserved in formaldehyde. But the 150-year-old museum, just outside Washington, D. C., is in truth an extensive collection of medical artifacts and an impressive educational facility. Even those exhibits that sound creepy are grounded in real science.

Scientific research was the museum founder's original intent when it was established during the Civil War. "Forward… all specimens of morbid anatomy," U.S. Army Surgeon General William A. Hammond instructed field doctors in 1862, soliciting contributions to the new Army museum dedicated to the study of military medicine and surgery.

"I have numerous specimens for you," a Union surgeon replied. "Have put them in ale barrels with some whisky & chlorinated soda." Bone fragments, pieces of tissue and other specimens from the battlefields poured in along with photos of wounded soldiers and handwritten accounts of case studies and surgical procedures.

As gruesome as the collecting may seem to modern sensibilities, it represented research at its most basic level. Often called the first modern war, the Civil War was fought with technologically advanced weaponry that left young men with horrible new injuries that taxed the ingenuity of field surgeons. More than anything the museum demonstrates how the horrors of war created urgency in the development of medicine. "This is the place death delights to help the living," a sign on one NMHM wall proclaims.

"It was essentially the first government-sponsored medical research project in the United States," says Laura Cutter, the museum's archivist. The battlefield collection became the basis for the six-volume *Medical and Surgical History of the War of the Rebellion, 1861–65*, a government publication detailing tens of thousands of diseases, wounds, and surgeries. Not only was it "highly valuable" to doctors for practical information, Cutter says, but it also statistically documented the occurrence of diseases. Based on the compilation, "the primary cause of military death during the war was diarrhea and dysentery," she adds.

"It was essentially the first government-sponsored medical research project in the United States," says Laura Cutter, the museum's archivist.

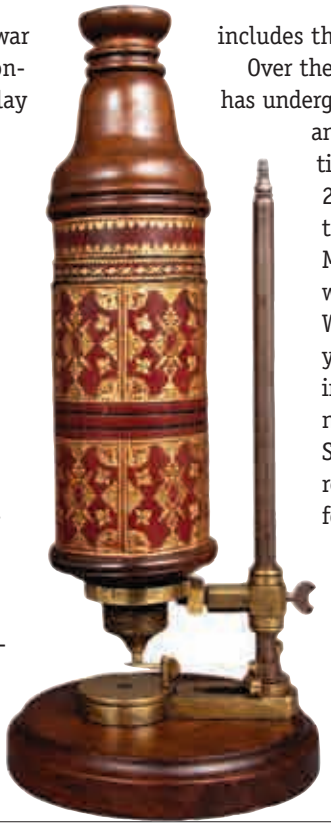
Dr. Mary Edwards Walker

In addition to housing 25 million artifacts, which include thousands of preserved organs and skeletal specimens, the museum showcases narratives about individuals who made

Back Story

a difference. An exhibition about Dr. Mary Edwards Walker, a surgeon in Union battlefield hospitals, contains her surgical kit, a small leather case about the size of a make-up bag. The Army's first female surgeon, she was once captured by the Confederates but she returned to the battlefield soon after she was released. She was later awarded the Medal of Honor, the first and only woman to ever receive it. Also on display is the beautifully crafted leather and gold microscope of 17th century scientist Robert Hooke, who used it to observe organisms that he described and illustrated in his book, *Micrographica,* a revolutionary scientific text at the time. Fascinated by the microscopic images, he coined the biological use of the word "cell."

A display of prosthetic limbs illustrates the advances made over the years to get war amputees functioning again; a similar display charts the history of facial reconstruction. Though steeped in Civil War history, the museum continues to collect, creating exhibitions of recent military medical innovations. One installation features a section of an emergency room tent used in Iraq. A traumatic brain injury exhibition displays computerized equipment alongside instruments from the 1800s, and a forensics exhibition tracing the evolution of the science so critical to identifying the fallen in battle includes the Sept. 11 tragedy.



Over the years, the museum has undergone name changes and numerous relocations. From 1971 to 2011 it was housed in the Walter Reed Army Medical Center, which was then located in Washington, D.C. A year ago NMHM moved into its own brand new building in Silver Spring, Maryland. It remains a destination for researchers, but is a favorite of families and, yes, curiosity seekers. ■

Holmes is the managing editor of ***Endocrine News****.*

EMD MILLIPORE

Versatility in a Complete Package.

MILLIPLEX®MAP magnetic bead-based immunoassay kits & MAGPIX® instruments.

Research can change direction in a minute—to keep the pace, you need a versatile assay platform.

With our analytically validated MILLIPLEX® MAP kits, using Luminex® xMAP® technology, measure one analyte per sample or fifty, in research areas including neuroscience, toxicity, oncology—using preconfigured or customized panels.

And, the versatility doesn't stop there—we're the original multiplex partner offering the full range of multiplex instruments, including MAGPIX®, the newest, most flexible, small-footprint instrument for the user-friendly xMAP® platform.

Get the complete package at
www.millipore.com/magbeads

EMD Millipore is a division of Merck KGaA, Darmstadt, Germany

THE POWER INSIDE Luminex | xMAP® TECHNOLOGY Because you want to know more

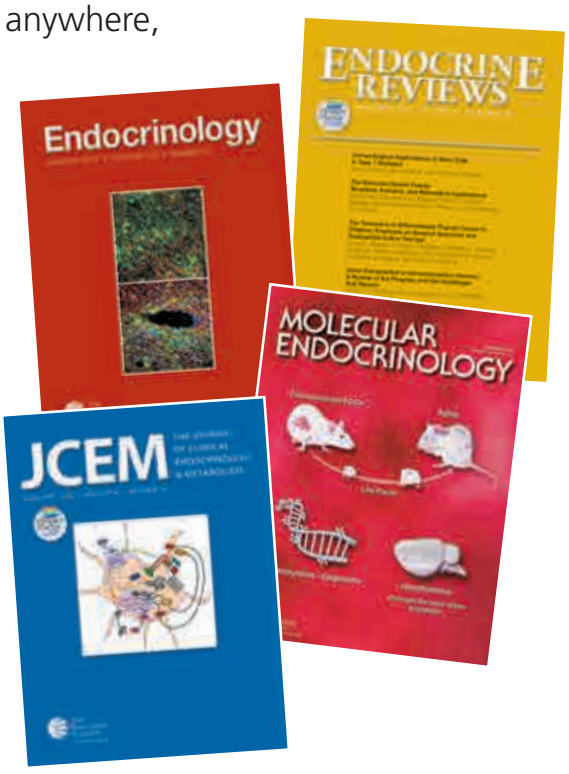
NEW! Endo Pubs App

The Endocrine Society's Full-Text Multi Journal App

Available for both iOS and Android platforms

Now you can read your Endocrine Society journals anywhere, anytime with the Endo Pubs App. Get instant access to these features and many more:

- Download, search, view, and save abstracts and full-text articles
- Full-text search on abstracts, title, authors, and keywords
- Social sharing: Facebook and Twitter posts
- Access supplemental material



Available at Apple App Store and Android Market.

THE ENDOCRINE SOCIETY®

www.endo-society.org