

Recently, the Federal Register published the Centers for Medicare and Medicaid Services' (CMS) proposed rule on the 2008 physician payment schedule. As anticipated, the proposed rule includes a 9.9% cut for all physician services in 2008. In addition to this, cuts to dual X-ray absorptiometry (DXA) resulting from the Deficit Reduction Act of 2005 (DRA) continue to have a negative effect on payments for these services. The Endocrine Society provided comments to CMS on its concerns about the proposed rule in late August. Included in those comments was a discussion of the Society's position that the formula used to calculate physician payments—the sustainable growth rate (SGR)—needs to be replaced with a more practical model. The Endocrine Society supports the American Medical Association's proposal to either replace the SGR with an entirely new model or to develop a plan that would eventually change the way payments are calculated that still uses the current SGR. Both the House and the Senate have stated that they do not intend to allow the 9.9% physician payment cut to take effect in 2008.

In August, the House approved the Children's Health and Medicare Protection Act of 2007 (CHAMP), which reauthorizes the State Children's Health Insurance Program (S-CHIP) and alters the SGR payment model. The SGR model has been a controversial process for some time because it uses the gross domestic product in combination with other factors to determine physician payments. The SGR requires that physicians must meet certain spending targets to receive payment updates. If those targets are not met, physician payments are reduced the following year so as to realign the overspending from the previous year. Not surpassing these assigned spending targets is particularly difficult with a Medicare beneficiary population that is growing, aging, and using more physician services than in previous years.

Under the CHAMP Act, physicians

2008 Medicare Physician Payments Remain in Flux

By Holly Whelan*



would see a 0.5% increase in payments for 2008 and 2009. In 2010, the Act requires the SGR to be revamped by dividing physician services into six categories, each assigned its own separate spending target, with particular emphasis on primary and preventive care. By assigning different spending targets to service categories, legislators believe that the problems plaguing the current formula will be eliminated.

The Senate passed its own version of the children's health care legislation in August, but this did not include any provisions to alter the physician payment formula. In early October, President Bush vetoed the legislation because he disagrees with the amount of funding provided to the S-CHIP program. Congress will have to override the

President's veto with a two-thirds majority vote or the bill will die. House and Senate leaders have pledged to find a compromise to the Medicare Physician Payment problem this year. ■

Working to Halt DXA Cuts

Society Action and Patient and Physician Advocacy Groups Coalition

By Stephanie Kutler*

Society staff has been actively working to halt the cuts to DXA payments that went into effect on January 1, 2007, and much progress has been made. If fully implemented in 2010, the cuts will reduce payment



rates to physicians performing DXA scans in their offices from \$140 in 2006 to \$35 in 2010. The Society has been working with the National Osteoporosis Foundation (NOF), the American College of Rheumatology (ACR), the American Association of Clinical Endocrinologists (AACE), and the International Society for Clinical Densitometry (ISCD) to develop a comprehensive legislative, regulatory, and public relations campaign.

The Society and NOF have been working aggressively on behalf of this coalition to secure a sponsor for a DXA-specific fix to the payment cuts and have met with key House and Senate members, including Sens. Lincoln (D-AR), Stabenow (D-MI), McCaskill (D-MO), Mikulski (D-MD), Snowe (R-ME), and Salazar (D-CO), and Reps. Berkley (D-NV) and Inslee (D-WA). The draft legislation developed by the working group asks for a halt to the payment cuts with a freeze at 2006 levels. During the freeze, the Institute of Medicine

the impact of the payment cuts on physicians' ability to provide DXA services in their offices. The first survey, in May, examined physicians' intentions regarding their plans for providing DXA scans if the cuts are fully implemented. Of the 750 physicians who responded to the survey, 93% believe they will not be able to provide DXA scans at the projected \$35 rate. The results of this survey will be used to emphasize the impact on patient access during future visits to Capitol Hill.

The Society has also helped fund a study by the Lewin Group to measure the actual cost of providing DXA scans in the physician's office and the cost to Medicare to freeze payments for DXA at 2006 levels. The survey was sent to 14,000 practicing physicians in the beginning of July, and data will be available for use in our advocacy efforts.

A Webcast aimed at health care providers and women's and patient advocacy groups will be hosted by the DXA working group in early October. The goal of the Webcast is to inform the health care community of the problem facing DXA providers and

ment and other issues facing lawmakers this year, the legislation may not be considered until 2008. ■

* Ms. Whelan is Manager, Health Policy, and Ms. Kutler is Associate Director, Government and Professional Affairs, both at The Endocrine Society.

Upcoming Science Writers Conference



News reports on cutting-edge medical discoveries and national health policy are among the most prominent and widely read. The public's strong interest in these topics creates a constant demand for stories on the latest breakthroughs in medical science and expert analysis of complex health care data. The Endocrine Society is frequently sought out by the media as an authoritative and responsive source for such information.

To further expand its media outreach, the Society is holding the second in its series of science writers conferences on December 7, 2007, in Washington, D.C. The theme of the conference is "Hormones through Life" and it will feature Society members from a wide range of disciplines who will talk about the intricate connections between hormones and health during specific stages of a person's life. This event aims to inform reporters and science writers about current directions in research, the fundamentals of clinical practice, and the connections between salient national health issues and the contributions of endocrinologists.

The science writers conference program was launched in December 2005 when the *Hormones & Health* symposium was held in New York City. The strong attendance and positive reviews of that event spurred the Society to plan the 2007 conference.

For more information, visit www.endo-society.org/writers07. ■

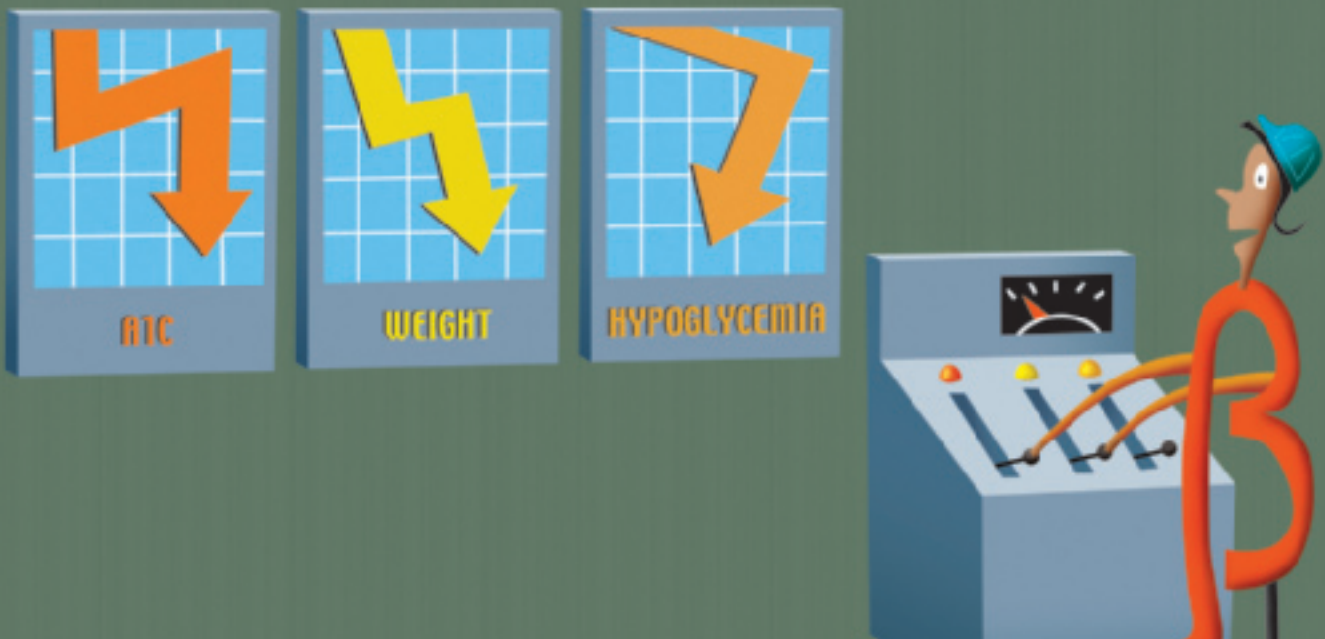


would analyze the impact of these cuts on patient access to DXA. Although this draft language represents the best-case scenario for a fix, the sponsor of the bill may offer alternative language.

To refine our lobbying messages, the Society has also been working with the aforementioned societies to survey our memberships to measure

patients, highlight the efforts and achievements of the DXA working group, and gain the community's support for our future activities.

Although much has been accomplished, much work remains. The coalition members hope that the DXA-specific legislation will be introduced and voted upon during 2007, but with the current fiscal environ-



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Important Safety Information

BYETTA is not a substitute for insulin in insulin-requiring patients, and should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Patients should be observed for signs and symptoms of hypersensitivity reactions.

BYETTA is not recommended for use in patients with end-stage renal disease, severe renal impairment, or severe gastrointestinal disease. The development of severe abdominal pain in a patient

treated with BYETTA should be investigated because it may be a warning sign of a serious condition.

Patients receiving BYETTA concomitantly with a sulfonylurea had an increased risk of hypoglycemia.

The most common adverse events associated with BYETTA were nausea, vomiting, diarrhea, feeling jittery, dizziness, headache, and dyspepsia.

BYETTA should be used with caution in patients receiving oral medications that require rapid gastrointestinal absorption. Increased INR sometimes associated with bleeding has been reported in postmarketing experience with concomitant use of warfarin.

For safety information and other important prescribing considerations, please see following page for Brief Summary of Prescribing Information.

*Open-label clinical trial results extended through 130 weeks with BYETTA 5 mcg or 10 mcg.

†Sulfonylureas increase the risk of hypoglycemia.³ When BYETTA is used with a sulfonylurea, there is an increased risk of hypoglycemia.

References: 1. IMS Health data. March 2007. 2. Data on file, Amylin Pharmaceuticals, Inc. and Eli Lilly and Company. 3. Del Prato S, Pulizzi N. The place of sulfonylureas in the therapy for type 2 diabetes mellitus. *Metabolism*. 2006;55(suppl 1):S20-S27. 02-07-4432-B. The BYETTA mark and BYETTA design mark are trademarks of Amylin Pharmaceuticals, Inc.

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

INDICATIONS AND USAGE: BYETTA is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione, but have not achieved adequate glycemic control.

CONTRAINDICATIONS: BYETTA is contraindicated in patients with known hypersensitivity to exenatide or to any of the product components.

PRECAUTIONS: General—BYETTA is not a substitute for insulin in insulin-requiring patients. BYETTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Patients may develop anti-exenatide antibodies following treatment with BYETTA, consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals. Patients receiving BYETTA should be observed for signs and symptoms of hypersensitivity reactions. In a small proportion of patients, the formation of anti-exenatide antibodies at high titers could result in failure to achieve adequate improvement in glycemic control.

The concurrent use of BYETTA with insulin, D-phenylalanine derivatives, meglitinides, or alpha-glucosidase inhibitors has not been studied.

BYETTA is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min; see Pharmacokinetics, Special Populations). In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well tolerated due to gastrointestinal side effects.

BYETTA has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Its use is commonly associated with gastrointestinal adverse effects, including nausea, vomiting, and diarrhea. Therefore, the use of BYETTA is not recommended in patients with severe gastrointestinal disease. The development of severe abdominal pain in a patient treated with BYETTA should be investigated because it may be a warning sign of a serious condition.

Hypoglycemia—In the 30-week controlled clinical trials with BYETTA, a hypoglycemia episode was recorded as an adverse event if the patient reported symptoms associated with hypoglycemia with an accompanying blood glucose <60 mg/dL or if symptoms were reported without an accompanying blood glucose measurement. When BYETTA was used in combination with metformin, no increase in the incidence of hypoglycemia was observed. In contrast, when BYETTA was used in combination with a sulfonylurea, the incidence of hypoglycemia was increased over that of placebo in combination with a sulfonylurea. Therefore, patients receiving BYETTA in combination with a sulfonylurea may have an increased risk of hypoglycemia (Table 1).

Table 1: Incidence (%) of Hypoglycemia* by Concomitant Antidiabetic Therapy

	BYETTA			BYETTA			BYETTA		
	Placebo BID	5 mcg BID	10 mcg BID	Placebo BID	5 mcg BID	10 mcg BID	Placebo BID	5 mcg BID	10 mcg BID
		With Metformin			With a Sulfonylurea			With MET/SFU	
N	113	110	113	123	125	129	247	245	241
Hypoglycemia	5.3%	4.5%	5.3%	3.3%	14.4%	35.7%	12.6%	19.2%	27.8%

* In three 30-week placebo-controlled clinical trials. BYETTA and placebo were administered before the morning and evening meals. Abbreviations: BID, twice daily; MET/SFU, metformin and a sulfonylurea.

Most episodes of hypoglycemia were mild to moderate in intensity, and all resolved with oral administration of carbohydrate. To reduce the risk of hypoglycemia associated with the use of a sulfonylurea, reduction in the dose of sulfonylurea may be considered (see DOSAGE AND ADMINISTRATION). When used as add-on to a thiazolidinedione, with or without metformin, the incidence of symptomatic mild to moderate hypoglycemia with BYETTA was 11% compared to 7% with placebo.

BYETTA did not alter the counter-regulatory hormone responses to insulin-induced hypoglycemia in a randomized, double-blind, controlled study in healthy subjects.

Information for Patients—Patients should be informed of the potential risks of BYETTA. Patients should also be fully informed about self-management practices, including the importance of proper storage of BYETTA, injection technique, timing of dosage of BYETTA as well as concomitant oral drugs, adherence to meal planning, regular physical activity, periodic blood glucose monitoring and HbA_{1c} testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications.

Patients should be advised to inform their physicians if they are pregnant or intend to become pregnant.

The risk of hypoglycemia is increased when BYETTA is used in combination with an agent that induces hypoglycemia, such as a sulfonylurea (see PRECAUTIONS, Hypoglycemia).

Patients should be advised that treatment with BYETTA may result in a reduction in appetite, food intake, and/or body weight, and that there is no need to modify the dosing regimen due to such effects. Treatment with BYETTA may also result in nausea (see ADVERSE REACTIONS).

Drug Interactions—The effect of BYETTA to slow gastric emptying may reduce the extent and rate of absorption of orally administered drugs. BYETTA should be used with caution in patients receiving oral medications that require rapid gastrointestinal absorption. For oral medications that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those drugs at least 1 h before BYETTA injection. If such drugs are to be administered with food, patients should be advised to take them with a meal or snack when BYETTA is not administered. The effect of BYETTA on the absorption and effectiveness of oral contraceptives has not been characterized.

Warfarin: Since market introduction there have been some spontaneously reported cases of increased INR with concomitant use of warfarin and BYETTA, sometimes associated with bleeding.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 104-week carcinogenicity study was conducted in male and female rats and benign thyroid C-cell adenomas were observed in female rats at all exenatide doses. The incidences in female rats were 8% and 5% in the two control groups and 14%, 11%, and 23% in the low-, medium-, and high-dose groups with systemic exposures of 5, 22, and 130 times, respectively, the human exposure resulting from the maximum recommended dose of 20 mcg/day.

In a 104-week carcinogenicity study in mice, no evidence of tumors was observed at doses up to 250 mcg/kg/day, a systemic exposure up to 95 times the human exposure resulting from the maximum recommended dose of 20 mcg/day.

Exenatide was not mutagenic or clastogenic, with or without metabolic activation, in the Ames bacterial mutagenicity assay or chromosomal aberration assay in Chinese hamster ovary cells.

Pregnancy—Pregnancy Category C—Exenatide has been shown to cause reduced fetal and neonatal growth, and skeletal effects in mice at systemic exposures 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day. Exenatide has been shown to cause skeletal effects in rabbits at systemic exposures 12 times the human exposure resulting from the maximum recommended dose of 20 mcg/day. There are no adequate and well-controlled studies in pregnant women. BYETTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant mice an increased number of neonatal 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.

Nursing Mothers—It is not known whether exenatide is excreted in human milk. 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—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.

ADVERSE REACTIONS: Use with metformin and/or a sulfonylurea—In the three 30-week controlled trials of BYETTA add-on to metformin and/or sulfonylurea, adverse events with an incidence $\geq 5\%$ (excluding hypoglycemia; see Table 1) that occurred more frequently in patients treated with BYETTA (N = 963) vs placebo (N = 483) were: 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%), and dyspepsia (6% vs 3%).

The adverse events associated with BYETTA generally were mild to moderate in intensity. The most frequently reported adverse event, mild to moderate nausea, 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. Adverse events reported in ≥ 1.0 to $<5.0\%$ of patients receiving BYETTA and reported more frequently than with placebo included asthenia (mostly reported as weakness), decreased appetite, gastroesophageal reflux disease, and hyperhidrosis. Patients in the extension studies at 52 weeks experienced similar types of adverse events observed in the 30-week controlled trials.

The incidence of withdrawal due to adverse events was 7% for BYETTA-treated patients and 3% for placebo-treated patients. The most common adverse events 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 0% due to vomiting.

Use with a thiazolidinedione—In the 16-week placebo-controlled study of BYETTA add-on to a thiazolidinedione, with or without metformin, the incidence and type of other adverse events observed were similar to those seen in the 30-week controlled clinical trials with metformin and/or a sulfonylurea. No serious adverse events were reported in the placebo arm. Two serious adverse events, namely chest pain (leading to withdrawal) and chronic hypersensitivity pneumonitis, were reported in the BYETTA arm.

The incidence of withdrawal due to adverse events was 16% (19/121) for BYETTA-treated patients and 2% (2/112) for placebo-treated patients. The most common adverse events leading to withdrawal for BYETTA-treated patients were nausea (9%) and vomiting (5%). For placebo-treated patients, $<1\%$ withdrew due to nausea. 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 anti-exenatide antibody.

Spontaneous Data—Since market introduction of BYETTA, the following additional adverse reactions have been reported. Because these events 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. *General:* injection-site reactions; dysgeusia; somnolence, INR increased with concomitant warfarin use (some reports associated with bleeding). *Allergy/Hypersensitivity:* generalized pruritus and/or urticaria, macular or papular rash, angioedema; rare reports of anaphylactic reaction. *Gastrointestinal:* nausea, vomiting, and/or diarrhea resulting in dehydration with some reports associated with increased serum creatinine/acute renal failure that may be reversible if treated appropriately; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis.

Immunogenicity—Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-exenatide antibodies following treatment with BYETTA.

OVERDOSAGE: Effects of an overdose include severe nausea, severe vomiting, and rapidly declining blood glucose concentrations. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

DOSAGE AND ADMINISTRATION: BYETTA therapy should be initiated at 5 mcg per dose administered twice daily at any time within the 60-minute period before the morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). BYETTA should not be administered after a meal. Based on clinical response, the dose of BYETTA can be increased to 10 mcg twice daily after 1 month of therapy. Each dose should be administered as a SC injection in the thigh, abdomen, or upper arm.

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RESEARCH BRIEFS

► Below are summaries of selected endocrinology studies to be published in the coming months. See the unedited reports at www.endojournals.org. Select the journal and click on "Rapid Electronic Publications."

Studies Coming in *The Journal of Clinical Endocrinology & Metabolism*

► **Increased androgen receptor CAG length is associated with idiopathic male infertility, suggesting that even subtle disruptions in the androgen axis might compromise male fertility.**

Davis-Dao CA, Tuazon ED, Sokol RZ, Cortessis VK. *Male infertility and variation in CAG repeat length in the androgen receptor gene: a meta-analysis.*

► **¹⁸F-FDG PET provides high sensitivity to malignant lesions and might be a potentially useful tool in evaluating thyroid nodules with indeterminate cytological findings, curbing unnecessary thyroidectomies 39%.**

Moreno Sebastianes F, Cerci JJ, Zanoni PH, et al. *Role of ¹⁸F-FDG PET in preoperative assessment of cytologically indeterminate thyroid nodules.*

► **Posttraumatic hypopituitarism is an independent predictor of the classical phenotypic features of hypopituitarism.**

Klose M, Watt T, Brennum J, Feldt-Rasmussen U. *Posttraumatic hypopituitarism is associated with an unfavorable body composition and lipid profile, and decreased quality of life 12 months after injury.*

► **Women randomized to a lifestyle intervention to prevent menopausal weight gain or promote modest weight loss experienced more hip bone loss than controls.**

Park HA, Lee JS, Kuller LH, Cauley

JA. *Effects of weight control during the menopausal transition on bone mineral density.*

Studies Coming in *Molecular Endocrinology*

► **Autocrine insulin signaling, compromised in diabetes, is essential to up-regulate both basal and glucose-stimulated levels of a vital family of second messengers that preserve and drive pancreatic β -cell function.**

Yu J, Berggren P-O, Barker CJ. *An autocrine insulin-feedback loop maintains pancreatic-cell 3-phosphorylated inositol lipids.*

► **Activin/Smad3 signaling is necessary for efficient signaling by FSH in *Inha*^{-/-} tumor cells. Interrupting this pathway uncouples FSH from its intracellular mitogenic effectors.**

Looyenga BD, Hammer GD. *Genetic removal of Smad3 from inhibin-null mice attenuates tumor progression by uncoupling extracellular mitogenic signals from the cell cycle machinery.*

► **The novel function observed for human HSD17B1 might lead to drugs against androgen-related dysfunctions in females.**

Saloniemi T, Lamminen T, Huhtinen K, et al. *Activation of androgens by hydroxysteroid dehydrogenase (17 β) 1 in vivo as a cause of prenatal masculinization and ovarian benign serous cystadenomas.*

► **By examining the role of these genes in TSD, we can begin to elucidate elements of conservation and divergence between sex-determining mechanisms.**

Shoemaker CM, Queen J, Crews D. *Response of candidate sex-determining genes to changes in temperature reveals their involvement in the*

molecular network underlying temperature-dependent sex determination.

Studies Coming in *Endocrinology*

► **MAP kinases ERK and p38 are probably essential pathways activated by Wnt proteins for the development of mesenchymal cells into osteoprogenitors.**

Caverzasio J, Manen D. *Essential role of Wnt3a-mediated activation of MAP kinase p38 for the stimulation of alkaline phosphatase activity and matrix mineralization in C3H10T1/2 mesenchymal cells.*

► **IGF-I infusion causes a dissociation of adrenal growth and function during late gestation.**

Ross TJ, McMillen IC, Lok F, Thiel AG, Owens JA, Coulter CL. *Intra-fetal insulin-like growth factor-1 infusion stimulates adrenal growth but not steroidogenesis in the sheep fetus during late gestation.*

► **The study shows rapid proteasome-dependent clearance of activated glucocorticoid receptors, but not mineralocorticoid receptors, allowing dynamic interaction with rapidly changing physiological and environmental conditions.**

Conway-Campbell BL, McKenna MA, Wiles CC, Atkinson HC, de Kloet ER, Lightman SL. *Proteasome-dependent downregulation of activated nuclear hippocampal glucocorticoid receptors determines dynamic responses to corticosterone.*

► **Xenoestrogens inhibit the endocrine functions of fetal Leydig cells through an ER α -dependent mechanism.**

Cederroth CR, Schaad O, Descombes P, Chambon P, Vassalli J-D, Nef S. *ER α is a major contributor to estrogen-mediated fetal testis dysgenesis and cryptorchidism.* ■

Diffuse Osteopenia & Vitamin D Deficiency: Case Study *

By Daniel D. Bikle, M.D., Ph.D.

Case

A 60-year-old white male enters your office with a complaint of low back pain. His primary physician had ordered a lateral spine X-ray that showed diffuse osteopenia, degenerative changes primarily in the lumbar spine, and the question of mild compression fractures in T6 and L1. Dual-energy X-ray absorptiometry (DXA) measurements of the spine and hip documented the osteopenia. You are asked to see the patient to help manage the osteoporosis.

The back pain is not severe, is not associated with neurologic problems, but is starting to interfere with routine activities around the house. The patient has no history of trauma to the back but gives a 40 pack/year history of cigarette smoking, which he quit 5 years ago. He drinks socially now, but was a heavier drinker during his 5 years in the military. He gives no history of malabsorption, but avoids dairy products because they give him gas. He is a bit of a couch potato and does not spend much time outside. As a child, he had an episode of glomerulonephritis, which he remembers as following a severe sore throat. An Army physical showed protein in the urine, but it was not enough to keep him out of the draft.

Your initial physical examination finds a mildly overweight male in no acute distress, but with some stiffness and pain on flexion of the back.

Questions

1. What lab tests should be ordered?
2. The serum calcium (Ca) and phos-

phorus (P) come back at 9.1 mg/dL (2.3 mmol/L) and 2.9 mEq (mmol/L), respectively. 25 hydroxyvitamin D (25OHD) is 15 ng/mL (37.4 nmol/L). 24-hour urine calcium is 70 mg (1.75 mmol/24 h),



with creatinine of 1600 mg/dL (141,440 μ mol/L). What additional information is needed? What should be your approach to treatment?

Answers

1. This begins as a workup for osteoporosis. Multiple factors need to be considered, including the heavy drinking and smoking history, avoidance of dairy products, lack of sunlight exposure, and potential for a protein-losing nephropathy. A standard minimum workup would include serum Ca, P, albumin, and a 24-h urine for Ca and creatinine. 25OHD should be ordered for a patient with this nutritional history.

Parathyroid hormone can be ordered if indicated, depending on the initial round of less-expensive tests. Tests such as serum protein electrophoresis (SPEP) can be reserved for cases in which the index of suspicion for multiple myeloma is higher. Testosterone levels are unlikely to be helpful in the absence of symptoms of libido loss and erectile dysfunction.

2. The initial tests come back indicative of vitamin D insufficiency. If the albumin levels were also low, both the Ca and the 25OHD levels would need correction. Assuming this is not the case, the etiology is likely to be nutritional. However, an occult malabsorption syndrome should be considered, and additional tests such as endomysial antibodies could be obtained. Nevertheless, it would be reasonable to treat this patient with 50,000 IU vitamin D weekly for 4–6 weeks, along with 500 mg calcium supplementation, in an attempt to restore 25OHD levels to above 30 ng/mL (75 nmol/L) and urine Ca levels to 100–200 mg/24 h (2.5–5 mmol/L), with maintenance vitamin D and calcium supplements daily thereafter. If restoring the 25OHD to normal proves difficult with this regimen, then a malabsorption workup should be considered. ■

* Case study from Clinical Endocrinology Update, 2006 syllabus. on "How & When of Vitamin D" was written by Dr. Bikle, VA Medical Center/University of California, San Francisco, (daniel.bikle@ucsf.edu).

Read More Case Studies

To obtain a Clinical Endocrinology Update syllabus from 2006 or 2007, at a cost of \$95 for Endocrine Society members or \$110 for nonmembers, please contact societyservices@endo-society.org.

The Hormone Foundation's

Patient Guide to the Management of Maternal Hyperthyroidism Before, During and After Pregnancy

Why were the guidelines written?

This patient guide is based on clinical guidelines written to help physicians who are evaluating and treating various types of thyroid dysfunction in women before, during, and after their pregnancy (postpartum). Pregnancy, even in women with no thyroid abnormalities, causes major changes in thyroid hormone levels. Because of the complex changes in thyroid function that occur during and after pregnancy, and because thyroid disease in the mother can affect the course of her pregnancy and the developing fetus, as well as the mother's health in the postpartum period, the diagnosis and management of thyroid diseases during pregnancy requires special considerations.

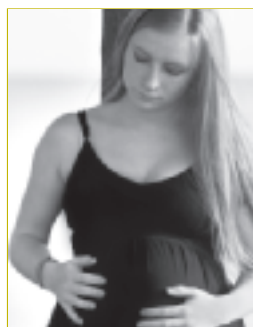
This guide summarizes information about the best way to diagnose and manage maternal hyperthyroidism, a condition in which the mother has too much of the thyroid hormones T3 and T4 (also called an overactive thyroid). A pregnant woman might overlook some of the symptoms of hyperthyroidism as just being part of pregnancy: for example, feeling warm, hard or fast heartbeats, nervousness, trouble sleeping, and nausea. However, hyperthyroidism during pregnancy, if left untreated, poses a risk for both mother and baby. Having too much thyroid hormone greatly increases your metabolism. Pregnant women with uncontrolled hyperthyroidism can develop high blood pressure and are at greater risk of heart problems. There is also a greater risk of miscarriage, premature birth, and having a baby with low birth weight. Furthermore, it is important for all women to know that thyroid dysfunction occurs in the first year postpartum in approximately 7% of all women, despite the fact that these women have had no known thyroid disease before pregnancy.

How were the guidelines developed?

The clinical guidelines were developed after an extensive review of the best clinical studies about thyroid dysfunction in pregnant and postpartum women and about the effects of treatment on the mother and baby. An international expert panel of The Endocrine Society examined evidence from studies that had been published in "peer-reviewed" medical journals (that is, the studies were carefully evaluated by the journal's scientists and editors). The panel's "recommendations" and "suggestions" were reviewed and approved by several committees and, finally, by the general membership of The Endocrine Society. No funding for the guidelines came from any pharmaceutical company.

Who is at higher risk of hyperthyroidism during pregnancy?

Eighty-five percent of all cases of hyperthyroidism during pregnancy is caused by Graves' disease. Graves' disease occurs when your immune system becomes overactive and forms antibodies (immune proteins) that attack the thyroid gland. This causes the thyroid to enlarge and make too much thyroid hormone.



Pregnancy causes major changes in thyroid hormone levels. Before becoming pregnant, consult with your doctor about your thyroid health.

Graves' disease runs in families with a history of thyroid disease, is more common in women and most often begins between the ages of 20–40. Because of the immune changes associated with pregnancy, some women develop new onset Graves' disease during the first postpartum year. Most of the remaining cases of hyperthyroidism during pregnancy are due to an enlarged thyroid gland that contains a small rounded lump or lumps called *nodules*, which produce too much thyroid hormone.

What special considerations apply to the diagnosis and management of hyperthyroidism during pregnancy and postpartum?

Because of the harmful effects hyperthyroidism can have on the course of pregnancy, it is best to know whether you have this



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condition before becoming pregnant. Women with a family history of thyroid disease or any autoimmune disease are at increased risk for hyperthyroidism. Typical symptoms of hyperthyroidism can include:

- Feeling too hot when others are comfortable
- Trembling hands
- Rapid heartbeat
- Tiredness/fatigue
- Weight loss even though you are eating normally or too much
- Trouble sleeping
- Irritability and anxiety



To ensure your health and the health of your baby, take your recommended medication as prescribed, keep regular appointments with your doctor, and adopt a healthy lifestyle.

A personal or family history of thyroid disease or any signs or symptoms of hyperthyroidism should alert your physician to perform blood tests to measure thyroid hormone and antibody levels. Hyperthyroidism is characterized by higher than normal levels of T4 and T3 and very low levels of *thyroid stimulating hormone* (TSH). TSH is a hormone made by the pituitary gland and stimulates the thyroid gland to make thyroid hormone. However, when the thyroid gland becomes overactive, there is no need for TSH and the pituitary gland stops making it. In addition to low TSH and high T4 and T3, most patients with Graves' disease also have measurable TSH receptor antibodies. These antibodies can be passed across the placenta from the mother to the baby and stimulate the baby's thyroid, causing fetal thyroid dysfunction and other medical problems. All newborns of mothers with Graves' disease should be examined for evidence of thyroid dysfunction and treated if necessary.

Postpartum thyroiditis (PPT)—a thyroid inflammation that occurs in 7% of all women during the first year postpartum. PPT has different phases, the first of which is the hyperthyroid phase. Frequently, the hyperthyroid phase of PPT clears up without treatment after a period of a few weeks or months and thyroid function returns to normal. However, in many women the hyperthyroid phase of PPT damages their thyroid gland and a hypothyroid phase of the disease follows. Women in the hypothyroid phase often have symptoms of weight gain, dry skin and tiredness and require treatment. Approximately 30% of women who have had PPT will develop permanent hypothyroidism within the next 10 years. Annual evaluation of thyroid hormone levels is, therefore, recommended.

What is the recommended treatment for hyperthyroidism?

For hyperthyroidism due to Graves' disease or overactive thyroid nodules, antithyroid drug therapy should either be started (for women with newly diagnosed hyperthyroidism) or adjusted (for those with a prior diagnosis) to maintain the maternal thyroid hormone levels in the appropriate range. For pregnant and breast-feeding women, the antithyroid drug propylthiouracil (PTU) is recommended. Methimazole may be prescribed if a patient has problems with PTU.

Pregnancy has a direct impact on the activity level of Graves' disease. Hyperthyroidism caused by Graves' diseases typically improves throughout pregnancy. On the other hand, Graves' disease frequently worsens during the first six months postpartum. Because of these changes your doctor may need to adjust your dose of antithyroid drug therapy, both during and after pregnancy.

Most cases of Graves' disease during pregnancy can be treated with antithyroid medication. On occasion, and under some circumstances, surgery to remove part of the thyroid may be needed:

- The patient has a very bad reaction to antithyroid drug therapy.
- The patient continues to require high doses of antithyroid drug therapy over time.
- The patient does not take her medication as prescribed and has uncontrolled hyperthyroidism.

The best time for such surgery is during the second trimester of pregnancy (months 4–6).

Treatment with radioactive iodine should not be given to a woman who is, or may become, pregnant because the radioactive iodine can cross the placenta and destroy the baby's thyroid.

What can you do to help your treatment process?

You and your doctor should be partners in your care. Before becoming pregnant, consult with your doctor about your thyroid status. It is important that you provide your doctor with a full description and history of your symptoms, however minor they may seem, as well as a thorough medical and family history. When a diagnosis of hyperthyroidism is made, discuss treatment options with your doctor. Radiation therapy should be avoided if you are pregnant or if you plan on becoming pregnant in the next 6–12 months. If antithyroid drug therapy is prescribed, it is important to take your medication as instructed during pregnancy and breast-feeding. Keep regular appointments with your doctor and ask questions. You should tell your doctor about any side effects you are having. Be sure to follow your health care provider's advice about your nutritional needs.

EDITORS

Leslie J. De Groot, MD
Alex Stagnaro-Green, MD
Robert Vigersky, MD

September 2007

This patient guide is the second of three guides based on the Endocrine Society's clinical guidelines on maternal thyroid dysfunction before, during and after pregnancy. Part 1 addresses maternal hypothyroidism and part 3 addresses thyroid nodules and thyroid cancer.

Society update

Trainee Corner

► Greetings from the Trainee Development Committee!

Now that fall has arrived, we bring your attention to information on funding sources. In addition to the various awards and fellowships offered to trainees by The Endocrine Society, several funding options and resources are available to you online.

If you are seeking funding to support your research, GrantsNet is a searchable database of funding options from a variety of organizations. The site, supported by the Howard Hughes Medical Institute and the American Association for the Advancement of Science, includes a great list of funding resources available in Europe, Asia, and the Americas. You may search this database at www.grantsnet.org.

The National Institutes of Health (NIH) is a long-standing source of funding. To help you navigate funding options at the NIH, a Career Award Wizard is available on the career development Web site, <http://grants.nih.gov/training/careerdevelopmentawards.htm>, and can help you find the most appropriate grant for patient- or non-patient-oriented research. In addition to grants and fellowships, the NIH also maintains a Career Resources Web site with information about grant writing and interviewing skills at <http://grants.nih.gov/training/resources.htm>. Finally, the NIH site, <http://grants.nih.gov/training/index.htm>, is invaluable for information on research training and career development.

In addition to grants and fellowships to support your career develop-

ment, there are financial resources to help trainees who face educational loan repayment and several organizations can help you become a well-informed consumer and successfully navigate the repayment process. For trainees with doctoral degrees, an NIH program provides up to \$35,000 in educational debt repayment (in addition to the corresponding federal taxes). Find more information at www.lrp.nih.gov/about/index.htm.

For trainees early in their career development, the Association of American Medical Colleges has a wealth of information on financing your medical education, from undergraduate school through residency, at www.aamc.org/students/financing/start.htm. For guidance about financial aid through graduate school, a good starting place is the Graduate and Professional Students section of the Federal Student Aid Web site, <http://studentaid.ed.gov/PORTALSWebApp/students/english/gradstudent.jsp>. Additionally, Access Group has a great online loan repayment calculator, a comprehensive glossary of terms, and additional links to programs and resources. Their site is at www.accessgroup.org/calculators/loan_repay.htm.

We hope these online resources provide you with the support and information you need as you navigate the funding process and develop your career. Also, take advantage of what The Endocrine Society has available by visiting the Awards section at www.endo-society.org.

Finally, if you have encountered additional resources that have been helpful to you in your career development, we'd love to hear from you so

we can include them in our growing list of resources for endocrine trainees.



All the best,
Rhonda Bentley-Lewis, M.D., M.B.A., M.M.Sc.

Attention Endocrine Society Members!

► It's time to renew your membership for 2008! And we have some good news. To keep the cost of your membership affordable, your membership dues for 2008 will not increase; you will pay the same for 2008 as you did for 2007!

To renew your membership today, simply visit The Endocrine Society's Web site at www.endo-society.org, click on "Renew My Membership," complete the form, and submit it along with your Visa or MasterCard payment. You will receive a confirmation email that will serve as your receipt. If you prefer not to pay online, look for your renewal invoice to be mailed to you in late October. Don't miss out on a single moment of The Endocrine Society membership experience: Renew now!

This is also the perfect time to join The Endocrine Society or reinstate your membership. For information on criteria for joining and to access application and reinstatement forms, visit www.endo-society.org/join. Your membership will begin immediately—an extra 3 months of membership for free!

To speak with a staff person about renewing or reinstating your membership, or about joining The Endocrine Society, please contact Society Services at 301-941-0210 or 888-363-6762. You can also email Society Services at societyservices@endo-society.org.

Share Your Research: ENDO 08 Abstract Submissions

► Get ready to submit your abstract for ENDO 08. The abstract submission

calendar

DECEMBER 5–6, 2007: WASHINGTON, D.C.
Targeting Bone Remodeling for the Treatment of Osteoporosis, co-sponsored by the Society for Bone and Mineral Research and The Endocrine Society. For more information, visit www.asbmr.org/other/programInfo.cfm.

JUNE 15–18, 2008: SAN FRANCISCO, CALIF.
The Endocrine Society's 90th annual meeting, ENDO 2008. For more information, visit www.endo-society.org.

SEPTEMBER 25–28, 2008: BOSTON, MASS.
CEU 2008.
Board Review, September 23
For more information, visit www.endo-society.org/educationevents/ceu.

NOVEMBER 8–12, 2008: RIO DE JANEIRO, BRAZIL.
International Congress of Endocrinology. Visit www.ice2008rio.com for program details.

Above events are Endocrine Society-related. See more events at www.endo-society.org, on the **Worldwide Endocrine Events Calendar**.

site will open on November 15, 2007. ENDO 08 is the world's largest gathering of endocrine professionals, to be held June 15–18, 2008.

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

Society's Bridge Grant Program in 2008

► The Endocrine Society is now accepting applications for its 2008 Bridge Grant Program. Begun as a pilot project in 2007, the program offers the opportunity for investigators to receive as much as \$50,000 in direct research costs for 1 year. Members of The Endocrine Society for at least 3 years who have encountered denial of a previously funded research project in a promising area of endocrinology are eligible. In response to member input, some changes have been made to the eligibility requirements for 2008. The new criteria are explained in detail on the Society's Web site and in application materials.

During the first cycle, applications will be accepted from October 1 through December 1, 2007, and the award period will begin February 1,

2008. More information and application instructions are available on the Society's Web site, www.endo-society.org.

Web Tip

► *Where can I find employment opportunities on The Endocrine Society's Web page?*

The Society's Web page has a special area for job seekers—and it's free! On the home page (www.endo-society.org), click on the "Jobs" link under the "Popular Resources" section at the upper left. This will take you to the "Placement Services" page. Use the "Employment Opportunities Database" to search through the more than 50 endocrine-related jobs presently posted. The search tool allows you to filter by:

- city, state, or country
- type of position
- required educational qualifications

You may also use the "Submit

Your CV" link to let employers know you're available.

In Memoriam

John W. Chriss, M.D.
Corpus Christi, Tex.
1920–2007

François Delange, M.D.
Brussels, Belgium
1935–2007

Herbert Fleisch, M.D.
Lausanne, Switzerland
1933–2007

Richard Donald Gambrell, Jr., M.D.
Augusta, Ga.
1932–2007

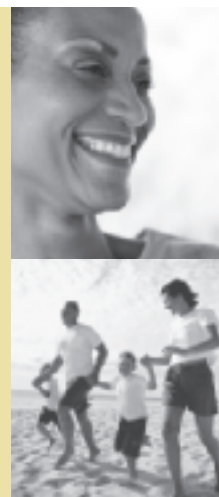
Howard Judd, M.D.
Los Angeles, Calif.
1935–2007 ■

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communication.

Educate patients.

Save time.

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www.hormone.org



Recognized for innovation in patient education, The Hormone Foundation's bilingual patient fact sheet series—**Hormones & You**—delivers easy-to-understand information in English and Spanish on more than 30 hormone-related topics. It's the easiest and most effective way to expand communication with your patients.



**Sunny Southern California Endocrinology Physician**

Southern California's leading physician-owned multi-specialty medical group has an opportunity for a full-time Endocrinology physician in our San Gabriel, California (Pasadena area) Region. Candidates must be Board certified and have a current California medical license. We are a large, dynamic and well-established group and offer a balanced professional and personal lifestyle, as well as excellent compensation with Partnership Track and benefits. Apply online at <http://www.healthcarepartners.com/careers/careers.asp>, Clinician/Physician Opportunities. Email CV to sdeming@healthcarepartners.com. HealthCare Partners Medical Group headquarters is located in Torrance, California.

Pediatric Endocrinologist

The Department of Pediatrics at Wayne State University School of Medicine/Children's Hospital of Michigan seeks candidate for Assistant or Associate Professor position on Clinician-Educator or Research-Educator

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

track. Please submit CV and letter of interest to Denise Henderson, Children's Hospital of Michigan. 3901 Beaubien, Rm 1K 40, Detroit, MI 48201. Phone 313-993-8786; fax 313-993-0390; email DHenders2@dmc.org.

Florida

Outstanding opportunity for a BC/BE Endocrinologist to join a well-established practice on the east of Central Florida. 100% consultative practice. Reasonable call. Generous base salary with productivity bonus, excellent benefits leading to early partnership. Diabetes center with 3 CDEs. Family-oriented community with excellent schools. Variety of recreational activities. Fax CV to 321-728-0226 or email deligdish@msn.com.

Postdoctoral Fellowships in Reproductive Endo

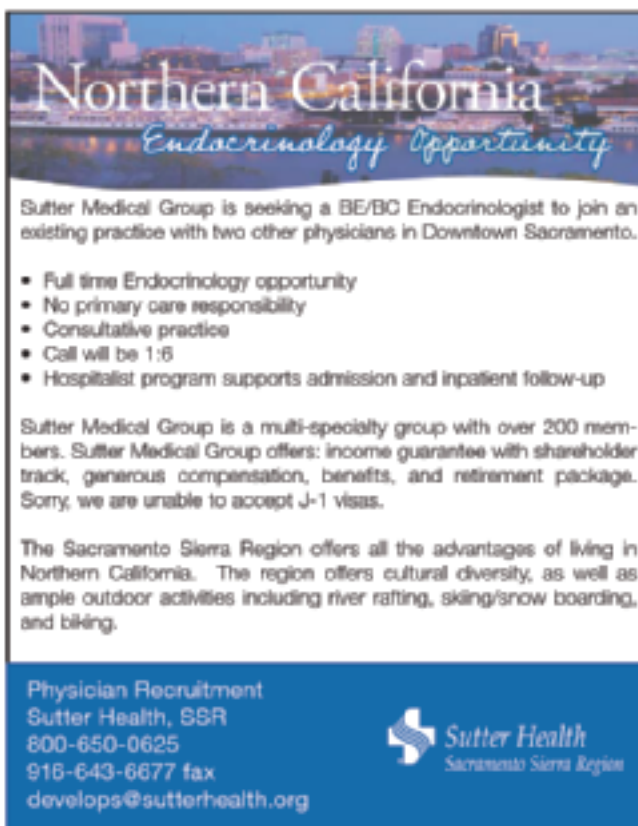
Post-doctoral Fellowship Positions Available in The Harvard Reproductive Endocrine Sciences Center, Boston, MA: The Harvard Reproduc-

tive Endocrine Sciences Center is seeking outstanding post-doctoral research fellows with a primary interest in an academic career in the scientific area of the neuroendocrine and genetic control of reproduction. Competitive candidates should be; a) US citizens (or have achieved Permanent Resident Status i.e. have a green card); b) have an MD, PhD, or MD/PhD degree; c) be seeking an academic career; d) have an interest in translational investigation; and e) be familiar with the contemporary investigative tools of genetics, molecular biology, physiology, structural biology, and human/animal investigation. Minorities and women are especially encouraged to apply. Appropriate candidates should send their CVs to Dr. William Crowley, Center Director, Harvard Reproductive Endocrine Sciences Center, Bartlett Hall Extension 5, 55 Fruit St., Massachusetts General Hospital, Boston, MA, 02114; crowley.william@mgh.harvard.edu.

CHARLOTTE METRO AREA

CaroMont Medical Group, an affiliate of CaroMont Health, is offering an outstanding opportunity for a BE/BC endocrinologist to practice with two other physicians in single specialty clinic. This is an employed position and is the only endocrinology practice in our community. Located just outside of the greater Charlotte metro area, our physicians have access to a modern and progressive 435-bed community hospital providing comprehensive care to patient base of over 350,000. We are especially proud of our Wound and Diabetes Centers, an outpatient program committed to providing training and self management education to patients with diabetes. Lovely community having easy access to the beautiful North Carolina Mountains and some of the most popular beaches on the East Coast and minutes from major international airport and two large lakes, community offers unlimited cultural and recreational amenities. A superb quality of life exists here with many lovely neighborhoods and good choice of public and private schools. If interested in learning more about this opportunity, please send CV to: Celia G. Billings, Manager, Physician Recruitment, CaroMont Health, 2240 Remount Road, Gastonia, NC 28054. Telephone: 704-834-2153, Fax: 704-834-4615, E-mail: billingsc@gmh.org, Web site: www.caromont.org.

Sorry, no J-1 opportunities available.



Northern California Endocrinology Opportunity


Sutter Medical Group is seeking a BE/BC Endocrinologist to join an existing practice with two other physicians in Downtown Sacramento.

- Full time Endocrinology opportunity
- No primary care responsibility
- Consultative practice
- Call will be 1:6
- Hospitalist program supports admission and inpatient follow-up

Sutter Medical Group is a multi-specialty group with over 200 members. Sutter Medical Group offers: income guarantee with shareholder track, generous compensation, benefits, and retirement package. Sorry, we are unable to accept J-1 visas.

The Sacramento Sierra Region offers all the advantages of living in Northern California. The region offers cultural diversity, as well as ample outdoor activities including river rafting, skiing/snow boarding, and biking.

Physician Recruitment
Sutter Health, SSR
800-650-0625
916-643-6677 fax
develops@sutterhealth.org



to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m²). No drug-induced tumors were observed in any organ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving ACTOS in clinical trials up to one year in duration, no new cases of bladder tumors were identified. In two 3-year studies in which pioglitazone was compared to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on pioglitazone and two (0.05%) on placebo.

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an *in vitro* cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an *in vivo* micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m²).

Animal Toxicology

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone HCl (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m²). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m²). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m²), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m²).

Pregnancy

Pregnancy Category C. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m², respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m²). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m²). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m²).

There are no adequate and well-controlled studies in pregnant women. ACTOS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

Pioglitazone is secreted in the milk of lactating rats. It is not known whether ACTOS is secreted in human milk. Because many drugs are excreted in human milk, ACTOS should not be administered to a breastfeeding woman.

Pediatric Use

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

Elderly Use

Approximately 500 patients in placebo-controlled clinical trials of ACTOS were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS

Over 8500 patients with type 2 diabetes have been treated with ACTOS in randomized, double-blind, controlled clinical trials. This includes 2605 high-risk patients with type 2 diabetes treated with ACTOS from the PROactive clinical trial. Over 6000 patients have been treated for 6 months or longer, and over 4500 patients for one year or longer. Over 3000 patients have received ACTOS for at least 2 years.

The overall incidence and types of adverse events reported in placebo-controlled clinical trials of ACTOS monotherapy at doses of 7.5 mg, 15 mg, 30 mg, or 45 mg once daily are shown in Table 2.

Table 2 Placebo-Controlled Clinical Studies of ACTOS Monotherapy: Adverse Events Reported at a Frequency ≥ 5% of Patients Treated with ACTOS

	(% of Patients)	
	Placebo N=259	ACTOS N=606
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth Disorder	2.3	5.3
Diabetes Mellitus Aggravated	8.1	5.1
Pharyngitis	0.8	5.1

For most clinical adverse events the incidence was similar for groups treated with ACTOS monotherapy and those treated in combination with sulfonylureas, metformin, and insulin. There was an increase in the occurrence of edema in the patients treated with ACTOS and insulin compared to insulin alone.

In a 16-week, placebo-controlled ACTOS plus insulin trial (n=379), 10 patients treated with ACTOS plus insulin developed dyspnea and also, at some point during their therapy, developed either weight change or edema. Seven of these 10 patients received diuretics to treat these symptoms. This was not reported in the insulin plus placebo group.

The incidence of withdrawals from placebo-controlled clinical trials due to an adverse event other than hyperglycemia was similar for patients treated with placebo (2.8%) or ACTOS (3.3%).

In controlled combination therapy studies with either a sulfonylurea or insulin, mild to moderate hypoglycemia, which appears to be dose related, was reported (see **PRECAUTIONS, General, Hypoglycemia**).

In U.S. double-blind studies, anemia was reported in ≤ 2% of patients treated with ACTOS plus sulfonylurea, metformin or insulin (see **PRECAUTIONS, General, Hematologic**).

In monotherapy studies, edema was reported for 4.8% (with doses from 7.5 mg to 45 mg) of patients treated with ACTOS versus 1.2% of placebo-treated patients. In combination therapy studies, edema was reported for 7.2% of patients treated with ACTOS and sulfonylureas compared to 2.1% of patients on sulfonylureas alone. In combination therapy studies with metformin, edema was reported in 6.0% of patients on combination therapy compared to 2.5% of patients on metformin alone. In combination therapy studies with insulin, edema was reported in 15.3% of patients on combination therapy compared to 7.0% of patients on insulin alone. Most of these events were considered mild or moderate in intensity (see **PRECAUTIONS, General, Edema**).

In one 16-week clinical trial of insulin plus ACTOS combination therapy, more patients developed congestive heart failure on combination therapy (1.1%) compared to none on insulin alone (see **WARNINGS, Cardiac Failure and Other Cardiac Effects**).

Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive)

In PROactive, 5238 patients with type 2 diabetes and a prior history of macrovascular disease were treated with ACTOS (n=2605), force-titrated up to 45 mg daily or placebo (n=2633) in addition to standard of care. Almost all subjects (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, ARBs, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates). Patients had a mean age of 61.8 years, mean duration of diabetes 9.5 years, and mean HbA_{1c} 8.1%. Average duration of follow-up was 34.5 months. The primary objective of this trial was to examine the effect of ACTOS on mortality and macrovascular morbidity in patients with type 2 diabetes mellitus who were at high risk for cardiovascular events. The primary efficacy variable was the time to the first occurrence of any event in the cardiovascular composite endpoint (see **Table 3** below). Although there was no statistically significant difference between ACTOS and placebo for the 3-year

incidence of a first event within this composite, there was no increase in mortality or in total macrovascular events with ACTOS.

Table 3

Number of First and Total Events for Each Component within the Cardiovascular Composite Endpoint	Placebo N=2633		ACTOS N=2605	
	First Events (N)	Total Events (N)	First Events (N)	Total Events (N)
Cardiovascular Events				
Any event	572	900	514	803
All-cause mortality	122	186	110	177
Non-fatal MI	118	157	105	131
Stroke	96	119	76	92
ACS	63	78	42	65
Cardiac intervention	101	240	101	195
Major leg amputation	15	28	9	28
Leg revascularization	57	92	71	115

Postmarketing reports of new onset or worsening diabetic macular edema with decreased visual acuity have also been received (see **PRECAUTIONS, General, Macular Edema**).

Laboratory Abnormalities

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with ACTOS appears to be dose related. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with ACTOS therapy and have rarely been associated with any significant hematologic clinical effects.

Serum Transaminase Levels: During all clinical studies in the U.S., 14 of 4780 (0.30%) patients treated with ACTOS had ALT values ≥ 3 times the upper limit of normal during treatment. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with ACTOS, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.9% of patients treated with ACTOS were withdrawn from clinical trials in the U.S. due to abnormal liver function tests.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see **PRECAUTIONS, General, Hepatic Effects**).

CPK Levels: During required laboratory testing in clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. An isolated elevation to greater than 10 times the upper limit of normal was noted in 9 patients (values of 2150 to 11400 IU/L). Six of these patients continued to receive ACTOS, two patients had completed receiving study medication at the time of the elevated value and one patient discontinued study medication due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to ACTOS therapy is unknown.

OVERDOSAGE

During controlled clinical trials, one case of overdose with ACTOS was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdose, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

Rx only

Manufactured by:
Takeda Pharmaceutical Company Limited
Osaka, Japan

Marketed by:
Takeda Pharmaceuticals America, Inc.
One Takeda Parkway
Deerfield, IL 60015

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L-PIO-0807-5

CLASSIFIEDS



Endocrinologist

Due to extensive practice growth and community need we are assisting a premier Endocrinologist in recruiting a future partner. This is an opportunity to work with a leader in Endocrinology services at the Rose Medical Center in Denver. The physician has been named by peers as one of Denver's top endocrinologists and has received prestigious teaching awards from the University. The practice has been in existence over 25 years and has to turn away patients. Rose Medical Center, a Solucient Top 100 U.S. Hospital, is located in Cherry Creek, an affluent in-town area with some of Denver's most elite homes, shopping and schools. You can be busy quickly and have the opportunity to take over this renowned practice. Contact Corey McDonald, HCA/HealthONE Physician Services Continental Division, Hospital Corporation of America, 125 E. Hampden Avenue, Englewood, CO 80113; office

303-788-9298; toll-free 877-422-3627; cell 303-815-0723; fax 866-826-7460; email Corey.McDonald@HCAHealthcare.com.

Texas

Diabetes & Glandular Disease Clinic of San Antonio is searching for an additional BC/BE Endocrinologist. We are located in one of the top ten best cities with a great life style, family activities and warm climate. Our city boasts a wealth of cultural, recreational and entertainment activities. The state has a cap on medical malpractice and there is no state income tax. All of our hospitals are within one mile of each other. We have our own in-house laboratory, 2 bone densitometers, 2 ultrasounds, full EMR and an ADA recognized diabetes education program. Our clinic consists of 8 Endocrinologists, 6 Nurse Practitioners, 1 Physician Assistant and 5 Certified Diabetes Educators. University appointments are available. This opportunity offers a starting salary range of \$200,000. If you are a serious candidate, please send a letter of interest along with your CV to rpyburn@dgdclinic.com.

Chicago Suburbs


Assist in building department. 120+ primary care referral base. Guaranteed salary plus bonus. Partnership after two years. 20 miles from Downtown Chicago. Contact Peggy Joerling at 800-678-7858, x63792 or pjoerling@cejkasearch.com. ID#26962A15. For more opportunities, visit www.cejkasearch.com.

Christian Hospital/BJC Healthcare

Seeking BC/BE Endocrinologist for St. Louis suburban practice. Call to be 1:5. Opportunity to be an integral part of their Diabetes Institute. Attractive starting compensation and benefits, plus outstanding earning potential. Call Michelle Kraft at 800-678-7858, x63705; fax 314-726-0026; e-mail kraft@cejkasearch.com. ID#29133A15.

Endocrinologist

BC/BE to join well established, thriving group practice on the north shore of Long Island, one hour from New York City. We have an exceptional



Endocrinologist
Scottsdale, Arizona

Mayo Clinic is known locally, nationally, and internationally for outstanding achievements in patient care, research, and education. In Arizona, Mayo Clinic is a 300-physician integrated practice, focusing on high-quality, compassionate medical care delivered in a multi-specialty academic environment. Education and research are an integral part of the Mayo Clinic Model of Care.

Mayo Clinic in Arizona is seeking an outstanding individual to serve as a member of the Division of Endocrinology within the Department of Internal Medicine. Candidates must be board certified or board eligible in endocrinology. Candidates should be interested in all aspects of endocrinology. The current division consists of four endocrinologists with excellent mid-level support staff and an ADA recognized diabetes center. The successful candidate should be interested in an academically oriented practice combined with clinical research opportunities. A record of academic endeavor is highly desirable. This position includes an academic appointment with the Mayo Clinic College of Medicine.


Mayo Clinic offers competitive compensation and comprehensive benefits, including a relocation package. Our desirable location in the beautiful Sonoran Desert of Phoenix offers every opportunity for a rewarding lifestyle.

For consideration, please forward your letter of interest and curriculum vitae to:

Michael D. Whitaker, M.D., FRCPC
Chair, Division of Endocrinology
Mayo Clinic
13400 East Shea Boulevard
Scottsdale, AZ 85259

Mayo Clinic is an affirmative action and equal opportunity educator and employer. Post-offer/pre-employment drug screening is required.

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Adult Endocrinology

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PEDIATRIC ENDOCRINOLOGISTS

University of Iowa Children's Hospital

Seeking two Pediatric Endocrinologists. These are open-rank, full-time positions on either the clinical or tenure track.

Requirements: Must hold an M.D. degree; Board certified in Pediatrics and certified/eligible in Pediatric Endocrinology; Candidates applying for a tenure track position must demonstrate evidence of scholarly investigation

Desirable qualifications: Clinical experience in Pediatric Endocrinology management; Strength in teaching; Experience in patient-oriented or basic research; Strong oral and written communication/interpersonal skills; Demonstrate ability to develop and implement new programs

Iowa City is a university town of broadly diverse cultural and recreational activities, superb public schools, and affordable, safe residential neighborhoods. The University of Iowa is a strong research institution, and the hospital complex is one of the nation's largest and best university teaching hospitals. Both the University of Iowa Children's Hospital and the Carver College of Medicine have pursued vigorous building programs in recent years, and the facilities for patient-care, education, and research are outstanding.

To learn more about the University of Iowa Children's Hospital and the Iowa City community, please visit <http://www.uihealthcare.com/depts/uichildrenshospital/index.html>.

Please send CV to: Michael Artman, MD, Professor and Head, Department of Pediatrics, Physician-in-Chief, University of Iowa Children's Hospital, 200 Hawkins Drive, 2632 JCP, Iowa City, IA 52242 (michael-artman@uiowa.edu)

The University of Iowa is an equal employment opportunity/affirmative action employer, and candidates who are women or members of minority groups are strongly encouraged to apply.

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Work with renowned pediatric endocrinologists in an expanding practice that is one of the largest private practices in the nation. Belong to a highly respected Pediatric and Perinatology multi-specialty medical group that is linked with one of the most respected hospital systems in the nation. This partnership includes the support of a sophisticated multidisciplinary diabetes care team along with a comprehensive pediatric unit with plans for building a new Women's and Children's Hospital. Experience a ready-built patient base with significant growth in your practice each year with a network of over 3,000 referring physicians. Have options for teaching and research.

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Endocrinologist Needed for Wausau, WI

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Neuroendocrinology & Aging: A Perspective

By Joseph Meites, Ph.D.*

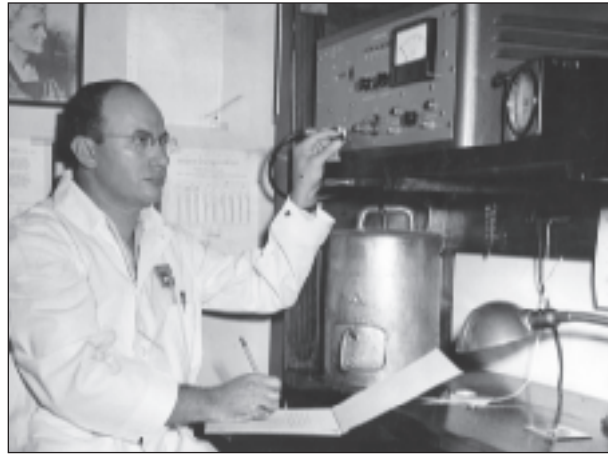
Charles Edouard Brown-Séquard was probably the first experimental neuroendocrinologist. Believing that testicular hormone secretion declined with age, he injected himself with crushed dog and guinea pig testes at 72 years of age, and announced, to considerable skepticism, that this reinvigorated him.

With no radioimmunoassays to accurately measure hormone levels and no knowledge of the hypothalamus's commanding role, early investigations were limited. Hormone-aging studies included measuring changes in endocrine gland size and weight, examining alterations in their gross and microscopic appearance, hormone bioassays, and observations of endocrine-related disorders in the elderly. Several leading investigators concluded that hormones played only a minor role in aging.

Then in the 1960s and early 1970s, Selmar Aschheim, M.T. Peng, and our own lab dealt with the relation of the hypothalamus to reproductive decline in rats. Aschheim and Peng showed that old non-cycling rats failed to exhibit estrous cycles when transplanted with young ovaries, but young ovariectomized rats resumed cycling after transplantation of ovaries from old rats. Peng further demonstrated that young hypophysectomized rats resumed cycling after receiving the pituitaries of old non-cycling rats. Apparently, neither the ovaries nor the pituitary caused loss of cycling.

We demonstrated direct hypothalamic involvement in 1969, showing that electrically stimulating the preoptic area induced ovulation in constant-estrous rats (as did epinephrine or progesterone injections). This suggested that sufficient luteinizing hormone-releasing hormone (LHRH) was present in the hypothalamus to elicit LH, but the necessary stimulus was lacking. The finding that epinephrine also evoked ovulation suggested catecholamine (CA) might be the missing stimulus. We found significantly reduced dopamine and norepinephrine in the hypothalamus of old rats. Drugs that increased hypothalamic CA induced estrous cycle resumption. Reduced hypothalamic CA also caused growth hormone (GH) and somatomedin-C secretion to decline in old male and female rats.

L-dopa injections restored pulsatile GH secretion in old male rats to young levels. A similar decline in GH and somatomedin-C secretion was observed in elderly men, also possibly related to reduced hypothalamic CA. Four different laboratories soon reported that drugs which elevated hypo-



Joseph Meites, Ph.D.

thalamic CA significantly lengthened average lifespan, decreased disease and tumor incidence, promoted sexual vigor and fertility, and improved memory in rats or mice.

The pituitary of old rats was also found less responsive to stimulation by gonadotropin-releasing hormone (GnRH), GH-releasing hormone (GHRH), thyrotropin-releasing hormone, and corticotropin-releasing factor. Similarly, the pituitary of elderly humans was less responsive to GnRH and GHRH, and evidence suggests a decline with age in target gland responses to pituitary hormones and body tissue responses to target gland hormones—likely of secondary importance to faults in the hypothalamus.

Because the neuroendocrine and immune systems form a bidirectional network, and both exhibit a functional lessening with age, determining how each affects the decline of the other is important. Reduced immune function appears to partly result from lower GH and thyroid hormone secretion.

Given to old rats, GH restores thymus gland size and function. Similarly, thyroxine elevates thymic function in old mice. The immune system's age effects on neuroendocrine function are presently unknown, but thymic peptides may alter hypothalamic, pituitary, and target gland hormone secretion.

Because the neuroendocrine and immune systems integrate body functions and maintain homeostasis, we believe genomic and environmental effects in aging are mediated through them. Others have emphasized errors in protein synthesis, increases in "free radicals" with resulting cell damage, cells failing to divide or function due to loss of a genetic program, etc.

No single theory is likely to explain all aspects of aging. The neuroendocrine approach, although relatively recent, has provided knowledge and insight into the causes of aging declines, and has suggested interventions that may inhibit or reverse them and perhaps lengthen life. ■

* Dr. Meites, who died in 2005 at age 91, was a pioneering neuroendocrinologist and professor of physiology at Michigan State University. His full article, "Remembrance: Neuroendocrinology and Aging—A Perspective," was published in *Endocrinology*, 1992;130:3107-3108.

norditropin®

somatropin (rDNA origin) injection

Norditropin® cartridges (somatropin [rDNA origin] injection)

Norditropin NordiFlex® (somatropin [rDNA origin] injection)

5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL

Rx Only

BRIEF SUMMARY. Please consult the package insert for full prescribing information.

INDICATIONS AND USAGE: Norditropin® is indicated for the long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone (GH) and for replacement of endogenous GH in adults with growth hormone deficiency (GHD) who meet either of the following two criteria: 1. Adult Onset (AO): Patients who have GHD, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; 2. Childhood Onset (CO): Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes. In general, confirmation of the diagnosis of adult growth hormone deficiency in both groups usually requires an appropriate growth hormone stimulation test. However, confirmatory growth hormone stimulation testing may not be required in patients with congenital/genetic growth hormone deficiency or multiple pituitary hormone deficiencies due to organic disease.

CONTRAINDICATIONS: Norditropin cartridges is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses. Somatropin is contraindicated in patients with active proliferative or severe nonproliferative diabetic retinopathy. In general, somatropin is contraindicated in the presence of active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Since growth hormone deficiency may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such tumors should be ruled out prior to initiation of treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor. Somatropin should not be used to treat patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. Two placebo-controlled clinical trials in non growth hormone-deficient adult patients (n=522) with these conditions in intensive care units revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin-treated patients (doses 5.3-8 mg/day) compared to those receiving placebo (see WARNINGS). Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see WARNINGS). Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Norditropin cartridges is not indicated for the long-term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

WARNINGS: See CONTRAINDICATIONS for information on increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin. If, during treatment with somatropin, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi syndrome treated with somatropin should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively (see CONTRAINDICATIONS). Unless patients with Prader-Willi syndrome also have a diagnosis of GHD, Norditropin® is not indicated for the long-term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

PRECAUTIONS: General: Norditropin® cartridges (somatropin [rDNA origin] injection) therapy should be carried out under the guidance of physicians with experience in the diagnosis and management of patients with GHD. Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity (including obese patients with Prader-Willi syndrome), Turner syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of antihyperglycemic drugs (ie, insulin or oral agents) may require adjustment when somatropin therapy is instituted in these patients. Patients with preexisting tumors or growth hormone deficiency secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process. In pediatric patients, clinical literature has revealed no relationship between somatropin replacement therapy and central nervous system (CNS) tumor recurrence or new extracranial tumors. However, in childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumors, in particular meningiomas in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence. Intracranial hypertension (IH) with papilloedema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose. Funduscopic examination

should be performed routinely before initiating treatment with somatropin to exclude preexisting papilloedema, and periodically during the course of somatropin therapy. If papilloedema is observed by funduscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome, chronic renal insufficiency, and Prader-Willi syndrome may be at increased risk for the development of IH. In patients with hypopituitarism (multiple hormone deficiencies), standard hormonal replacement therapy should be monitored closely when somatropin therapy is administered. Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism. In patients with growth hormone deficiency, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients treated with somatropin should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated. Patients should be monitored carefully for any malignant transformation of skin lesions. When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site. As is the case with any protein product, local or systemic allergic reactions may occur. Parents/Patient should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

Pediatric Patients: Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including pediatric growth hormone deficiency and Turner syndrome) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated. Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis. However, somatropin has not been shown to increase the occurrence of scoliosis. Skeletal abnormalities including scoliosis are commonly seen in untreated Turner syndrome patients. Scoliosis is also commonly seen in untreated patients with Prader-Willi syndrome. Physicians should be alert to these abnormalities, which may manifest during somatropin therapy.

Adult Patients: Adult patients with epiphyseal closure who were treated with somatropin replacement therapy in childhood should be reevaluated according to the criteria in INDICATIONS AND USAGE before continuation of somatropin therapy. Fluid retention during somatropin replacement therapy in adults may occur and is usually transient and dose dependent (see ADVERSE REACTIONS). Experience with prolonged treatment in adults is limited.

Laboratory Tests: Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH), and IGF-1 may increase after somatropin therapy.

Drug Interactions: Somatropin inhibits 11 β -hydroxysteroid dehydrogenase type 1 (11 β HSD-1) in adipose/hepatic tissue and may significantly impact the metabolism of cortisol and cortisone. As a consequence, in patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of these drugs to their biologically active metabolites is dependent on the activity of the 11 β HSD-1 enzyme. Excessive glucocorticoid therapy may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement therapy should be carefully adjusted in children with concomitant GH and glucocorticoid deficiency to avoid both hypoadrenalism and an inhibitory effect on growth. Limited published data indicate that somatropin treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (eg, corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CP450 liver enzymes. However, formal drug interaction studies have not been conducted. In adult women on oral estrogen replacement, a larger dose of somatropin may be required to achieve the defined treatment goal (see DOSAGE AND ADMINISTRATION). In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral agent may require adjustment when somatropin therapy is initiated (see PRECAUTIONS, General).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity, and fertility studies have not been conducted with Norditropin®.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with Norditropin®.

Nursing Mothers: It is not known whether Norditropin® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Norditropin is administered to a nursing woman.

Geriatric Patients: The safety and effectiveness of Norditropin in patients aged 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of somatropin, and therefore may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: As with all protein drugs, a small percentage of patients may develop antibodies to the protein. GH antibodies with binding capacities lower than 2 mg/L have not been associated with growth attenuation. In some cases, when binding capacity is greater than 2 mg/L, interference with growth response has been observed. In clinical trials, patients receiving Norditropin® for up to 12 months have been tested for induction of antibodies and 0/358 patients developed antibodies with binding capacities above 2 mg/L. Among these patients, 165 had previously been treated with other preparations of GH and 193 were previously untreated naive patients. Since antibodies to somatropin have the potential to inhibit further linear growth, only patients failing to respond to treatment should be tested for antibodies.

The following adverse events have been reported from clinical studies in pediatric patients: headache, local reactions at the injection site, localized muscle pain, rash, weakness, mild hyperglycemia, glucosuria

and arthralgia. Fluid retention and peripheral edema may occur. Leukemia has been reported in a small number of children who have been treated with GH, including GH of pituitary origin and recombinant somatropin and somatropin. On the basis of current evidence, experts cannot conclude that GH therapy is responsible for these occurrences. The risk, if any, remains to be established.

The following table displays adverse events with an incidence of $\geq 5\%$ occurring in patients with AO GHD during the 6-month, placebo-controlled portion of the largest of the 6 adult GHD Norditropin® trials. During the placebo-controlled portion of this study, approximately 5% of patients without pre-existing diabetes mellitus treated with Norditropin® were diagnosed with overt type 2 diabetes mellitus compared with none in the placebo group, consistent with the known hyperglycemic effects of somatropin.

Adverse Events With $\geq 5\%$ Overall Incidence in Adult Onset Growth Hormone Deficient Patients Treated With Norditropin® During a Six-Month, Placebo-Controlled Clinical Trial

Adverse Event	Norditropin® (N=53)		Placebo (N=52)	
	n	%	n	%
Peripheral Edema	22	42	4	8
Edema	13	25	0	0
Arthralgia	10	19	8	15
Leg Edema	8	15	2	4
Myalgia	8	15	4	8
Infection (non-viral)	7	13	4	8
Paraesthesia	6	11	3	6
Skeletal Pain	6	11	1	2
Headache	5	9	3	6
Bronchitis	5	9	0	0
Flu-like Symptoms	4	8	2	4
Hypertension	4	8	1	2
Gastroenteritis	4	8	4	8
Other Non-Classifiable Disorders (excludes accidental injury)	4	8	3	6
Increased Sweating	4	8	1	2
Glucose Tolerance Abnormal	3	6	1	2
Laryngitis	3	6	3	6

OVERDOSAGE: Short-term overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia and is likely to cause fluid retention. Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess GH.

HOW SUPPLIED AND STORAGE: Norditropin® cartridges (somatropin [rDNA origin] injection) are individually cartoned in 5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL cartridges which must be administered using the corresponding color-coded NordiPen® injection pen. Norditropin NordiFlex® (somatropin [rDNA origin] injection) is individually cartoned in 5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL prefilled pens.

Non-injected/unused Norditropin® cartridges and prefilled pens must be stored at 2°C-8°C/36°F-46°F (refrigerator). Do not freeze. Avoid direct light. 5 mg/1.5 mL (orange) and 10 mg/1.5 mL (blue) cartridges and 5 mg/1.5 mL (orange) and 10 mg/1.5 mL (blue) Norditropin NordiFlex® prefilled pens:

After a Norditropin® cartridge has been inserted into the NordiPen® injector (NordiPen® 5 or NordiPen® 10 respectively) or after the initial injection of a Norditropin NordiFlex® prefilled pen, it may be EITHER stored in the pen in the refrigerator (2°C-8°C/36°F-46°F) and used within 4 weeks OR may be stored for up to 3 weeks at not more than 25°C (77°F). Discard unused portion.

15 mg/1.5 mL (green) cartridges and 15 mg/1.5 mL (green) Norditropin NordiFlex® prefilled pens:

After a Norditropin® cartridge has been inserted into the NordiPen® injection pen, it must be stored in the pen in the refrigerator (2°C-8°C/36°F-46°F) and used within 4 weeks. Discard unused portion after 4 weeks. After the initial injection, Norditropin NordiFlex® prefilled pens must be stored in the refrigerator and used within 4 weeks. Discard unused portion after 4 weeks.

Norditropin® cartridges and prefilled pens retain their biological potency until the date of expiry indicated on the label.

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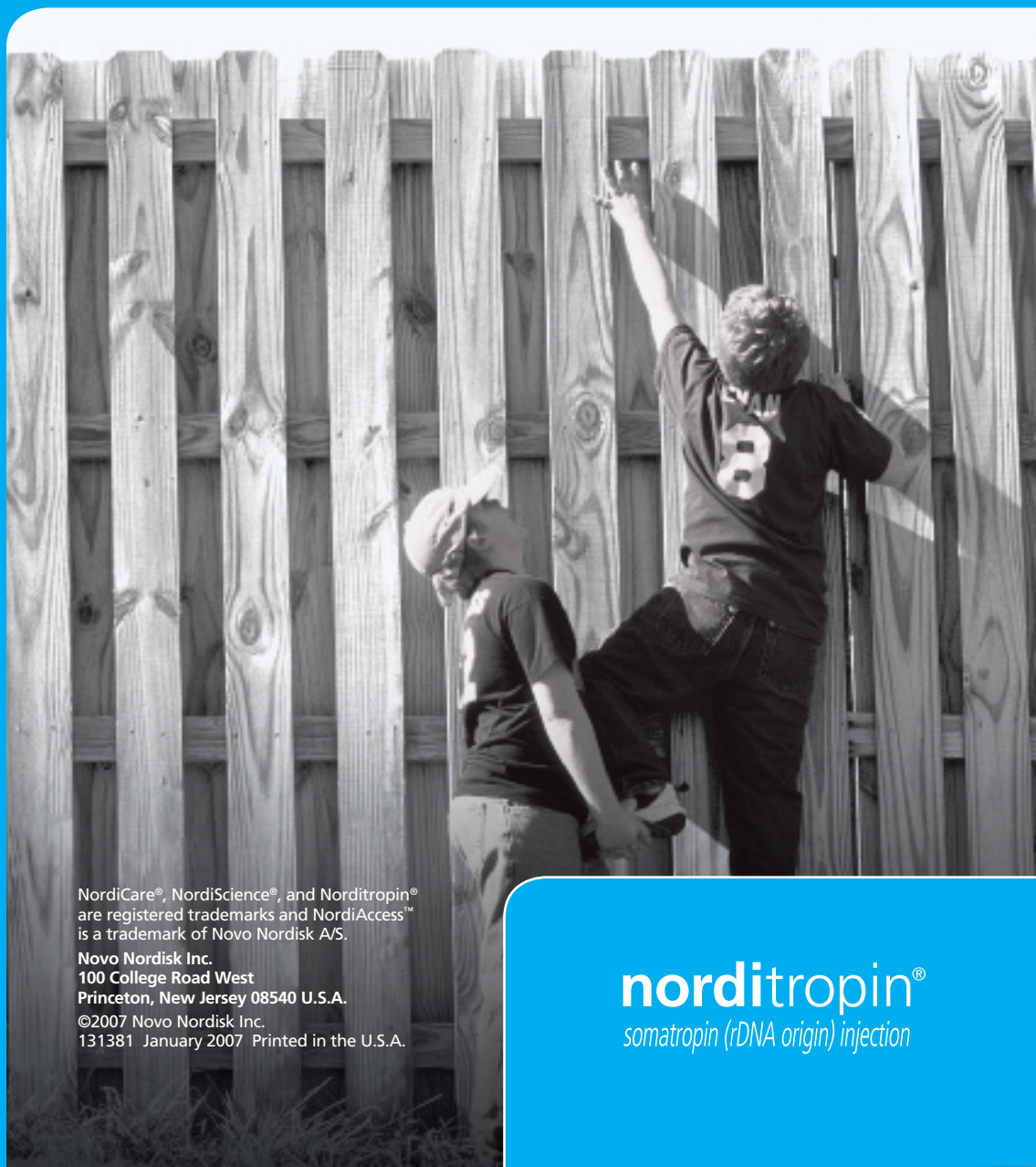
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