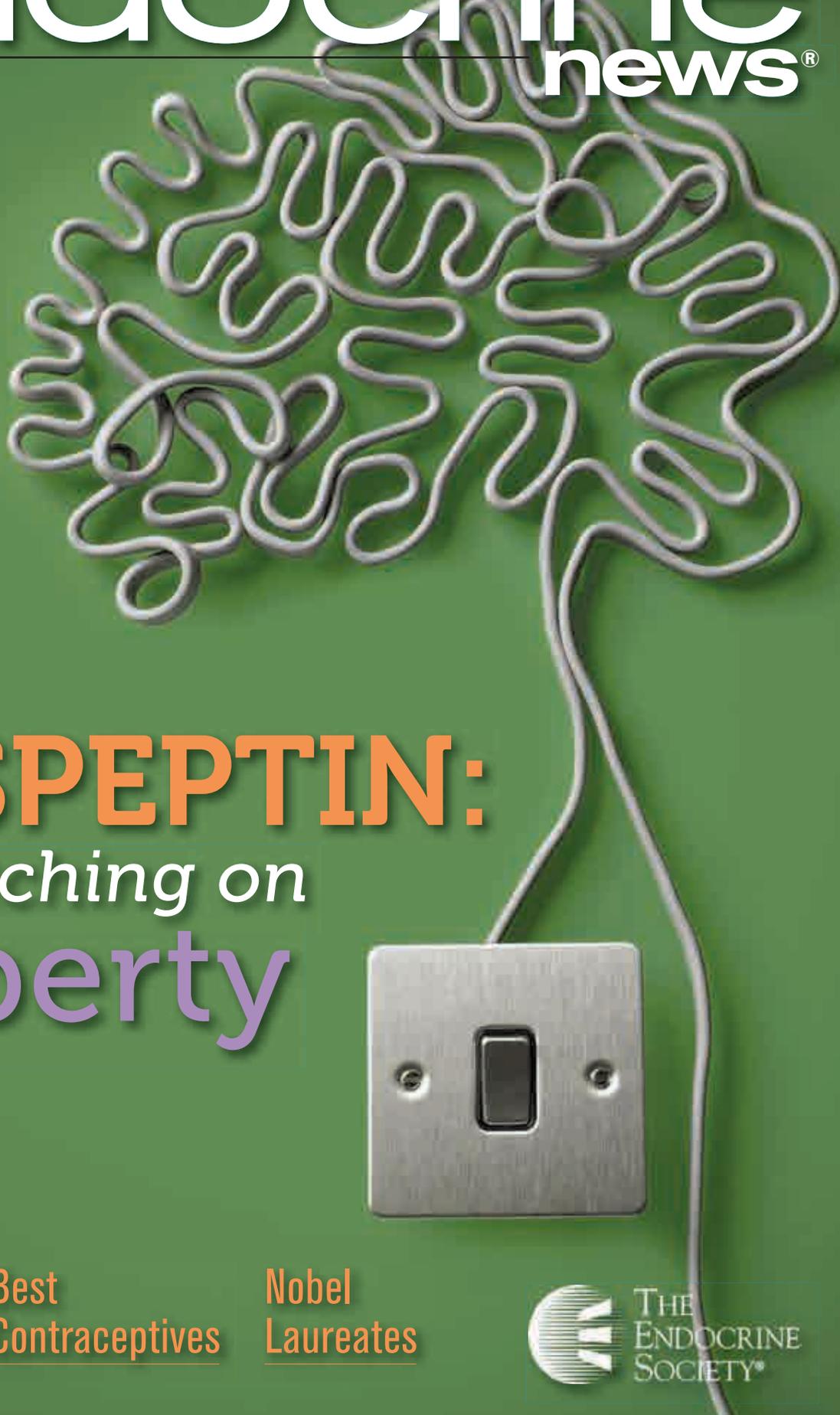


# Endocrine news®

AUGUST 2012



## KISSPEPTIN: *Switching on* Puberty

**PLUS**

Anti-Aging  
Strategies

Best  
Contraceptives

Nobel  
Laureates





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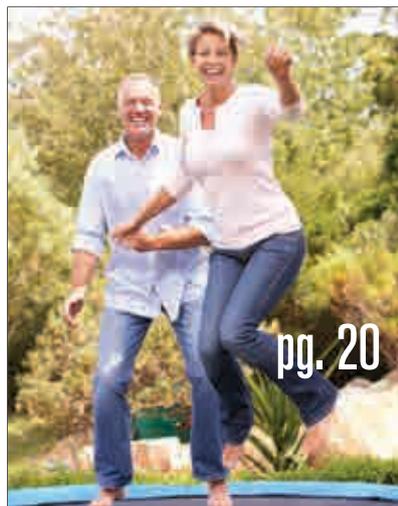
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Not your mother's contraceptive, today's intrauterine devices and implants prevent pregnancy far more effectively than "the Pill."

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### What is Osteoporosis in Men?

Find out by reading the Hormone Health Network's fact sheet on Osteoporosis in Men (pages 31, 32).



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



## The Society Launches an International Exchange Program

As I begin my presidential term, I would like to share some of my plans for the coming year. One of my first priorities is to build on the initiatives launched during Janet Hall's presidency. Many of her initiatives, such as the focus on health disparities and international outreach, will no doubt become part of The Endocrine Society's core activities. I will also be launching a new initiative this year: The Endocrine Society Ambassador Exchange Program.



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

During Dr. Hall's presidency, two task forces were established: the Basic Science Task Force and the ENDO Task Force. The Basic Science Task Force was created to address the challenges facing our basic science members. The ENDO Task Force was charged to review The Endocrine Society's Annual Meeting from the perspective of all the constituencies (basic science, clinical science, clinician in practice, trainee, and international) and that of Strategic Plan 3 and to create new venues for evaluative feedback. I will ensure that the recommendations resulting from these two task forces are reviewed and considered for implementation by the relevant Society committees or groups.

### The Endocrine Society Ambassador Exchange Program

The Ambassador Exchange Program will begin this year as a pilot, with hopes that eventually it will develop into a sustainable program. The concept is a giving-back initiative in which an endocrinologist and a trainee from an established U.S. center visit an international center where resources are limited and indigent populations are served. In turn, an endocrinologist and a trainee from the host international center then visit the U.S. center to complete the exchange. This exchange will prove to be an invaluable opportunity for trainees and their mentors to observe how national, ethnic, economic, and cultural factors shape endocrine care. Throughout my professional career, I have been fortunate to participate in such exchanges, which I consider life-changing experiences.

This type of outreach program will position the Society to lead a unique international collaboration and, in the process, to give back to the world endocrine community. The Society's Strategic Plan 3 emphasizes its commitment to "the goal of improved human health worldwide." Although many of our current activities touch on different aspects of this theme, none specifically embodies a "giving-back"

initiative. Therefore, I believe the time is right to mobilize and connect our members through a Society-based international agenda. The ambassador exchange program has three specific objectives:

- Establish international networks of medical centers as vehicles for sharing best practices.
- Increase the cultural competency of the current and future endocrine workforce.
- Improve the health of underserved populations through clinician and patient education appropriate to local needs and cultures.

Earlier this year, a working group was established to develop a business plan, which The Endocrine Society Council subsequently approved. This working group and Society staff will coordinate all the logistic and programmatic details to ensure these exchanges are a success. The two international centers that will participate in the pilot program are King Edward Memorial Hospital in Mumbai, India, and Chris Hani Baragwanath Hospital in Soweto, South Africa.

### Document Exchanges with Magazine and Online Stories

Because only a limited number of members will be able to participate in the program, the participants' experiences will be shared with all Society members via our diverse communication vehicles. Some examples include documenting each exchange with photographs at both centers in an article in *Endocrine News*, dedicating a page to the program on the Society's Web site, publishing a perspective article coauthored by each exchange team in one of the Society's journals, and presenting a special Meet-the-Proffessor session and Trainee Day session at ENDO.

I will continue to communicate the progress on this initiative throughout my presidential year. If you have any questions or comments, feel free to contact me at [president@endo-society.org](mailto:president@endo-society.org). I look forward to a productive and successful year for The Endocrine Society. ■

Sincerely,

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



Dear Readers,

The 1996 discovery of kisspeptin in the human brain added significantly to understanding how children turn into adults. For this issue, we invited three medical experts to give their perspectives on how kisspeptin functions and what promise it holds for developing treatments for pubertal and reproductive disorders (page 14). Kisspeptin owes its whimsical name to the popular chocolate candy, Hershey's Kisses—the hormone was first identified by researchers in Hershey, Pennsylvania, headquarters of the candymaker.

History is replete with rumors of a legendary spring with restorative powers that can keep us young forever. Today's scientists, however, postulate that the key to anti-aging and longevity lies within the human body, most likely in the endocrine system. Science writer Margie Patlak shares the latest

research findings on hormones and aging (page 20).

Continuing with the idea of controlling our own medical destinies, frequent contributor Melissa Mapes writes about birth control, in particular intrauterine devices (IUDs), which were much maligned 40 years ago. A new study shows that IUDs and implants are vastly more effective than "the Pill" as long-term reversible contraceptives (page 30).

Associate editor Jacqueline Ruttimann salutes Nobel Prize-winning endocrinologists in Back Story. We learn not only of the landmark research that won them the prestigious award but also of struggles some endured to pursue their careers (page 44). ■

Sincerely,

Marian Smith Holmes  
Managing Editor  
**Endocrine News**

### ENDOCRINE NEWS ONLINE EXCLUSIVES

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



#### Anti-obesity Drug

What's the skinny on Belviq, the first prescription diet pill to win FDA approval in more than a decade?



#### Art and Wellness

Drawings by Cushing's patients help health-care providers understand the psychological impact of long-term remission.



#### Is a Calorie Just a Calorie?

A new study finds that a low-carb diet burns more calories and helps dieters keep the weight off.



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

*President*  
young.william@mayo.edu

**Teresa K. Woodruff, Ph.D.**

*President-Elect*  
tkw@northwestern.edu

**Janet E. Hall, M.D.**

*Past President*  
hall.janet@mgh.harvard.edu

**John C. Marshall, M.D., Ph.D.**

*Secretary-Treasurer*  
jcm9h@virginia.edu

**Scott Hunt**

*Executive Director & CEO*  
shunt@endo-society.org

**Eleanore Tapscott**

*Senior Director of Publications*  
etapscott@endo-society.org

**Doug Byrnes**

*Director of Publications*  
dbyrnes@endo-society.org

**Marian Smith Holmes**

*Managing Editor*  
mholmes@endo-society.org

**Jacqueline Ruttimann, Ph.D.**

*Associate Editor*  
jruttimann@endo-society.org

**Cynthia Richardson**

*Product/Production Manager*  
crichardson@endo-society.org

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## Bioengineered Hair Follicles Suggests Baldness Cure

➤ Japanese scientists have taken another step toward organ regeneration through stem cell bioengineering: successfully implanting reconstituted hair follicles into the skin of nude mice.

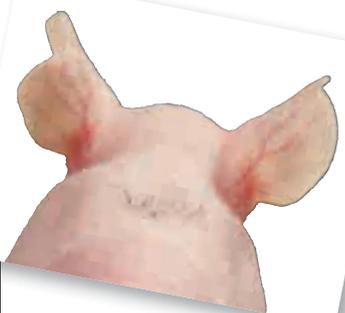
Last year, this same team, led by Takashi Tsuji, Ph.D., of the Tokyo University of Science, de-

scribed a similar technique to transplant a bioengineered tooth unit, which included mature tooth, periodontal ligament, and bone, into the upper jawbone of a mouse.

In the new study, the researchers applied their bioengineering skills to three different types of hair. They reconstituted pelage follicle germ cells, dark and coarse hair stem cells, using mouse embryonic skin epithelial cells

and mesenchymal cells. They also regenerated vibrissa follicle germs, light and fine hair stem cells, using adult mice stem cells from bulge region epithelial cells and dermal papilla cells. Harvesting small pieces of occipital scalp from human male donors, researchers repeated the method to engineer new hair follicles using intact dermal papilla cells and bulge-region epithelial cells. The researchers rearranged the follicular cells and stem cells into their niches, grew them in culture, and then implanted them on hairless mice.

The implanted hair had the correct structures of natural hair follicles and shafts, and formed normal connections with surrounding host tissues such as the epidermis. For example, when the researchers injected the neurotransmitter acetylcholine, the hairs stood up—this piloerection



ability indicated that the follicles had made functional connections to appropriate muscles and nerve fibers. The researchers even demonstrated an ability to choose cells that affected hair pigmentation.

As the researchers' methods to regenerate ectodermal glands such as teeth and hair continue to progress, they say in their report in *Nature Communications*\* that transplantation of these bioengineered follicle germs offers a path for hair loss treatment. ■

Eric Seaborg

\*Toyoshima K, Asakawa K, Ishibashi N, et al. Fully functional hair follicle regeneration through the rearrangement of stem cells and their niches. *Nat Commun*, 2012, 17(3):784, doi:10.1038/ncomms1784.



## Women's Verbal Ability Declines During Menopause

➤ Cognitive decline is common among aging men and women, but a new study investigated whether loss of cognitive function in women can be linked to the hormonal changes of menopause.

Researchers from the University of Michigan, led by Alison Berent-Spillson, Ph.D., studied 67 women, ages 42–61 years, who were part of an ongoing menopause study. The women were grouped according to three hormonal stages: premenopause, perimenopause, and postmenopause. They were given neuropsychological as-

essments of their cognitive function based on visual memory tests and on their ability to process abstract and concrete meaning of words. Functional magnetic resonance imaging was used to observe the neural activation patterns during the tasks.

Menopause status affected the women's verbal fluency independent of age. Declines in verbal cognitive functioning were observed in the women during menopause transition. In their article soon to be published in *The Journal of Clinical Endocrinology & Metabolism*,\* the research-

ers conclude that their results suggest verbal functioning was affected by hormonal differences both on a behavioral and neuroanatomical level.

The researchers suggested that with the awareness that verbal fluency is vulnerable during this transitioning time of life, pharmacological and non-pharmacological interventions may be targeted to preserve function of this critical cognitive domain. ■

Glenda Fauntleroy

\* Berent-Spillson A, Persad CC, Love T, et al. Hormonal environment affects cognition independent of age during the menopause transition. *J Clin Endocrinol Metab*. doi:10.1210/jc.2012-1365.

## A Taste for Fat among Obese Subjects

➤ Salty, sweet, sour, bitter, and umami. Can we add fat to this well-known list of tastes? A new study published in the *Journal of Lipid Research*\* suggests a sixth basic taste component for obese subjects in detection of dietary fat.

Traditionally dietary fat is thought to activate the somatosensory and olfactory systems exclusively on aromatic and textual cues. Recent research at the Washington University School of Medicine, however, finds detection of triolein and oleic acid to be higher for subjects with high expression levels of the gene *CD36*, commonly accepted as

a lipid taste receptor. Sensitivity to triolein decreases with reductions in fatty acid release through the addition of orlistat, a tasteless lipase inhibitor and popular weight loss pill. Detection of oleic acid goes unchanged, suggesting that taste, in addition to texture, contributes to dietary fat detection.

This is especially significant for the obese. Aside from a diet high in fat content, low sensitivity to oleic acid associates with higher body mass index (BMI). Whether fat taste receptors are altered by increased BMI is unknown. Obesity may cause low oral sensitivity to fat or vice

versa. Other studies show sensitivity increasing after four weeks of a low-fat diet.

In measuring triacylglycerols and fatty acids together, the new study makes further understanding of the body's ability to directly taste fat. Future studies of lipase inhibition and genetic variance of lipid taste reception may provide inroads to improving dietary therapy for obesity. ■

Dan Kelly

\* Pepino MY, Love-Gregory L, Klein S, Abumrad NA. The fatty acid translocase gene *CD36* and lingual lipase influence oral sensitivity to fat in obese subjects. *J Lipid Res*. 2012. 53:561–566. doi: 10.1194/jlr.M021873.

## Resveratrol's Role in Treating PCOS

➤ The beneficial effects of red wine, grape juice, and peanuts might extend to ameliorating the excess androgen production in patients with polycystic ovary syndrome (PCOS).

Resveratrol is a naturally occurring polyphenol found in these foods and some medicinal plants. It has anti-inflammatory, antioxidant, cardioprotective, and neuroprotective effects—and studies in rats have shown it can inhibit steroidogenesis. Researchers led by Antoni J. Duleba, M.D., of the University of California, Davis, explored whether this latter effect could be useful in women with the androgen-overproducing disorder, PCOS.

Theca cells play an important role in ovarian steroidogenesis; ovaries of women with PCOS are enlarged and characterized by theca-interstitial hyper-

plasia. Researchers cultured rat theca-interstitial cells and tested the effects of adding resveratrol.

The polyphenol reduced androgen production in these cells but did not affect progesterone levels. This inhibitory effect correlated with a decrease in mRNA expression of genes regulating androgen production, especially *Cyp17a1*. Resveratrol decreased activity of a cell-signaling pathway involved in ovarian steroidogenesis, apparently by decreasing phosphorylation in the pathway.

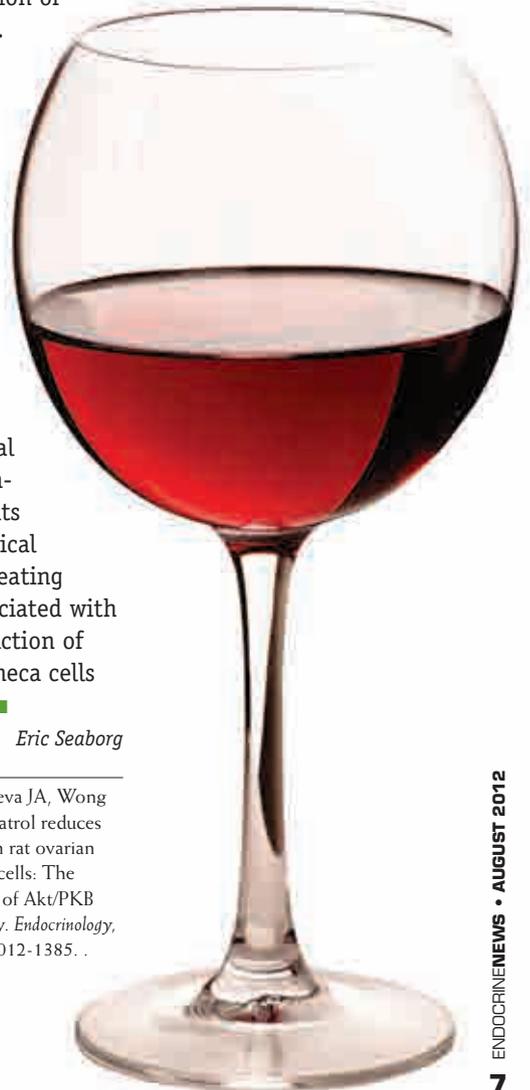
Resveratrol can activate sirtuins, a family of deacetylases involved in cellular processes such as genomic stability and DNA repair. This activation has been shown to extend lifespan in mice. To test whether sirtuins were involved in the steroid effects, the researchers added sirtuin inhibitors to the culture, which did not reverse the resveratrol-

induced inhibition of steroidogenesis.

In an article accepted for publication in **Endocrinology**,\* the researchers say this study is the first they know of for evaluating the role of resveratrol on theca-interstitial cell steroidogenesis. Their results could be of clinical relevance for treating conditions associated with excessive production of androgens by theca cells such as PCOS. ■

Eric Seaborg

\* Ortega I, Villanueva JA, Wong DH, et al. Resveratrol reduces steroidogenesis in rat ovarian theca-interstitial cells: The role of inhibition of Akt/PKB signaling pathway. *Endocrinology*. doi:10.1210/en.2012-1385.



## Bees Provide Key to Anesthesia Jet Lag

➤ Surgery can have a disorienting effect on patients. The altered perception of time that often follows anesthesia has been described as post-operative jet lag by researchers at the University of Auckland in New Zealand. Using honeybees as subjects, the researchers studied the effects of anesthesia. Dosing honeybees with the com-

mon anesthetic, isoflurane, the research team saw marked significant delays in timed behavior and circadian rhythms.

Bees keep to an obsessively controlled schedule with highly timed field behaviors. Their circadian clocks are molecularly similar to mammals, oscillating through mRNA and protein levels to regulate a 24-hour rhythm. A six-hour administration of isoflurane inhalant during

the bees' subjective day, as published in the *Proceedings of the National Academy of Sciences*,\* produced a four- to five-hour delay in field behavior and clock gene expression.

Night dosing had little to no effect, and the reason may be found in the mRNA oscillations during this time. Isoflurane is thought to increase mRNA expression, causing a time shift forward when levels are rising and a delay

when levels are declining. When levels hold steady at their highest point, as at night, isoflurane and similar anesthetics cause no shift.

Isoflurane is known to increase GABA reception, which forms much of the brain's daily rhythm. Manipulation of the GABA receptors modifies circadian clock responses to light. Although isoflurane had no effect at night, a night-time light pulse causes a circadian phase delay. Administered during the day, light causes a phase advance.

Administration of light and isoflurane together may be an important next step possibly making post-op jet lag treatable during anesthesia, the researchers suggested. ■

Dan Kelly



\* Cheeseman JF, Winnebeck EC, Millar CD, et al. General anesthesia alters time perception by phase shifting the circadian clock, *Proc Natl Acad Sci, USA* doi:10.1073/pnas.1201734109.

## How Dietary Fiber Fights Type 2 Diabetes Mellitus

➤ Studies show that a high-fiber diet helps people maintain a healthy body weight, suggesting a possible role in the prevention and control of type 2 diabetes mellitus (T2DM). Specifically, researchers wanted to test the efficacy of an insoluble dietary fiber derived from maize, high-amylose maize-resistant starch 2 (HAM-R2), which has been shown both to increase insulin sensitivity and reduce adipose tissue.

Scientists led by Denise Robertson, Ph.D., at the University of Surrey, Guilford, United Kingdom, investigated just how HAM-R2 affects metabolism and precisely where.

Fifteen obese, insulin-resistant men and women consumed a daily diet with powdered HAM-R2 supplements (Hi-Maize) or control (Amioca starch) for eight weeks. Researchers then measured glucose levels, discriminating between hepatic and peripheral insulin sensitivity. They also biopsied adipose tissue from the participants' buttocks to quantify gene expression there. In their paper, to be published soon in *The Journal of Clinical Endocrinology & Metabolism*,\* the researchers report a 65 percent increase in postprandial glucose uptake and 10 percent less fasting insulin resistance among the HAM-R2 group,

which also demonstrated increased expression of hormone-sensitive lipase and lipoprotein lipase mRNA. Expression of these enzymes, in turn, indicates increased adipose tissue differentiation.

The researchers conclude that HAM-RS2 intake increased peripheral, but not hepatic, insulin sensitivity. These findings represent a big step toward an intervention for obese patients at risk of developing T2DM, they reported. ■

Kelly Horvath

\* Robertson D, Wright J, Loizon E, et al. Insulin sensitizing effects on muscle and adipose tissue following dietary fiber intake in men and women with metabolic syndrome. *J Clin Endocrinol Metab*, doi:10.1210/jc.2012-1513.

## Thyroid Hormone Finds Alternative Paths into Growth Cells

► Like commuters finding their way around a closed road, thyroid hormones can sometimes find alternative routes for getting to work.

Patients with the low hormone levels of congenital hypothyroidism suffer from short stature, but those with problems related to thyroid hormone transport may not. Thyroid hormone must find its way into a cell via transporter proteins to exert its actions on the nucleus, a process that is disrupted in conditions such as Allan-Herndon-Dudley syndrome (AHDS), which features mutations that interfere with the workings of a main thyroid hormone transporter, monocarboxylate transporter 8 (MCT8). AHDS patients grow to a fairly normal size but have severe

neurological symptoms, including mental and motor retardation.

AHDS patients have high T3 levels, indicating that the thyroid is producing hormone that is not always getting where it needs to be. Researchers led by Noriyuki Namba, M.D., Ph.D., of Osaka University in Japan, hypothesized that AHDS patients grow because the thyroid hormone gains access to growth plate cartilage cells via transporters other than MCT8.

When the scientists analyzed thyroid hormone transporter mRNA expression in mouse chondrogenic ATDC5 cells, they found that monocarboxylate transporter 10 (MCT10) was abundantly expressed. MCT10 mRNA was also expressed abundantly

in the growth plate resting zone chondrocytes.

When the researchers silenced MCT10 mRNA expression in ATDC5 cells, they detected a significant decrease in T3 influx and reduced effects of the hormone. The results demonstrate that MCT10 serves as a thyroid hormone transporter into these cells.

In an article slated for publication in *Endocrinology*,\* the researchers say that the role of MCT10 in bone growth warrants further investigation for potential application in addressing unresolved causes of short stature and skeletal dysplasias. ■

Eric Seaborg

\* Abe S, Namba N, Abe M, et al. Monocarboxylate transporter 10 functions as a thyroid hormone transporter in chondrocytes. *Endocrinology*, doi:10.1210/en.2011-1713.

## Regulating the Human Birth Clock

► The placenta is thought to be the site of the hormonal clock that coordinates the complex gestational interplay of biologic processes between mother and fetus, resulting in the timing of parturition. Corticotropin-releasing hormone (CRH) of placental origin is one such substance that steadily increases during gestation, culminating with delivery. Based on the demonstration of nuclear factor  $\kappa$ B (NF- $\kappa$ B) in term cytotrophoblastic nuclei coupled with NF- $\kappa$ B's known roles in cell survival, differentiation, and proliferation, a new study investigated NF- $\kappa$ B as the possible positive placental CRH regulator.

Scientists led by Bingbing Wang, M.D., Ph.D., at the UMDNJ-Robert Wood

Johnson Medical School, New Brunswick, New Jersey, performed chromatin immunoprecipitation assays, among other tests, in primary cytotrophoblasts to determine whether the RelB/NF- $\kappa$ B2 complex, the alternate NF- $\kappa$ B pathway, is activated in the placenta at term. In their paper, to be published soon in *Molecular Endocrinology*,\* the researchers report that RelB/NF- $\kappa$ B binds to a newly discovered NF- $\kappa$ B enhancer of CRH gene promoter to stimulate CRH transcription, thereby positively regulating CRH expression.

The researchers conclude that the non-canonical NF- $\kappa$ B pathway is necessary for CRH expression. Moreover, impairment in placental CRH regulation likely correlates with incongruous gestational duration and

leads to preterm labor and birth, they said. ■

Kelly Horvath

\* Wang B, Parobchak N, Rosen, T. RelB/NF- $\kappa$ B2 regulates corticotropin-releasing hormone in the human placenta. *Mol Endocrinol*, doi:10.1210/me.2012-1035.



## Low Testosterone Is Not a Natural Result of Aging

➤ A new population-based study shows that testosterone levels can be more or less sustained throughout a man's lifespan if he is healthy. Declining testosterone, the study said, is likely to be the result of lifestyle and chronic disease-related factors rather than aging.

Led by Gary Wittert, M.D., Freemasons Foundation Centre for Men's Health, University of Adelaide in Australia, scientists took blood testosterone measurements from 1,382 men ages 35–80 years during two separate clinic visits 5 years apart. Of the total popula-

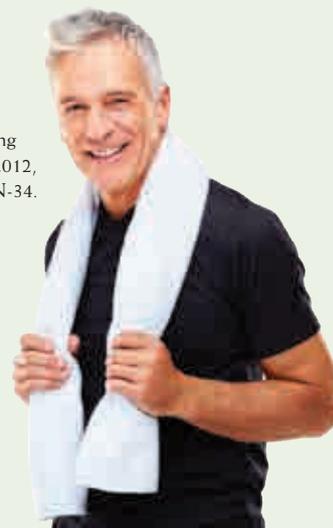
tion studied, about 290 of the men were bachelors, about 162 smoked, about 414 were overweight or obese, nearly half had central obesity, and about 110 suffered from depression. In their paper, presented at **ENDO 2012\*** by Andre B. Araujo, Ph.D., Department of Epidemiology, New England Research Institutes, Inc., Watertown, Massachusetts, the researchers reported that on average, testosterone levels decreased less than one percent each year. The men who revealed significant declines in serum measurements were those who became obese, had chronic cardiovascular disease, were depressed, quit smoking, or were unmarried.

The researchers concluded that testosterone decline is caused by health and lifestyle factors rather than a de facto result of aging. Mak-

ing health care providers aware of this fact is critical for targeting the problems underlying the decline in testosterone, they added. ■

Kelly Horvath

\* Araujo AB, Shi Z, Martin SM, Wittert GA. Longitudinal changes in testosterone over 5 Years in community-dwelling men. ENDO 2012, Abstract MON-34.



# TALES

Worldwide, about

## 5 million

babies have been born from assisted reproductive technologies such as in vitro fertilization and intracytoplasmic sperm injection.

Source: News Release. European Society of Human Reproduction and Embryology Annual Meeting, July 2, 2012, Istanbul, Turkey. [www.eshre.eu/ESHRE/English/Press-Room/Press-Releases/Press-releases-2012/ESHRE-2012/5-million-babies/page.aspx/1606](http://www.eshre.eu/ESHRE/English/Press-Room/Press-Releases/Press-releases-2012/ESHRE-2012/5-million-babies/page.aspx/1606).

## Zebrafish, a Big Catch for Vitamin D Studies

➤ The tiny zebrafish (*Danio rerio*), a popular organism for scientific experiments because of its transparency and rapidly progressive embryonic state, is helping researchers unlock the role of the hormonal form of vitamin D,  $1\alpha,25\text{-dihydroxyvitamin } 3\text{ D } (1\alpha,25(\text{OH})_2\text{D}_3)$ , during early development.

Based on previous findings that  $1\alpha,25(\text{OH})_2\text{D}_3$

regulates hundreds of genes in vitro and that zebrafish abundantly begin to express the vitamin D receptor just 48 hours post-fertilization, scientists led by Rajiv Kumar, M.D., at the Mayo Clinic, Rochester, Minnesota, investigated vitamin D's effects on gene expression patterns and metabolic pathways in vivo. After administering  $1\alpha,25(\text{OH})_2\text{D}_3$  in

ethanol or ethanol only for control, to the medium of groups of 25–30 zebrafish larvae 24 hours after fertilization, the scientists shotgun-sequenced these larvae's whole transcriptomes. In their paper, to be published soon in **Molecular Endocrinology**,\* the researchers report altered expression in more than 2,000 genes in response to  $1\alpha,25(\text{OH})_2\text{D}_3$ .

The hormonal form of vitamin D regulates several mechanisms it was not previously known to influ-

ence, including transcription factors, fatty acid, amino acid, and xenobiotic metabolic pathways, and peptide hormones. Vitamin D, it turns out, is crucial for more than just calcium homeostasis and bone. ■

Kelly Horvath

\* Craig TA, Zhang Y, McNulty MS, et al. Research resource: Whole transcriptome RNA sequencing detects multiple  $1\alpha,25\text{-dihydroxyvitamin } \text{D}_3\text{-sensitive}$  metabolic pathways in developing zebrafish. *Mol Endocrinol*, doi:10.1210/me.2012-1113.



## Benefits of Soy Diet for Prostate Cancer Linked to Estrogen

➤ The mighty soybean is full of antioxidants and has been linked to a lower risk of prostate cancer. Soy contains genistein, a phytoestrogen shown to be an anti-cancer compound, and a new study looks at whether genistein relies on estrogen receptors to provide its shield against cancer.

A team of researchers, led by Anna Slusarz, Ph.D., and Glenn Jackson, D.V.M., from the Department of Biochemistry at the University of Missouri in Columbia bred mice lacking estrogen receptors alpha or beta (ER $\alpha$  and ER $\beta$ ) and randomly assigned them to three different diet groups: casein alone, casein with 300 mg genistein/kg, or casein with 750 mg genistein/kg. The mice were fed these diets from 6 weeks of age until 5 months of age

and then euthanized for tissue examination.

The researchers found that genistein consumption reduced the incidence of cancer in the mice with normal estrogen receptors (ERWT/TRAMP). Cancer occurred in 70 percent of the ERWT mice fed only casein, while the cancer incidence in ERWT mice fed low-dose genistein (300 mg/kg) was 47 percent and only 32 percent in the 750-mg/kg genistein group. Genistein had no effect

on total cancer incidence in the mice bred without estrogen receptors. The data imply that genistein requires the presence of both estrogen receptors (ER $\alpha$  and ER $\beta$ ) to enact its protective action.

The researchers conclude in their upcoming article in *Endocrinology*\* that their study offers unique insight into the effects of estrogen receptor signaling on the develop-

ment of prostate cancer. They add that although many questions remain, their data suggest that targeting both ER $\alpha$  and ER $\beta$  would be useful in preventing and treating prostate cancer. ■

Glenda Fauntleroy

\* Slusarz A, Jackson GA, Day JK, et al. Aggressive prostate cancer is prevented in ER $\alpha$ KO mice and stimulated in ER $\beta$ KO TRAMP mice. *Endocrinology*. doi:10.1210/en.2012-1030.



## High-Dose Estrogen Treatment for Tall Girls Linked to Infertility

➤ Taking high doses of estrogen can stunt undesired tall height in girls, but it may also have a lasting impact on their later fertility.

For decades, adolescent girls have requested treatment to reduce their final height. In the 1960s daily doses of ethinyl estradiol (EE) as high as 500 mg were prescribed, but in later decades were reduced to 100 mg or 200 mg. Although previous research has linked the treatment to later infertility, a new study examines whether or not a higher estrogen dose is associated with increased infertility.

A team of Dutch researchers led by A. E.J. Hendriks, M.D., from Erasmus Medical Center-Sophia in Rotterdam, the Netherlands, studied

125 women ages 20–42 years who were treated with high doses of EE beginning at age 12 for 23–24 months. Fifty-two participants had been treated with 100 mg/day and 43 were treated with 200 mg/day. At the start of treatment, the girls were about 177 cm (69.7 inches) tall and were predicted to have final heights of 188–189 cm (74 inches).

Compared with untreated women, women taking the high doses of estrogen took longer to conceive their first pregnancy. Of the untreated women, 80 percent got pregnant within one year compared to 69 percent of those treated with 100 mg EE and 59 percent of the women treated with 200 mg. Estrogen treatments of

both 100 and 200 mg also reduced the women's fecundity compared with untreated women, and the incidence of women seeking fertility treatment increased significantly with increased estrogen dose.

In an upcoming article in *The Journal of Clinical Endocrinology & Metabolism*,\* the researchers write that their results demonstrate for the first time the dose-dependent association between estrogen treatment and infertility. ■

Glenda Fauntleroy

\* Hendriks AEJ, Drop SLS, Laven JSE, Boot AM. Fertility of tall girls treated with high-dose estrogen, a dose-response relationship. *J Clin Endocrinol Metab*, 2012 doi: 10.1210/jc.2012-1078.

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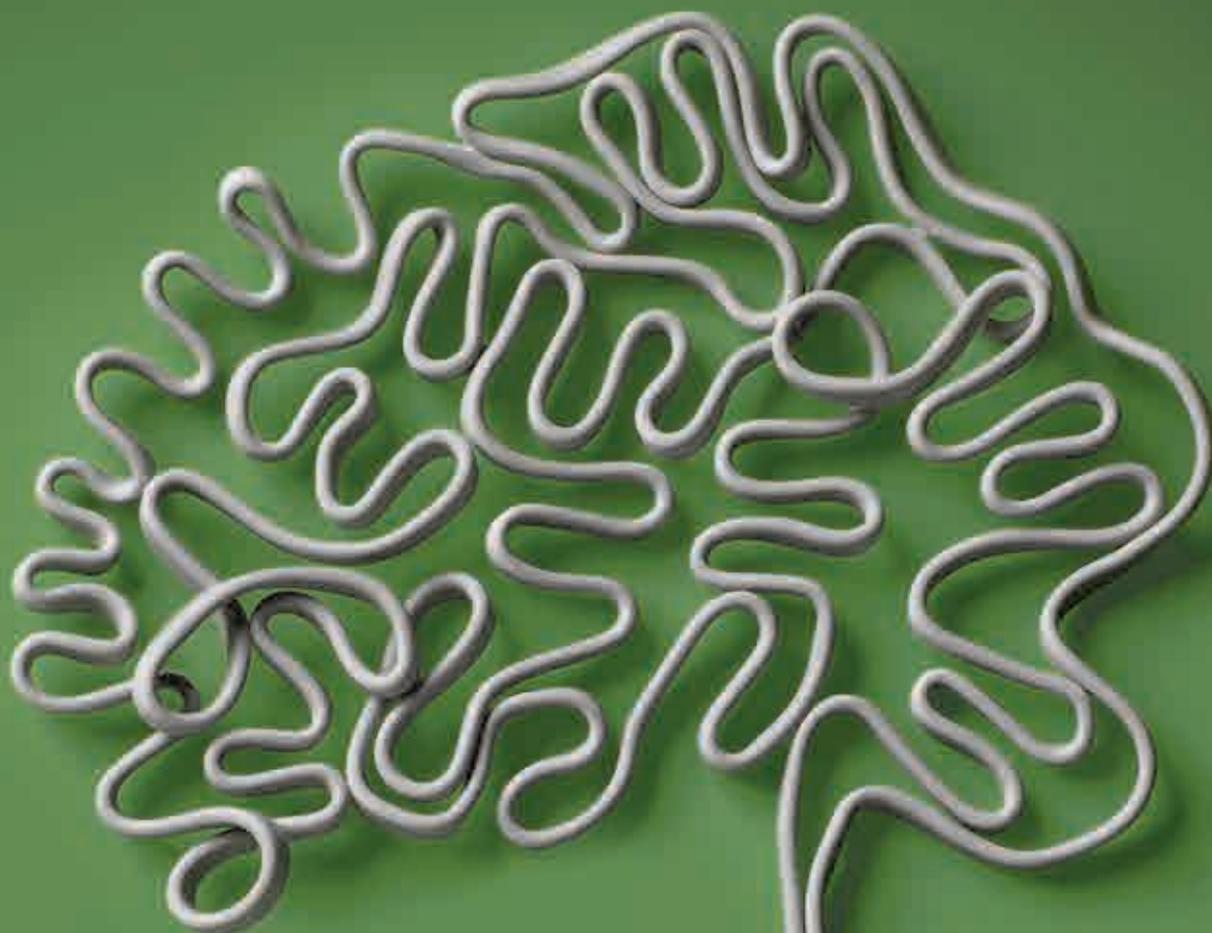


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# KISSPEPTIN: *Switching on* Puberty

## Introduction

The switch that turns on pubertal development remains one of the most elusive triggers in science. One successful approach to uncovering pubertal mechanisms has been the study of the genetic causes of delayed puberty and hypogonadotropic hypogonadism. The discovery of kisspeptin and its receptor, which are critical stimulatory factors for GnRH release, brings us one step closer to understanding the events that initiate puberty. Three experts present their perspectives on kisspeptin.



## Clinical Practitioner Perspective

By Ana Claudia Latronico, M.D., Ph.D.

Dr. Latronico is professor of medicine and chief of the Endocrinology and Metabolism Division, University of São Paulo Medical School, Brazil.



### Highlights

- Kisspeptins are a family of structurally related peptides, encoded by the *KISS1* gene, that operate through the G protein-coupled receptor 54 (known as *KISS1R* or *GPR54*).
- Kisspeptin peptides are the most powerful stimulators of GnRH secretion and consequently gonadotropin release from anterior pituitary.
- Recessive inactivating mutations of *KISS1* and *KISS1R* genes cause congenital hypogonadotropic hypogonadism.
- Dominant activating mutations of *KISS1* and *KISS1R* genes are associated with premature activation of GnRH release, leading to precocious puberty.
- Agonists and antagonists of kisspeptin peptides are potential therapeutic tools for reproductive disorders.

In a family of eight children, five siblings failed to enter puberty or showed only partial signs of puberty in their late teens. In another case, an eight-year-old girl presented with central precocious puberty without neurologic symptoms or exposure to sex steroids. As described in more detail below, each of these individuals was found to have mutations in the kisspeptin receptor/ligand system that affected the activation of puberty.

Kisspeptin-1 and its cognate receptor are required for normal function of the hypothalamic-pituitary-gonadal axis and play an important role in the physiologic regulation of puberty. Evidence indicates that kisspeptin acts directly on hypothalamic GnRH neurons, stimulating GnRH secretion and consequently gonadotropin release from the anterior pituitary.<sup>1</sup>

### Defects in the kisspeptin system cause hypogonadotropic hypogonadism

The failure of gonadal function secondary to deficient pituitary gonadotropin secretion results in a clinical syndrome defined as isolated hypogonadotropic hypogonadism. The biological hallmark of this disorder is a decreased level of sex steroids associated with low or normal levels of FSH and LH without other pituitary hormonal deficiencies. Loss-of-function mutations in the *KISS1R* gene were first described in consanguineous families with isolated hypogonadotropic hypogonadism without olfaction abnormalities.<sup>2,3</sup> Since then, other inactivating mutations have been

described in *KISS1R* in patients with sporadic and familial normosmic isolated hypogonadotropic hypogonadism.<sup>4,5</sup> To date, the frequency of mutations in *KISS1R* as a cause of this autosomal recessive disorder is relatively low. Further, the types of mutations have been unique, including point mutations, partial deletions and insertions. Very recently, a homozygous inactivating mutation in *KISS1* gene was also identified in a large consanguineous family. This mutation results in failure of pubertal progression, confirming that kisspeptin signaling is a critical element in the human hypothalamic-pituitary-gonadal axis.<sup>6</sup>

### Kisspeptin-1 and its cognate receptor are required for normal function of the hypothalamic-pituitary-gonadal axis and play an important role in the physiologic regulation of puberty.

### Kisspeptin system in central precocious puberty

Precocious puberty is characterized by the development of secondary sexual characteristics before the age of eight years in girls and nine years in boys. The premature activation of GnRH secretion leading to central precocious puberty has remarkable female gender predominance and more than 90 percent of the affected girls have the idiopathic form. The relevance of the kisspeptin system in human puberty onset was highlighted by the identification of activating mutations of the *KISS1R* and *KISS1* genes in children with central precocious puberty.<sup>7-9</sup> A unique, heterozygous, non-constitutively activating mutation of the *KISS1R* gene was associated with a central precocious puberty phenotype. In vitro studies demonstrated that this mutation leads to sustained activation of intracellular signaling pathways in response to kisspeptin.<sup>8</sup>

### Kisspeptins as potential therapeutic tools

Central or peripheral administration of the kisspeptin peptides has been demonstrated to stimulate gonadotropin release in several mammalian species, including humans.<sup>10</sup> Kisspeptin peptides stimulate gonadotropin release in men, and in women during the preovulatory phase of the menstrual cycle, but fail to stimulate gonadotropin release in women during the follicular phase.<sup>10</sup> The sexually dimorphic responses of healthy men and women to kisspeptin administration have important clinical implications for the potential of kisspeptin to treat disorders of reproduction such as infertility. Taken together, potential agonists and antagonists of kisspeptin may have potential for pharmacological intervention in human reproductive diseases and facilitate understanding of the physiological roles of the kisspeptin system.



*Kisspeptin is now recognized as critical in regulating the timing of sexual maturation and gonadotropin secretion by gonadal hormones in adults; it also controls fertility by metabolic and environmental cues.*

in modulating GnRH release. Kisspeptin was soon discovered to be a powerful stimulus for GnRH-induced LH secretion, and displaced GnRH from its premier position at the top of the reproductive cascade. Kisspeptin is now recognized as critical in regulating the timing of sexual maturation, gonadotropin secretion by gonadal hormones in adults, and the control of fertility by metabolic

and environmental (e.g., photoperiod) cues.<sup>3</sup>

Although the physiologic story of the kisspeptin system began to grow very quickly, the human genetics story took longer to evolve. In 2008, an activating mutation in *KISS1R* was identified in a girl with central precocious puberty.<sup>4</sup> Not only did this observation reinforce the notion that kisspeptin is an important gatekeeper of pubertal function in the human, but it was also the first identification of loss- and gain-of-function mutations critical to the hypothalamic control of GnRH leading to opposite reproductive phenotypes.

### Identifying mutations in *KISS1R*, *KISS1*

Throughout this period, investigators struggled to identify large cohorts of patients carrying kisspeptin pathway mutations. Perhaps because of the importance of the kisspeptin pathway in modulating GnRH secretion or its other biologic roles in placental development and metastasis suppression, the total number of cases of individuals bearing mutations in *KISS1R* remains relatively small. Moreover, despite the obvious candidacy of the kisspeptin gene itself, the identification of mutations in *KISS1* eluded investigators for eight years. However, in 2011, heterozygote mutations in *KISS1* were reported in patients with GnRH deficiency, validated by in vitro and animal studies.<sup>5</sup> This report was followed by the identification of a homozygote mutation in *KISS1* in 2012.<sup>6</sup>

Kisspeptin is now understood to be co-expressed with neurokinin B (NKB) and dynorphin, giving rise to the term KNDy neurons (Kisspeptin-Neurokinin B-Dynorphin). NKB is a member of the substance P-related tachykinin family and its receptor is expressed both on KNDy and GnRH neurons. Dynorphin is an opioid that participates in progesterone-mediated negative feedback control of

## Clinical Researcher Perspective

By Stephanie Seminara, M.D.

Dr. Seminara is a doctor of reproductive endocrinology at Massachusetts General Hospital, in Boston.



### Highlights

- Loss of function mutations in the kisspeptin receptor were discovered in patients with GnRH deficiency.
- Kisspeptin works with other co-expressed neuropeptides, including neurokinin B and dynorphin.
- Mutations in the neurokinin B signaling pathway have also been identified in patients with GnRH deficiency.

The hypothalamic hormone GnRH has traditionally been touted as the central driver of pituitary gonadotropin secretion, controlling pulsatile gonadotropin secretion, modulating gonadal steroid feedback, and bringing about full fertility in the adult. Understanding GnRH neuronal regulation is essential to understanding the neurohumoral control of human reproduction. In 2003, two groups discovered that in both the human and the mouse, mutations in *GPR54* (encoding the kisspeptin receptor, also known as *KISS1R*) cause hypogonadotropic hypogonadism. This can be corrected by the administration of exogenous GnRH.<sup>1,2</sup> Soon thereafter, several groups began assembling genetic, expression, physiologic, transgenic, knockdown, and electrophysiologic data to characterize the physiology of kisspeptin and its seminal role

GnRH release. Loss-of-function mutations in the genes encoding neurokinin B (*TAC3*) and its receptor (*TAC3R*) result in hypogonadotrophic hypogonadism and pubertal failure.<sup>7</sup> Although mutations in the dynorphin or its receptor have not yet been reported, the presence of mutations in the other two signaling pathways in GnRH-deficient states demonstrates the importance of this neuropeptide ensemble in the hypothalamic control of reproduction.

These genetic discoveries have come back to the bedside. Exogenous kisspeptin has now been administered to healthy men and women, and patients with reproductive disorders, including those with mutations in the neurokinin B signaling pathway.<sup>8-14</sup> Its power as a physiological probe lies in its ability to teach us about the fundamental secretory properties of GnRH neurons *in vivo*, and studies to date have revealed fascinating insights into GnRH neuronal responsiveness in different sex steroid milieu and GnRH pulse generation.

## Basic Researcher Perspective

By Manuel Tena-Sempere, M.D., Ph.D.

Dr. Tena-Sempere is professor of physiology at the University of Cordoba and senior researcher at the Instituto Maimónides de Investigación Biomédicas de Córdoba (IMIBIC) and the National Biomedical Research Center in Obesity and Nutrition (CIBERObn), Cordoba, Spain.



### Highlights

- Distinct populations of kisspeptin-producing (*Kiss1*) neurons have been identified in the hypothalamus, with different distributions depending on the species.
- *Kiss1* neurons in the ARC transmit the negative feedback from sex steroids that controls pulsatile GnRH, and hence gonadotropin, secretion.
- Experimental data in rodents strongly suggest that rostral *Kiss1* neurons are involved in mediating the positive feedback effects of estradiol and generation of the pre-ovulatory gonadotropin surge.
- *Kiss1* neurons participate in the central sensing and transmission of the regulatory actions of diverse reproductive modifiers, such as nutritional/metabolic & photoperiodic cues.

### Mechanistic insight: Kisspeptins and the control of GnRH neurons

The source of brain kisspeptins has been actively investigated. In rodents, two prominent hypothalamic populations of *Kiss1* neurons exist: one in the arcuate nucleus (ARC) and another in the rostral periventricular area of the third ventricle.<sup>1</sup> In other mammals, including humans, *Kiss1* neurons are present in the ARC/infundibular region, but

the existence of a population equivalent to the rodent RP3V has yet to be confirmed.<sup>1,2</sup> ARC and RP3V *Kiss1* neurons are functionally dissimilar: they respond differently to several key regulators, express different sets of co-transmitters, and seem to be differently wired to GnRH neurons.

Kisspeptin projections to GnRH neuronal cell bodies in rodents seem to originate mainly from RP3V, although projections from some ARC *Kiss1* neurons may also exist.<sup>3</sup> Studies in monkeys have shown kisspeptin fibers in close proximity to GnRH terminals in the median eminence, suggesting a regulatory role on GnRH release.<sup>2</sup> The above evidence is compatible with additional, indirect kisspeptin effects on GnRH neurons<sup>1,2</sup>, but other evidence points to direct actions at the pituitary level.<sup>4</sup>

### Kiss1 neurons as gatekeepers of puberty and ovulation

The absence of puberty in humans and mice with genetic inactivation of *Gpr54* or *Kiss1*<sup>1,5</sup> fueled mechanistic studies on how kisspeptins participate in the control of mammalian puberty. These analyses documented the complex pattern of activation of *Kiss1* neurons, which seems to be essential for the normal timing of puberty. This phenomenon includes not only the increase of kisspeptin tone, but also of the sensitivity to the stimulatory effects of kisspeptins. In addition, there is a rise in the number of kisspeptin neurons and their projections to GnRH neurons during puberty.<sup>6</sup> Blockade of *Gpr54* or timed ablation of *Kiss1* neurons at the infantile-juvenile transition has been shown to disturb puberty onset.<sup>7,8</sup> Experimental manipulations known to alter brain sex differentiation have been shown to perturb the development of the hypothalamic *Kiss1* system.<sup>6</sup>

Compelling experimental evidence suggests a crucial role of kisspeptins in the generation of the pre-ovulatory surge of gonadotropins, which triggers ovulation. Indeed, *Kiss1* neurons in the RP3V are activated in rodents during the pre-ovulatory period, whereas blockade of kisspeptin action abrogates the ovulatory LH surge.<sup>7,9</sup> Experimental evidence suggests that the pre-ovulatory rise of estrogen is responsible for the activation of *Kiss1* neurons in the RP3V before ovulation, as a major mechanism for its *positive feedback* effects.<sup>9</sup>

### Kiss1 neurons as conduits for sex steroid and metabolic regulation of GnRH neurons

*Kiss1* neurons are sensitive to changes in sex steroid milieu and are involved in conveying the *negative feedback* of sex steroids in the tonic control of gonadotropin secretion.<sup>9</sup> ARC *Kiss1* neurons, which express ER $\alpha$  and androgen receptors, increase *Kiss1* expression after sex steroid withdrawal and decrease *Kiss1* expression following gonadal steroid replacement. The functional relevance of such changes is illustrated by the finding that the normal gonadotropin increases that occur upon removal of sex steroids are lost in the absence of kisspeptin signaling.<sup>1,9</sup>

Metabolic cues also appear to use *Kiss1* neurons as a conduit for their well-known influence on puberty onset and

fertility.<sup>10</sup> For example, metabolic stress linked to reproductive failure, including not only persistent negative energy balance but also obesity, blunt the hypothalamic (mainly ARC) expression of *Kiss1*/kisspeptins, whereas kisspeptin replacement can overcome the gonadotropic defects in some of those conditions.<sup>1,10</sup> Leptin was initially suggested to operate as direct metabolic regulator of *Kiss1* neurons. Yet this model has been recently challenged by expression and functional genomic data suggesting that leptin actions on *Kiss1* neurons might be preferentially indirect.<sup>11</sup>

*Kiss1* neurons may also funnel additional regulatory signals onto GnRH neurons, including ageing, stress, and environmental cues. This reinforces the view that *Kiss1* neurons are upper-order sensors of a wide array of reproductive regulators, which drive GnRH secretion as result of their capacity to integrate diverse regulatory signals.

### Future directions in kisspeptin research

Considerable effort is being invested in elucidating the signals that interact with and/or modulate kisspeptin signaling in the brain. Although interest has focused on kisspeptin-NKB interactions<sup>12</sup>, many other central and peripheral transmitters are also under investigation.<sup>13</sup> Similarly, recent data strongly suggest that, in addition to transcrip-

tional mechanisms, epigenetic and post-transcriptional regulation of *Kiss1* pathways is likely to play important roles.<sup>1,14</sup> Experimental efforts along these lines will allow an integrated understanding of how kisspeptins operate to control puberty and fertility; a *basic* knowledge that may enable the refinement of current strategies for clinical care and management of reproductive disorders. ■

*This article was reviewed by Corrine Welt, MD, Mark Bach, MD, PhD, Peter Fuller, MBBS, PhD, FRACP and The Endocrine Society's Research Affairs Core Committee*



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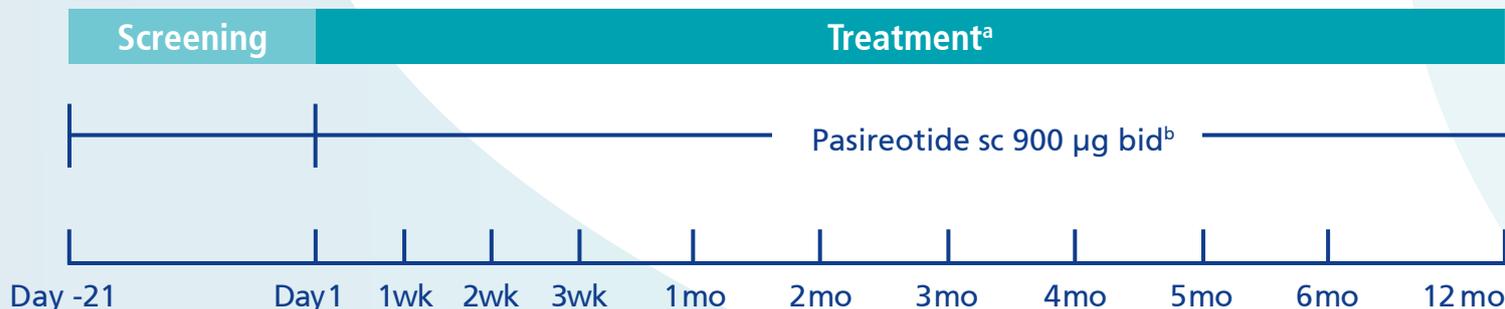
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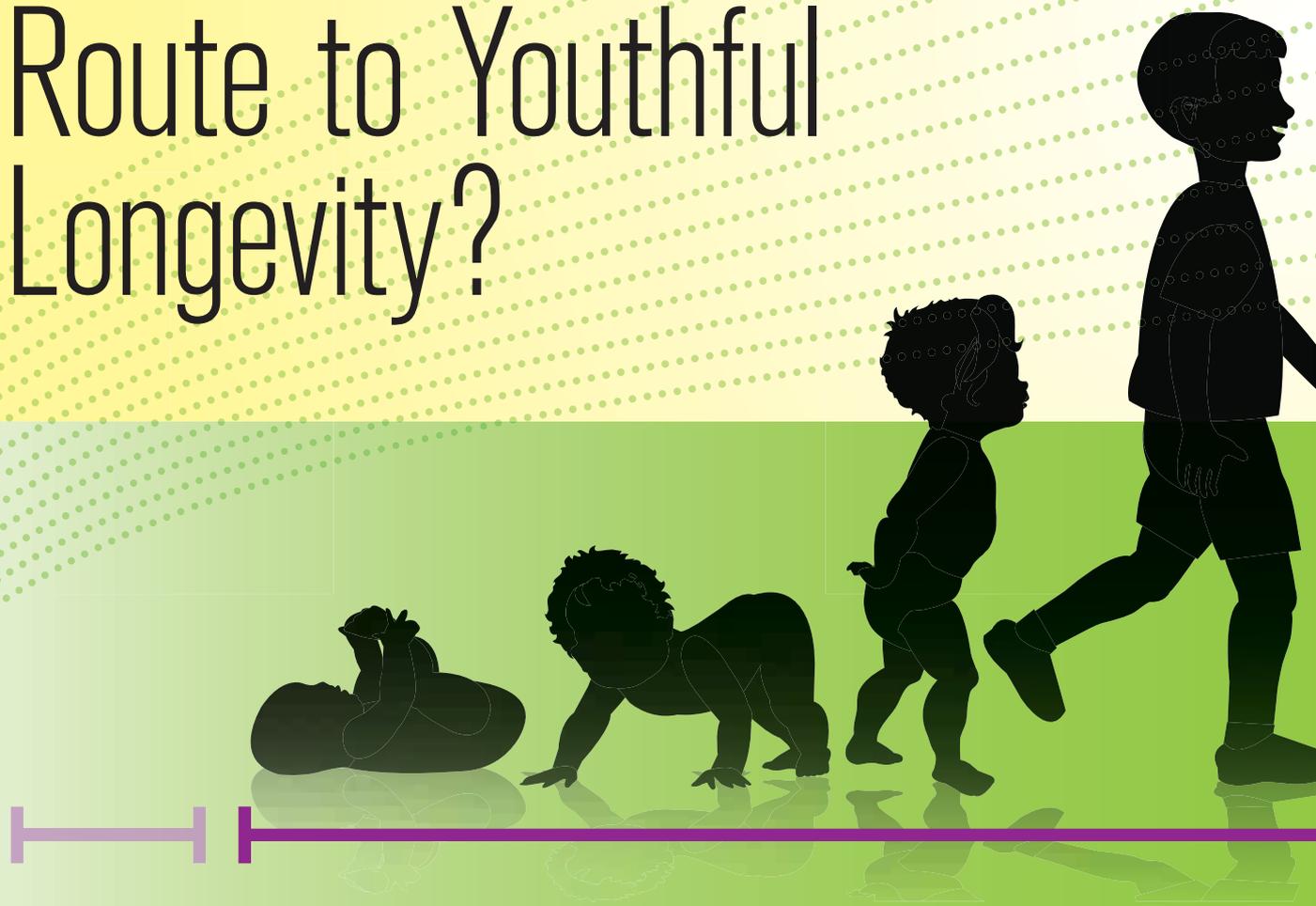
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# ENDOCRINE PATHWAY—

## Route to Youthful Longevity?



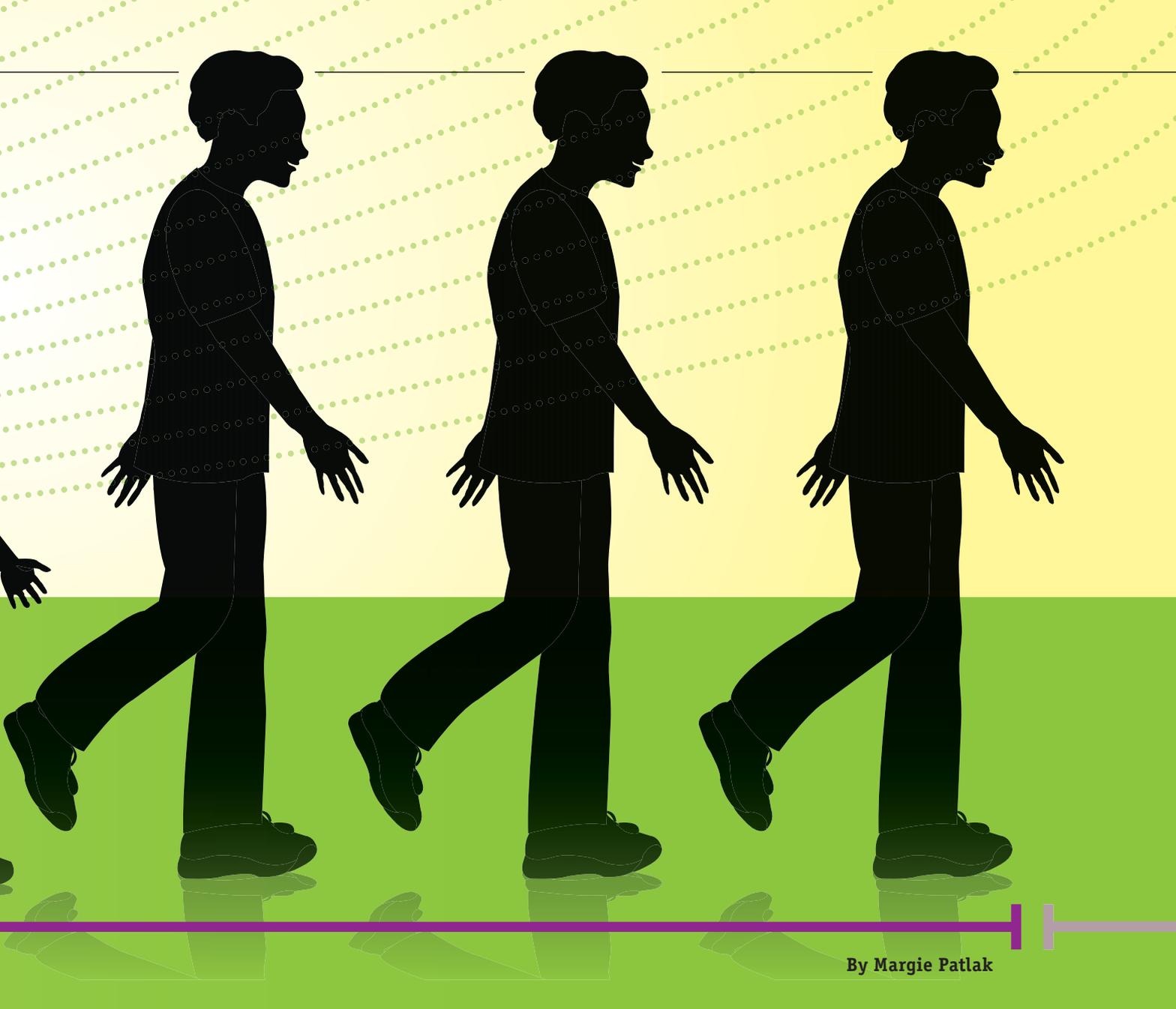
In the never-ending search for the fountain of youth, human growth hormone has become the latest celebrity health craze. The effectiveness and safety of using growth hormone (GH) supplements to stave off aging, however, remain controversial in the medical community. In another approach to figuring out the path to longevity, scientists are now aiming their anti-aging therapies at hormones and other compounds that genetic studies suggest play a key role in the aging process. The new anti-aging focus is due to mounting evidence that mutations in genes affecting an endocrine signaling pathway, called the somatotropic axis, play a major role in determining not only lifespan but also in delaying the onset of debilitating illnesses that come with aging.

“Changing single genes within these pathways can extend lifespan dramatically,” Cynthia Kenyon, Ph.D., at the University of California, San Francisco, wrote in a

2005 article in *Cell*. Kenyon’s studies on worms in 1993 showed that mutations in a single gene not only doubled the animals’ lifespans, but the mutant worms were also more mobile and exhibited fewer signs of physical deterioration than those without the mutations. “Some of these long-lived mutants are breathtaking; in human terms, they look like forty-year-olds when they are actually eighty or even older,” she wrote.

The discovery that a change in just one or two genes could change lifespan was significant, said Joseph Baur, Ph.D., of the University of Pennsylvania, who also studies aging. “Most people thought there were thousands of different things going wrong during aging and you would never be able to change enough of them to make a difference.”

The mutations occurred in genes that in humans determine the activity of insulin, growth hormone (GH), or



By Margie Patlak

insulin-like growth factor one (IGF-I), a trinity of compounds that work together to enable animals to grow and reproduce when food is sufficient. These compounds trigger growth in stature in immature animals and influence the growth of girth in adults when food is abundant. A lack of food or stress reduces their actions, but in doing so triggers a number of health-promoting mechanisms. "If you reduce food intake, you turn down insulin-GH-IGF-I activity," explained Andrzej Bartke, Ph.D., an expert on aging at Southern Illinois University.

Recently, researchers have linked changes in this growth-promoting pathway to long life in humans. Studies in 2008 and 2011 found that people with impaired IGF-I activity were more likely to live 100 years or more. In contrast, mice with mutations that increased their GH or IGF-I activity die young, as do people with acromegaly due to excessive secretions of GH and IGF-I.

Not only does a lack of GH or IGF-I activity seem to promote longevity, it also appears to delay aging. Many long-lived animals with GH or IGF-I receptor mutations never develop a number of age-related diseases, including cancer and heart disease, "suggesting the possibility of forestalling multiple diseases all at once by targeting aging itself," Kenyon said.

Some evidence suggests that this might be the case in humans as well. Laron dwarfs in Ecuador and other populations that are unresponsive to growth hormones seem to have remarkable protection from developing cancer and diabetes. The Laron community, however, is not immune to cardiovascular disease, researchers have noted, and the findings on the effects of reduced GH or IGF-I signaling on heart function remain inconclusive.

In contrast to Laron dwarfs, acromegalics have increased growth hormone activity and an increased risk of diabetes, heart disease, and cancer. Studies in both mice and humans

link elevated IGF-I levels with heightened risk for developing a number of different types of cancers.

Insulin, GH, or IGF-I activity in the brain might also play a role in fostering age-related brain disorders, such as Alzheimer's disease. When researchers suppressed insulin activity only in brain cells, mice lived longer. Genetic reduction of IGF-I activity also slowed the deterioration of cognitive faculties and the death of brain cells or their connections in mice with Alzheimer's disease.



"Aging may be a common denominator for most diseases," said Bartke. "The data from long-lived people suggest that whatever is extending their lives is also protecting them from disease. These folks don't seem to experience serious chronic disease until the very end of their lives—until the age of 95 or so they are in very good shape. This teaches us that you can postpone age-related health problems."

How could one signaling pathway affect so many facets of aging and disease? Numerous researchers are currently seeking answers to this question, and results from studies done in the last few years suggest several interacting mechanisms, including increased stress protection, suppressed inflammation, enhanced insulin sensitivity, reduced protein clumping, and greater cleanup of protein trash within cells.

"If you reduce insulin or IGF-I action you get a lot of bang for your buck because you activate all these beneficial pathways," Kenyon noted.

Several studies find that reduced GH or IGF-I activity triggers the production of antioxidant enzymes that protects cells from damage by free radicals and other reactive oxygen compounds. Studies in worms and mice also reveal that suppression of insulin, GH, or IGF-I activity appears to protect neurons from the clumping of the beta amyloid protein that is the hallmark of Alzheimer's disease. Worm studies find such suppression increases production of chaperone proteins that help other proteins fold properly or escort misfolded proteins to cellular garbage cans, thereby perhaps preventing the harmful buildup of amyloid plaques in the brain.

There's also evidence that deficient GH action in mice favorably alters the distribution and function of fat tissue. Although this deficiency boosts the amount of fat tissue in mice, that fat tissue is less likely to be deposited in the abdomen and promote insulin resistance, inflammation, and other ills linked to abdominal obesity and the metabolic syndrome in people. GH deficiency also boosts the amount of adiponectin, a hormone secreted by fat cells that promotes insulin sensitivity and has anti-inflammatory and anti-atherogenic actions that increase longevity in both mice and humans.

### Calorie Restriction Extends Life

The findings on the effects of growth hormone and IGF-I on aging may help explain why extreme calorie restriction extends life. When an animal is stressed by a lack of food or other factors, it suppresses energy-consuming growth and reproduction in favor of biochemistry that promotes repair and survival.

"What really matters from an evolutionary standpoint is leaving offspring and not how long you live," Bartke explained. "Growth hormone fits into that concept because it makes you grow and reach sexual maturation and leave offspring." For humans, who stop growing in stature relatively early in life but tend to still grow in girth due to an ever present abundance of food, growth hormone and IGF-I action, even at normal levels, may be harmful to health and longevity.

This conclusion is striking given our current obesity epidemic, Bartke and Kenyon pointed out. "People are overeating for their energy expenditure and becoming overweight," said Bartke. "We're doing something that is very wrong in terms of health and longevity and the current generation may be the first generation in recent history that won't live longer than their parents."

"I believe that we need to get rid of much of the sugar that's in our diets and exercise more," Kenyon added. The whole focus is on fat, but sugar is what triggers insulin activity and prevents the body from using its stored fat reserves. If you can maintain a lower insulin state, you can do wonders."

This is already apparent in people who stick rigidly to extremely low-calorie diets with the hopes of forestalling aging. Studies on these individuals reveal they have very

low insulin and blood glucose levels, impressive blood lipid profiles, and the blood pressures of people half their age. "They certainly look like they are not likely to get most of the things that kill people, but it remains to be seen whether they will live longer," Bartke said.

Although inducing major stress or severely restricting food intake are not likely to be successful therapies in our culture, the recent findings on GH, IGF-I, and aging suggest that medications may be developed to adjust the amount of these compounds, or others downstream, so that the age of 60 may one day be the new 30. Studies in mice show it is possible to extend life with the drug rapamycin, even when the drug regimen isn't started until the mice are middle-aged.

### "Perturbing the Pathway"

But there could potentially be tradeoffs in tampering with Mother Nature. Although rapamycin causes mice to live longer healthier lives, for example, it is an immune suppressant that might have unacceptable side effects. And although low levels of IGF-I are tied to a lower risk of cancer, they are also linked to greater risk of developing type 2 diabetes, osteoporosis, and poor cognitive function.

It might be possible to "cause some modest reduction in GH and IGF-I activity that is within the physiological range

and won't be life threatening, but will keep insulin levels and sensitivity youthful," Bartke suggested.

"You can imagine getting in there and perturbing the pathway in a way that doesn't create unfavorable side effects," said Kenyon. "I think that's feasible because after all, small-breed dogs are small because they have low IGF-I levels, and they also live longer than large dogs and are very healthy."

Another approach to lengthening the "youthspan" might be to induce a minor stress by administering a small amount of a toxin or some other substance, that might cause the body to roll out the protective responses triggered by reducing insulin-GH and IGF-I activity, Kenyon added. She is currently testing such an approach on human cells. She said she looks forward to the day when "people can take a drug that makes them naturally more resilient and able to live longer and resist disease." ■

*Patlak is a freelance science writer in Philadelphia.*



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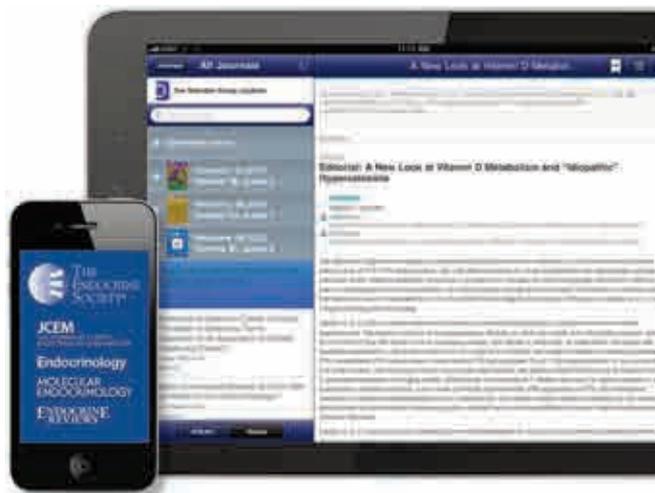
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# HER FIRST OSTEOPOROTIC FRACTURE COULD LEAD TO ANOTHER



## INDICATIONS AND USAGE

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

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

### **WARNING: POTENTIAL RISK OF OSTEOSARCOMA**

*See the Important Safety Information for Complete Boxed Warning.*

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

**Find out how FORTEO forms new bone at [www.FORTEOhcp.com](http://www.FORTEOhcp.com)**

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

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



## FORTEO SELECT SAFETY INFORMATION

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

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

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

## INDICATIONS AND USAGE

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

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

# IMPORTANT SAFETY INFORMATION

### WARNING: POTENTIAL RISK OF OSTEOSARCOMA

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

### CONTRAINDICATIONS

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

### WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

### ADVERSE REACTIONS

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

### USE IN PREGNANCY/NURSING MOTHERS

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

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

### INSTRUCTIONS FOR FORTEO USE

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

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

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

*Lilly*

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

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

### **WARNING: POTENTIAL RISK OF OSTEOSARCOMA**

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

### **INDICATIONS**

FORTEO is indicated: for the treatment of postmenopausal women with osteoporosis at high risk for fracture; to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; for the treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy at high risk for fracture.

### **CONTRAINDICATIONS**

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

### **WARNINGS AND PRECAUTIONS**

**Osteosarcoma** In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. FORTEO should not be prescribed for patients at increased baseline risk of osteosarcoma. These include Paget's disease of bone (unexplained elevations of alkaline phosphatase may indicate Paget's disease of bone); pediatric and young adult patients with open epiphyses; prior external beam or implant radiation therapy involving the skeleton. Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting [www.forteoregistry.rti.org](http://www.forteoregistry.rti.org).

**Treatment Duration** The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years during a patients' lifetime is not recommended.

**Bone Metastases and Skeletal Malignancies** Patients with bone metastases or a history of skeletal malignancies should not be treated with FORTEO.

**Metabolic Bone Diseases** Patients with metabolic bone diseases other than osteoporosis should not be treated with FORTEO.

**Hypercalcemia and Hypercalcemic Disorders** FORTEO has not been studied in patients with pre-existing hypercalcemia. These patients should not be treated with FORTEO because of the possibility of exacerbating hypercalcemia. Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with FORTEO.

**Urolithiasis or Pre-existing Hypercalciuria** In clinical trials, the frequency of urolithiasis was similar in patients treated with FORTEO and placebo. However, FORTEO has not been studied in patients with active urolithiasis. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered. FORTEO should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

**Orthostatic Hypotension** FORTEO should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur. In short-term clinical pharmacology studies with teriparatide, transient episodes of symptomatic orthostatic

hypotension were observed in 5% of patients. Typically, an event began within 4 hours of dosing and spontaneously resolved within a few minutes to a few hours. When transient orthostatic hypotension occurred, it happened within the first several doses, it was relieved by placing the person in a reclining position, and it did not preclude continued treatment.

**Drug Interactions** Hypercalcemia may predispose patients to digitalis toxicity. Because FORTEO transiently increases serum calcium, patients receiving digoxin should use FORTEO with caution.

### **ADVERSE REACTIONS**

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

***Treatment of Osteoporosis in Men and Postmenopausal Women*** The safety of FORTEO in the treatment of osteoporosis in men and postmenopausal women was assessed in two randomized, double-blind, placebo-controlled trials of 1382 patients (21% men, 79% women) aged 28 to 86 years (mean 67 years). The median durations of the trials were 11 months for men and 19 months for women, with 691 patients exposed to FORTEO and 691 patients to placebo. All patients received 1000 mg of calcium plus at least 400 IU of vitamin D supplementation per day. The incidence of all cause mortality was 1% in the FORTEO group and 1% in the placebo group. The incidence of serious adverse events was 16% in FORTEO patients and 19% in placebo patients. Early discontinuation due to adverse events occurred in 7% of FORTEO patients and 6% of placebo patients. **Percentage of Patients with Adverse Events Reported by at Least 2% of FORTEO-Treated Patients and in More FORTEO-Treated Patients than Placebo-Treated Patients from the Two Principal Osteoporosis Trials in Women and Men Adverse Events are Shown Without Attribution of Causality (FORTEO, N=691, Placebo, N=691):**

**Body as a Whole:** Pain (21.3%, 20.5%), Headache (7.5%, 7.4%), Asthenia (8.7%, 6.8%), Neck Pain (3.0%, 2.7%); **Cardiovascular:** Hypertension (7.1%, 6.8%), Angina Pectoris (2.5%, 1.6%), Syncope (2.6%, 1.4%); **Digestive System:** Nausea (8.5%, 6.7%), Constipation (5.4%, 4.5%), Diarrhea (5.1%, 4.6%), Dyspepsia (5.2%, 4.1%), Vomiting (3.0%, 2.3%), Gastrointestinal disorder (2.3%, 2.0%), Tooth disorder (2.0%, 1.3%); **Musculoskeletal:** Arthralgia (10.1%, 8.4%), Leg cramps (2.6%, 1.3%); **Nervous System:** Dizziness (8.0%, 5.4%), Depression (4.1%, 2.7%) Insomnia (4.3%, 3.6%), Vertigo (3.8%, 2.7%); **Respiratory System:** Rhinitis (9.6%, 8.8%), Cough increased (6.4%, 5.5%), Pharyngitis (5.5%, 4.8%), Dyspepsia (3.6%, 2.6%), Pneumonia (3.9%, 3.3%); **Skin and Appendages:** Rash (4.9%, 4.5%), Sweating (2.2%, 1.7%).

**Immunogenicity** In the clinical trial, antibodies that cross-reacted with teriparatide were detected in 3% of women (15/541) receiving FORTEO. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions or allergic reactions among these patients. Antibody formation did not appear to have effects on serum calcium, or on bone mineral density (BMD) response.

**Laboratory Findings Serum Calcium:** FORTEO transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Serum calcium measured at least 16 hours post-dose was not different from pretreatment levels. In clinical trials, the frequency of at least 1 episode of transient hypercalcemia in the 4 to 6 hours after FORTEO administration was increased from 2% of women and none of the men treated with placebo to 11% of women and 6% of men treated with FORTEO. The number of patients treated with FORTEO whose transient hypercalcemia was verified on consecutive measurements was 3% of women and 1% of men.

**Urinary Calcium:** FORTEO increased urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with FORTEO and placebo. **Serum Uric Acid:** FORTEO increased serum uric acid concentrations. In clinical trials, 3% of FORTEO patients had serum uric acid concentrations above the upper limit of normal compared with 1% of placebo patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis. **Renal Function:** No clinically

important adverse renal effects were observed in clinical studies. Assessments included creatinine clearance; measurements of blood urea nitrogen (BUN), creatinine, and electrolytes in serum; urine specific gravity and pH; and examination of urine sediment. *Studies in Men and Women with Glucocorticoid-Induced Osteoporosis* The safety of FORTEO in the treatment of men and women with glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with  $\geq$  5mg per day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to FORTEO and 214 patients exposed to oral daily bisphosphonate (active control). All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day. The incidence of all cause mortality was 4% in the FORTEO group and 6% in the active control group. The incidence of serious adverse events was 21% in FORTEO patients and 18% in active control patients, and included pneumonia (3% FORTEO, 1% active control). Early discontinuation because of adverse events occurred in 15% of FORTEO patients and 12% of active control patients, and included dizziness (2% FORTEO, 0% active control). Adverse events reported at a higher incidence in the FORTEO group and with at least a 2% difference in FORTEO-treated patients compared with active control-treated patients were: nausea (14%, 7%), gastritis (7%, 3%), pneumonia (6%, 3%), dyspnea (6%, 3%), insomnia (5%, 1%), anxiety (4%, 1%), and herpes zoster (3%, 1%), respectively. **Postmarketing Experience:** The following adverse reactions have been identified during postapproval use of FORTEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **Osteosarcoma:** Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to FORTEO use is unclear. Long term osteosarcoma surveillance studies are ongoing. **Hypercalcemia:** Hypercalcemia greater than 13.0 mg/dL has been reported with FORTEO use. Adverse events reported since market introduction that were temporally (but not necessarily causally) related to FORTEO therapy include the following: **Allergic Reactions:** Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria; **Investigations:** Hyperuricemia; **Respiratory System:** Acute dyspnea, chest pain; **Musculoskeletal:** Muscle spasms of the leg or back; **Other:** Injection site reactions including injection site pain, swelling and bruising; oro-facial edema.

## USE IN SPECIFIC POPULATIONS

**Pregnancy Category C.** There are no adequate and well-controlled studies of FORTEO in pregnant women. In animal studies, teriparatide increased skeletal deviations and variations in mouse offspring at doses more than 60 times the equivalent human dose and produced mild growth retardation and reduced motor activity in rat offspring at doses more than 120 times the equivalent human dose. FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In animal studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses 8 to 267 times the human dose. At doses  $\geq$  60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received subcutaneous teriparatide during organogenesis at doses 16 to 540 times the human dose, the fetuses showed no abnormal findings. In a perinatal/postnatal study, pregnant rats received subcutaneous teriparatide from organogenesis through lactation. Mild growth retardation in female offspring at doses  $\geq$ 120 times the human dose (based on surface area, mcg/m<sup>2</sup>). Mild growth retardation in male offspring and reduced motor activity in both male and female offspring occurred at maternal doses 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively. Exposure multiples were normalized based on body surface area (mcg/m<sup>2</sup>). Actual animal doses: mice (30 to 1000 mcg/kg/day); rats (30 to 1000 mcg/kg/day). **Nursing Mothers:** It is not known whether teriparatide is excreted

in human milk. Because of the potential for tumorigenicity shown for teriparatide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** The safety and efficacy of FORTEO have not been established in any pediatric population. FORTEO should not be prescribed in patients at an increased baseline risk of osteosarcoma which include pediatric and young adult patients with open epiphyses. Therefore, FORTEO is not indicated for use in pediatric or young adult patients with open epiphyses. **Geriatric Use:** Of the patients receiving FORTEO in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving FORTEO in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** No studies have been performed in patients with hepatic impairment. **Renal Impairment:** In 5 patients with severe renal impairment (CrCl $<$ 30 mL/min), the AUC and T<sub>1/2</sub> of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased.

## OVERDOSAGE

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

## DOSAGE FORMS AND STRENGTHS

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

## PATIENT COUNSELING INFORMATION

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

12/13/2010

**PLEASE SEE FULL PRESCRIBING INFORMATION FOR ADDITIONAL INFORMATION.**

Literature revised December 13, 2010

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## Society Advocates Principles on EDCs in the U.S. and Abroad

By Loretta L. Doan, Ph.D.

In a recently issued statement of principles, The Endocrine Society proposed a streamlined definition of endocrine-disrupting chemicals (EDCs). “Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society” clarifies the definition of an EDC and outlines the key concepts of endocrinology needed to ensure that regulatory decisions are based on the cutting-edge science of the last decade.

The statement defines an endocrine disruptor as an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action. It also includes several recommendations designed to strengthen screening for EDCs. In June, the new statement was presented to the news media at an **ENDO 2012** press conference and released online. It will also appear in the September issue of *Endocrinology*.

In 2009, the Society released a Scientific Statement on EDCs in which it made a number of recommendations regarding research and regulation of such chemicals. In subsequent discussions, policy makers asked the Society specifically how to improve the regulatory process. In response to these questions, the Society developed the statement of principles, which has been presented in a number of settings, including the Society’s first international meeting on EDCs.

### International Presence

The Society presented the latest statement to policymakers and various interest groups assembled in Brussels in June by the European Commission.

Like the United States, the European Union (EU) faces the complex and complicated problem of regulating EDCs under a number of legislative vehicles. The Commission is charged with providing criteria for the assessment of, and regulatory decisions about, the endocrine-disrupting properties of chemicals by December 2013.

The Commission specifically requested the perspective of the Society, the only endocrinology group to contribute to the European EDC debate. R. Thomas Zoeller, Ph.D., the statement’s lead author, presented the key points of the statement of principles to the assembled group of more than 250 policymakers, regulators, scientists, non-governmental organizations, and industry representatives from the United States, the European Union, and other nations. He stressed the importance of incorporating endocrinology into the risk assessment paradigms for EDCs and of engaging endocrinologists in the design and interpretation of studies that guide regulation.

### National Leadership

The Society also met with U.S. Environmental Protection Agency (EPA) Acting Assistant Administrator Jim Jones and his staff in May to review the principles, which the statement frames in the context of the EPA’s Endocrine Disruptor Screening Program (EDSP). The EPA has regulatory authority over EDCs through the Food Quality Protection Act and under amendments to the Safe Drinking Water Act. During the meeting, the Society and EPA discussed ways in which the organizations can collaborate to improve EDC screening and testing.

During a Horizons@Heinz lecture series briefing in May sponsored by the H. John Heinz III Center for Science, Economics, and the Environment in Washington, D.C., the Society pressed U.S. policy makers to incorporate endocrine principles into the EDSP and other risk assessment programs that test chemicals for endocrine activity. The lecture series raises the profile of urgent and emerging issues through national and international policy debate.

The chair of the lecture program invited the Society to participate in the event because of its leadership in the science and policy of endocrine-disrupting chemicals. Among the attendees were Senators John Kerry (D-MA) and Sheldon Whitehouse (D-RI). Congressional staff and representatives of federal agencies, including the EPA, Food and Drug Administration, and the White House Office of Science and Technology Policy, also attended. Advocacy groups, media, green chemists, industry, and the French Embassy were also represented.

### The Society’s Commitment

At all of these forums, Zoeller described critical principles of endocrinology that differ from those of classic toxicology and recommended changes to the regulatory process to ensure it is equipped to identify potential endocrine-disrupting activity. The Society will continue to work domestically and internationally to ensure that the decisions being made by regulators incorporate the latest endocrine science available for evaluating EDCs. ■

*Doan is the director of Science Policy at The Endocrine Society.*



## A Renaissance for Long-Acting Reversible Contraception

By Melissa Mapes



The intrauterine device (IUD) has come a long way since the 1970s when many were pulled off the market after being linked to pelvic inflammation, infections, and even death. The modern redesigned IUDs, plus recommended testing for sexually transmitted diseases (STDs) prior to insertion, have all but eradicated such complications, allowing a new generation of women to revive the IUD.

Studies show that IUDs and the subdermal implant prevent unintended pregnancies far more effectively than other reversible options on the market, with a maximum of 1 contraceptive failure per 100 women in a year. The Depo-Provera shot came in second with an incidence of 3 per 100, followed by the pill at 8 per 100 and condoms at 15 per 100.

The IUD's convenience, which requires replacement every five years for the Mirena, a device that releases the synthetic hormone levonorgestrel, and 10 years for the copper-only ParaGard, has won over

many providers and patients, but these devices still comprise a small share of the contraceptive market. According to Jeffrey F. Peipert, M.D., M.P.H., M.H.A., Robert J. Terry Professor of Obstetrics & Gynecology and vice chair of clinical research

**Studies show that IUDs and the subdermal implant prevent unintended pregnancies far more effectively than other reversible options on the market.**

at Washington University School of Medicine, and author of the "Effectiveness of Long-term Reversible Contraception" recently published in *The New England Journal of Medicine*, there are three barriers slowing the spread of IUDs: education, access, and affordability.

The U.S. Food and Drug Administration did not approve IUDs for women who had not given birth until 2005. Jesuit hospitals often will not prescribe IUDs because they prevent fertilization and implantation rather than ovulation. Insurers frequently deny coverage for IUDs over other types of birth control, making the up-front costs of about \$400-\$1,000 a barrier.

Despite these obstacles, Catherine M. Gordon, M.D., M.Sc., director of the Bone Health Program in the Divisions of Adolescent Medicine and Endocrinology at Boston Children's Hospital and lead author of the recent article "Approach to the Adolescent Requesting Contraception" in *The Journal of Clinical Endocrinology & Metabolism*, has noticed a distinct rise in Mirena IUD requests among her patients. "Generally older adolescents have an interest in this method." The initial discomfort of IUD insertion into the cervix can be difficult for younger teens. She noted that Children's Hospital does not have physicians trained to insert IUDs, meaning that patients must go to the neighboring adult hospitals. Special training is required, which has also slowed the popularity of the IUD.

Complications during and after insertion may occur if not done correctly. Alexandra Glorioso, 25, a financial systems specialist in New York City, had an unfortunate experience at her university's student health services: "It took like 45 minutes, and they gave me Vicodin afterward, which is atypical." Despite the initial pain, she says the Mirena IUD was worth it in the long run. "In general I don't even remember that I have it," said Glorioso. She explained that the IUD provides security and simplicity that other forms of birth control cannot. She has tried everything from the pill to Depo Provera shots to NuvaRing. She said she is considering switching to the Implanon arm implant when her Mirena turns five next year, but she still highly

# Hormone Health Network's Patient Guide to Osteoporosis in Men

In osteoporosis, bones become weak and are more likely to fracture (break). It is a “silent” condition, causing no symptoms (what you feel) unless you break a bone. About 20% of the 44 million Americans who have osteoporosis or osteopenia (mildly low bone mass) are men.

The lifetime risk of having a fracture due to osteoporosis for men ages 50 and older is 13% to 30%. Fractures occur most often at the hip, spine, and wrist. These fractures—above all, hip fractures—can greatly reduce the quality of life and even lead to early death. Though osteoporosis affects men less often than women, men are two to three times more likely than women to die after breaking a hip.

Fortunately, osteoporosis can be prevented. However, many men are unaware that they are at risk for this dangerous disorder. This guide is based on The Endocrine Society's practice guidelines for physicians about testing for, treating, and preventing osteoporosis in men.

## Osteoporosis Risk Factors

### Personal and family history:

- White race
- Age 70 and older
- Thinness
- Prior fracture as an adult, mainly after age 50
- History of delayed puberty
- Family history of osteoporosis or a parent who had a fracture

### Lifestyle:

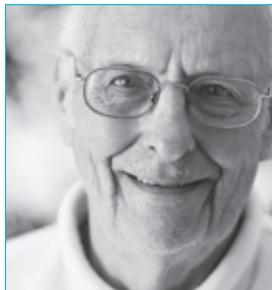
- Cigarette smoking
- Excess alcohol use
- Low calcium and vitamin D intake
- Lack of physical activity

### Health problems and medicines:

- Low testosterone (hypogonadism), including low testosterone caused by treatment for prostate cancer
- High calcium levels in the blood (hypercalcemia) or urine (hypercalciuria)
- Vitamin D deficiency
- Disorders that affect many parts of the body including hyperthyroidism (overactive thyroid), hyperprolactinemia, kidney failure, liver failure, celiac disease, and certain cancers
- Use of steroid medications such as prednisone and cortisone for more than 3 months—called *glucocorticoid-induced osteoporosis*

## What causes osteoporosis in men?

Osteoporosis occurs when your body cannot replace bone as quickly as it breaks down old bone (a natural process called “bone turnover”). Certain factors raise a man's risk of developing osteoporosis.



About 20% of Americans who have osteoporosis or osteopenia are men.

## How is osteoporosis in men diagnosed?

Your doctor may suspect osteoporosis based on your medical history, risk factors, and physical exam, including your height, balance, and mobility.

The most common way to detect osteoporosis is with a bone density test such as a dual-energy x-ray absorptiometry (DXA or DEXA) scan. This test measures bone mineral density (BMD) at your lower spine and hip, and gives a score called a T-score. A T-score of  $-2.5$  or lower indicates osteoporosis, and a T-score between  $-1.0$  and  $-2.5$  shows osteopenia. A score above  $-1.0$  is normal.

DXA can also show vertebral fractures (breaks in the bones that make up your spine). People who have had a vertebral fracture are more likely to have more fractures, so vertebral fracture assessment can have important clinical implications.

You may need other lab tests, such as blood or urine tests, if your DXA scan finds osteoporosis. These tests look for chronic health problems that may be the cause of your poor bone health. Blood tests also can check for abnormal levels of calcium or vitamin D that may cause bones to become weak.



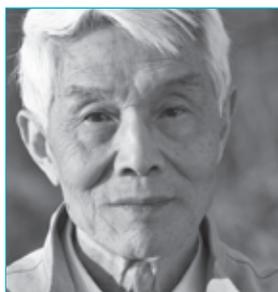
To find an endocrinologist and obtain free publications, visit [www.hormone.org](http://www.hormone.org) or call 1-800-HORMONE.

## Who should get a DXA test?

Men at increased risk of osteoporosis should consider having their BMD measured. This includes men ages 50 to 69 who have any other osteoporosis risk factors (see box on page one). Doctors may suggest that men ages 70 and older, even those who have no other risk factors, have a BMD test.

If your doctor orders a BMD test, you should get a central DXA of the spine and hip. However, spine DXA may be hard to interpret in older men. In this case, your doctor may consider measuring BMD at the forearm.

Depending on your bone density results, other risk factors for fracture, and any treatment you are receiving, you may need another DXA in one to three years to check for further bone loss or response to treatment.



Whether you need treatment for osteoporosis depends partly on your future chance of breaking a bone.

## Who should receive treatment?

Whether you need treatment for osteoporosis depends partly on your future chance of breaking a bone.

Fracture risk calculators can help predict your risk of fracture. These Web-based tools compute your estimated risk after you input information such as your age, body weight, past fractures, and BMD. They include the World Health Organization Fracture Risk Assessment Tool (FRAX) and one from the Garvan Institute of Medical Research (Garvan Fracture Risk Calculator).

Doctors will consider prescription drug treatment for adult men who:

- Have had a hip or spine fracture without having major trauma
- Have a DXA T-score at the spine or hip of  $-2.5$  or worse
- Have a DXA T-score between  $-1$  and  $-2.5$  along with high fracture risk
- Are receiving long-term glucocorticoid therapy
- Are receiving androgen deprivation therapy (ADT) for prostate cancer along with high fracture risk

## What is the treatment for osteoporosis?

The best type of medication to treat osteoporosis depends on the individual. Your doctor will consider your DXA T-scores, your future fracture risk, any fractures you had in the past, and other health problems you may have. The cost of the medicine and other factors also may affect your choice.

In the United States, four medications are approved for treatment of osteoporosis in men. They are

- *Alendronate* (tablets taken daily or weekly)
- *Risedronate* (tablets daily, weekly, or monthly)
- *Zoledronic acid* (intravenous, or IV, once a year)
- *Teriparatide* (once daily injection under the skin)

The first three drugs are in the class of drugs called bisphosphonates. These drugs slow bone loss and slightly increase bone mass. Both risedronate and zoledronic acid also have approval from the Food and Drug Administration (FDA) to prevent osteoporosis in men taking glucocorticoid medicine.

In contrast, *teriparatide* stimulates new bone formation. Because it requires daily injections and is expensive, doctors usually prescribe it only for men with severe osteoporosis.

Men at high fracture risk who are receiving ADT for prostate cancer also have the choice of a new medication named *denosumab*. Given as an injection under the skin, this drug increases bone density.

Testosterone therapy appears to increase BMD in men with low levels of this male hormone (below 200 nanograms per deciliter, or ng/dL), but its effect on fractures has not been studied. So, unless men have a clear need for testosterone therapy other than for bone health, an FDA-approved osteoporosis medicine is usually the first choice for these men. This is especially true if they have a high fracture risk.

Ask your doctor which treatment is best for you and about its benefits and risks.

## What can you do to prevent and treat osteoporosis?

You can help prevent osteoporosis by making changes in your diet and lifestyle. If you are a man at risk of osteoporosis, you should

- Consume 1,000 to 1,200 mg of calcium daily from foods (including calcium-fortified foods and drinks) and, if needed, calcium supplements.
- Take daily vitamin D supplements (1,000 to 2,000 International Units [IU] or more if your doctor prescribes it) if your blood level of vitamin D is low (less than 20 to 30 ng/mL).
- Do weight-bearing activities, such as walking, running, and weight lifting, three or four times a week for 30 to 40 minutes each.
- Drink no more than 10 alcoholic drinks a week (1 drink in the U.S. = 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of hard liquor; in the U.K. or Australia = 1/2 pint of beer, 1 small glass of wine, or a single measure of spirits)
- Quit smoking.

If you already have osteoporosis, you should take 1,000 to 1,200 mg per day of calcium, plus as much vitamin D as your doctor suggests. Also, take your prescribed dose of other medications, keep appointments with your doctor, and get DXA scans as advised. This will help ensure the success of your treatment and healthy bones.

## EDITORS

Robert A. Adler, MD  
Joel Finkelstein, MD

June 2012



recommends the IUD.

Many other women are also singing the praises of the Mirena IUD. The Contraceptive Choice Project, conducted by Peipert, educated women on their birth control options and allowed them to choose their preference free of charge. The researchers found that the Mirena IUD had the highest overall satisfaction rate, with 88 percent sticking with it after one year. The ParaGard and Implanon implants were not far behind, at 84 percent and 83 percent, but all other forms were under 60 percent in the same time period. After removing the three barriers, 75 percent of the 9,256 participants chose long-acting reversible contraception with almost 50 percent deciding upon the Mirena IUD.

Long-term satisfaction with Mirena is often driven by reduced men-

strual flow and dysmenorrhea. About 20 percent stop having periods altogether after one year, and even more in the following two to three years. Gordon sometimes prescribes it to patients with mild endometriosis. But, when asked if the discontinued menstruation could affect bone density, both doctors agreed that it requires further investigation. Currently, evidence is insufficient to know if Mirena has such risks, but Peipert hypothesizes that the localized nature of the device should not affect bone health.

Studies also show that most women return to fertility quickly after IUD removal. Gordon explained that the World Health Organization endorses the use of IUDs, even in teens. She says that an increased incidence of STDs in women with IUDs is a myth, and it is an accepted form of "safe and effective contra-

ception." Only women at very high risk for STDs may not be candidates for an IUD.

The future of long-term reversible contraception is bright. Peipert is currently seeking grants for studies that could extend the accepted lifespan of Mirena from five to eight years. "I believe IUDs are probably good for a lot longer than they're approved for," he said. "So I don't think it's a major concern if people leave it in longer. They just have to be aware that it's not approved for that long." Insurance coverage remains a primary hurdle, but once cost-reducing benefits are recognized, such as reduced incidents of unintended pregnancy, dysmenorrhea, endometriosis, and patient attrition, birth control pills may become a thing of the past. ■

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

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# Start a smart partnership

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



## Indication and usage

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

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

## Important Safety Information

### Contraindications

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

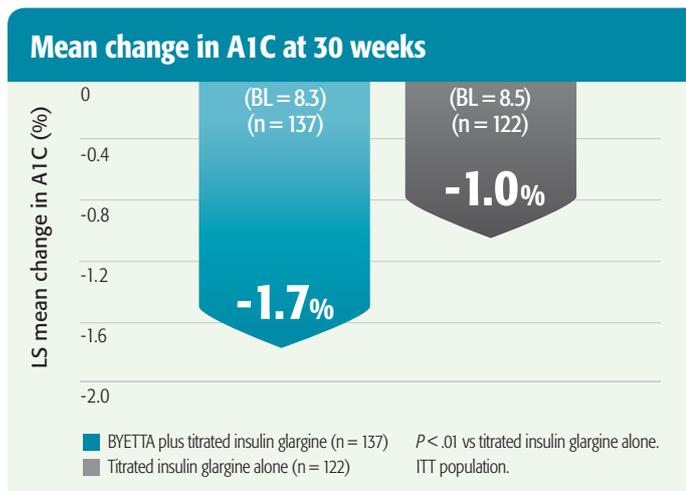
### Warnings and precautions

- Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation and dose increases of BYETTA, observe patients carefully for pancreatitis (persistent severe abdominal pain, sometimes radiating to the back, with or without vomiting). If pancreatitis is suspected, BYETTA should be

discontinued promptly. BYETTA should not be restarted if pancreatitis is confirmed.

- Increased risk of hypoglycemia when used in combination with glucose-independent insulin secretagogues (eg, sulfonylureas); reduction of the sulfonylurea dose may be needed. When used with insulin, evaluate and consider reducing the insulin dose in patients at increased risk of hypoglycemia.
- Postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure, and acute renal failure, sometimes requiring hemodialysis and kidney transplantation. BYETTA should not be used in patients with severe renal impairment or end-stage renal disease. Use with caution in patients with renal transplantation or when initiating or escalating the dose in patients with moderate renal failure.
- Not recommended in patients with severe gastrointestinal disease (eg, gastroparesis).
- Patients may develop antibodies to exenatide. In 3 registration trials, antibody levels were measured in 90% of patients, with up to 4% of patients having high-titer antibodies and attenuated glycemic response. If worsening of or failure to achieve adequate glycemic control occurs, consider alternative antidiabetic therapy.
- Postmarketing reports of serious hypersensitivity reactions (eg, anaphylaxis and angioedema). If this occurs, patients should discontinue BYETTA and other suspect medications and promptly seek medical advice.

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



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

### Warnings and precautions (cont'd)

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

### Adverse reactions

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

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

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

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

### Drug interactions

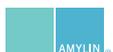
- BYETTA slows gastric emptying and can reduce the extent and rate of absorption of orally administered drugs. Use with caution with medications that have a narrow therapeutic index or require rapid gastrointestinal absorption. Medications dependent on threshold concentrations for efficacy should be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

### Use in specific populations

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

To learn more, visit [www.ByettaHCP.com](http://www.ByettaHCP.com).

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



## BYETTA® (exenatide) injection

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

### INDICATIONS AND USAGE

#### Type 2 Diabetes Mellitus

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

#### Important Limitations of Use

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

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

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

### DOSAGE AND ADMINISTRATION

#### Recommended Dosing

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

### CONTRAINDICATIONS

#### Hypersensitivity

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

### WARNINGS AND PRECAUTIONS

#### Acute Pancreatitis

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

#### Use with Medications Known to Cause Hypoglycemia

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

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

#### Renal Impairment

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

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

#### Gastrointestinal Disease

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

#### Immunogenicity

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

#### Hypersensitivity

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

### Macrovascular Outcomes

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

### ADVERSE REACTIONS

#### Clinical Trial Experience

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

#### Hypoglycemia

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

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

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

† When BYETTA was initiated in combination with insulin glargine, the dose of insulin glargine was decreased by 20% in patients with an HbA<sub>1c</sub> ≤ 8.0 % to minimize the risk of hypoglycemia. See Table 9 for insulin dose titration algorithm.

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

#### Immunogenicity

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

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

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

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

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

#### Other Adverse Reactions

##### Monotherapy

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

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

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

##### Combination Therapy

##### Add-on to metformin and/or sulfonylurea

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

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

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

##### Add-on to thiazolidinedione with or without metformin

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

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

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

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

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

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

#### Post-Marketing Experience

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

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

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

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

Neurologic: dysgeusia; somnolence

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

Skin and Subcutaneous Tissue Disorders: alopecia

#### USE IN SPECIFIC POPULATIONS

##### **Pregnancy**

##### **Pregnancy Category C**

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

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

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

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

##### **Pregnancy Registry**

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

##### **Nursing Mothers**

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

##### **Pediatric Use**

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

##### **Geriatric Use**

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

#### OVERDOSAGE

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

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

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

1-800-868-1190

<http://www.BYETTA.com>

Literature Revised December 2011

# RESEARCH BRIEFS

► The following studies will be published in Endocrine Society journals. Before print, they are edited and posted online in each journal's Early Release section. You can access the journals via [www.endo-society.org](http://www.endo-society.org).

## Endocrinology

► **VSG performed in prediabetic UC Davis-Type 2 Diabetes Mellitus rats delays disease onset by improving islet function and decreasing circulating lipids.**  
Cummings BP, Bettaieb A, Graham JL, et al. *Vertical sleeve gastrectomy improves glucose and lipid metabolism and delays diabetes onset in UCD-T2DM rats.*

► **Estrogen receptor  $\alpha$  plays a role in hearing-related behavior.**  
Charitidi K, Meltser I, Canlon B. *Estradiol treatment and hormonal fluctuations during the estrous cycle modulate the expression of estrogen receptors in the auditory system and the prepulse inhibition of acoustic startle response.*

► **Elderly subjects might benefit from ghrelin treatment to inhibit osteoclastogenesis and improve bone structure.**  
van der Velde M, van der Eerden BCJ, Sun Y, et al. *An age-dependent interaction with leptin unmasks ghrelin's bone-protective effects.*

► **Cdc80-deficient mice fed high-fat diets have metabolic abnormalities similar to prediabetes: hyperglycemia, glucose intolerance, and impaired insulin secretion.**  
Tremblay F, Huard C, Dow J, et al. *Loss of coiled-coil domain containing 80 negatively modulates glucose homeostasis in diet-induced obese mice.*

## The Journal of Clinical Endocrinology & Metabolism

► MAS-associated gonadal pathology is not significantly more common in

females than males.  
Boyce AM, Chong WH, Shawker TH, et al. *Characterization and management of testicular pathology in McCune-Albright syndrome.*

► **Mid-life weight gain leads to changes in sex steroids rather than the converse.**  
Wildman RP, Tepper PG, Crawford S, et al. *Do changes in sex steroid hormones precede or follow increases in body weight during the menopause transition? Results from The Study of Women's Health Across the Nation.*

► **Osteoblast progenitor cell maturation is inhibited in T2DM patients.**  
Manavalan JS, Cremers S, Dempster DW, et al. *Circulating osteogenic precursor cells in type 2 diabetes mellitus.*

► **Over the last 15 years, BRAF<sup>V600E</sup> mutations have been seen more often than RET/PTC rearrangements in PTC patients.**  
Romei C, Fugazzola L, Puxeddu E, et al. *Modifications in the papillary thyroid cancer gene profile over the last 15 years.*

## Molecular Endocrinology

► **E2 promotes the secretion of stromal cell-derived enolase 1, which associates with PCa cells and activates plasminogen, thereby promoting extracellular matrix remodeling and cancer cell migration.**  
Yu L, Shi J, Chen S, et al. *Estrogen promotes prostate cancer cell migration via paracrine release of ENO1 from stromal cells.*

► **At term, low levels of PTB-associated splicing factor contribute to increased myometrial contraction-associated protein gene expression and to labor onset by removing the repressive function of progesterone on the myometrium.**

Xie N, Liu L, Li Y, et al. *Expression and function of myometrial PSF suggest a role in progesterone withdrawal and the initiation of labour.*

► **Secretin receptors play a proliferative role, via the P13K/AKT signaling pathway, in pheochromocytoma and adrenocortical carcinoma cells.**  
Lee M, Waser B, Reubi J-C, Pellegata NS. *Secretin receptor promotes the proliferation of endocrine tumor cells via the P13K/AKT pathway.*

## Hormones and Cancer

► **Cancer BioChip Systems could be used in personalized targeted cancer therapy.**  
Abbud-Antaki RA, Marhefka JN, DeLuca AL, Zuromskis MP. *The Cancer BioChip System: A functional genomic assay for anchorage-independent three-dimensional breast cancer cell growth.*

## AUGUST 2012 issue of Endocrine Reviews

Dalamaga M, Diakopoulos KN, Mantzoros CS. *The role of adiponectin in cancer: A review of current evidence.*

Böhm M, Grässel S. *Role of proopiomelanocortin-derived peptides and their receptors in the osteoarticular system. From basic to translational research.*

Brooks CL. *Molecular mechanisms of prolactin and its receptor.*

Prudente S, Sesti G, Pandolfi A, Andreozzi F, Consoli A, Trischitta V. *The mammalian tribbles homolog TRIB3, glucose homeostasis, and cardiovascular diseases.*

Stefater MA, Wilson-Peréz HE, Chambers AP, Sandoval DA, Seeley RJ. *All bariatric surgeries are not created equal: Insights from mechanistic comparisons.* ■

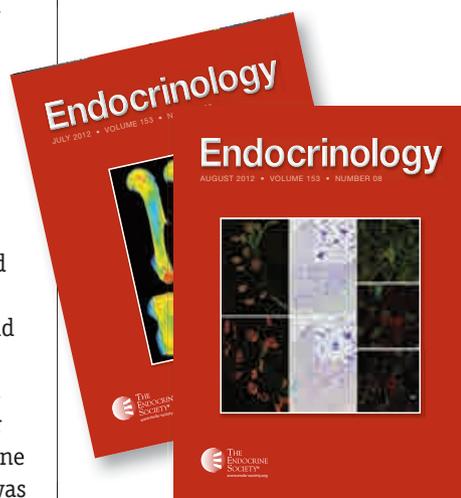
# Society update

## ENDO 2012's Media Wrap-Up

Endocrinologists are not the only ones interested in **ENDO 2012**—so are the media. This year's annual meeting yielded 2,550 news pick-ups from numerous television, online, and print outlets, including *CNN*, the *Los Angeles Times*, *Associated Press*, *WebMD*, *MedPage Today*, *The Atlantic*, and *Science News*. Stories from the conference appeared worldwide in such nations as Canada, England, Cambodia, Malaysia, India, United Arab Emirates, and North Korea. Twenty-one journalists on-site and an equal number online attended six **ENDO 2012** press conferences organized by Aaron Lohr, director of Media Relations at The Endocrine Society. The most popular story was a promising reversible testosterone gel contraceptive for men. Among the other news disseminated were reports on vitamin D deficiency linked to weight gain in postmeno-

pausal women, weight loss by eating dessert at breakfast time, and secondhand smoke increasing the risk of type 2 diabetes and obesity.

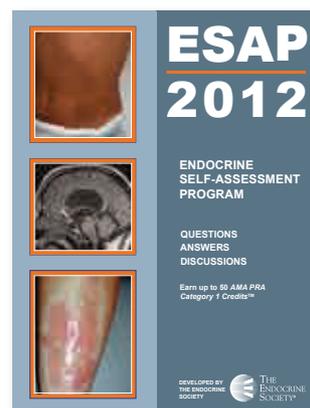
## Endocrinology Editors Selected



Andrea C. Gore, Ph.D., the new Editor-in-Chief of *Endocrinology*, finalized her selection of editors who will be working with her on the journal. The Publications Core Committee subsequently approved Gore's choices. Spanning the world and various disciplines, the editors include Adrian V. Lee, Ph.D., Baylor College of Medicine, Houston; Anthony N. Hollenberg, M.D., Harvard Medical School, Boston; Daniel D. Bikle, M.D., Ph.D., University of California, San Francisco; Emilie Rissman, Ph.D., University of Virginia School of Medicine, Charlottesville; Gail S. Prins, Ph.D., University of Illinois at Chicago; Hugh S. Taylor, M.D., Yale School of Medicine, New Haven, Connecticut; Manuel Tena-Sempere, M.D., Ph.D., University of Cordoba, Spain; Patricia Brubaker,

Ph.D., University of Toronto, Canada; and Richard J. Auchus, M.D., University of Texas Southwestern Medical Center, Dallas.

## ESAP2012™ Now Available



Since its publication in 2006, The Endocrine Society's best-selling *Endocrine Self-Assessment Program (ESAP™)* has served as an indispensable tool to countless physicians seeking initial certification or recertification in endocrinology, as well as clinicians seeking a self-assessment and a broad review of endocrinology. The newest edition, *ESAP 2012™*, provides 160 multiple-choice case-based questions and an extensive discussion of each answer. Written by expert faculty, it is available in an online interactive module and printed book. *ESAP 2012™* delivers powerful guidance to help clinicians looking to learn more about their knowledge and skills, as well as the latest in endocrinology, diabetes, and metabolism. Society members can purchase *ESAP 2012™* at a special member discounted price. For more information, visit [www.endoselfassessment.org](http://www.endoselfassessment.org). ■

## In Memoriam

**Sander Paul Klein, M.D.**  
West Bloomfield, Michigan  
1918–2012

**Henry A. Lardy, Ph.D.**  
Madison, Wisconsin  
1917–2012



# SMART MOVES

developments in the endocrinology world

**Deborah Guadalupe Duran, Ph.D.**, became chief of the Office of Strategic Planning, Legislation, and Science Policy at the National Institutes of Health's National Institute on Minority Health and Health Disparities (NIMHD). She previously served as deputy director of the National Cancer Institute's Center to Reduce Cancer Health Disparities.



**Zhenqui Liu, M.D.**, was appointed chief of the Division of Endocrinology and Metabolism at the University of Virginia, Charlottesville. Dr. Liu is a professor of medicine at UVA and currently serves as member of the Trainee and Career Development Core Committee and co-chair of the International Endocrine Scholars Program of The Endocrine Society.

**David M. Murray, Ph.D.**, has been appointed associate director for disease prevention and director of the Office of Disease Prevention at the National Institutes of Health (NIH). He comes to NIH from Ohio State University, where he is chair and professor of the Division of Epidemiology, College of Public Health.

\* *Member of The Endocrine Society.*

#### Share Your News

If you or others you know change jobs, receive a promotion, are granted an award, or otherwise make endocrinology-related career news, please don't hesitate to let us know at [endocrinenews@endo-society.org](mailto:endocrinenews@endo-society.org).

## More for You from Endocrine news®

**Endocrine News Online** has a fresh, new look each month to bring you even more content. Our expanded Web site is updated frequently and carries additional information you don't want to miss.

#### e-Edition:

An interactive PDF with pages you can turn, carrying links to videos, audios, and more.

#### Online Exclusives:

Summaries of late-breaking research.

#### The Hormone Health Network News:

Links to the latest patient information about endocrine disorders.



Go to [www.endo-society.org/endo\\_news](http://www.endo-society.org/endo_news) or scan this QR Code with your smartphone's QR Reader to see the many new online features, headlines, news briefs, interactive text, photos, and links, among other enhancements.

# calendar

**AUG 8–9: SANTA FE, NEW MEXICO**  
The 10th Annual Osteoporosis Update Conference.

[www.endo-society.org/meetings/symposia/osteoupdate.cfm](http://www.endo-society.org/meetings/symposia/osteoupdate.cfm)

**SEPT 11–15: MIAMI, FLORIDA**  
Endocrine Board Review and Clinical Endocrinology Update.

[www.endo-society.org/miami](http://www.endo-society.org/miami)

**SEPT 19–23: QUEBEC CITY, CANADA**  
American Thyroid Association 82st Annual Meeting

[www.thyroid.org/ann\\_mtg/index.html](http://www.thyroid.org/ann_mtg/index.html)

**SEPT 20–24: SAN ANTONIO, TEXAS**  
The Obesity Society's 30th Annual Scientific Meeting

[www.obesity.org/meetings-and-events/annual-meeting.htm](http://www.obesity.org/meetings-and-events/annual-meeting.htm)

**OCT 13–17: NEW ORLEANS, LOUISIANA.**

Society for Neuroscience 42nd Annual Meeting.

[www.sfn.org/am2012](http://www.sfn.org/am2012)

**OCT 17–19: PHILADELPHIA, PENNSYLVANIA**

American Academy of Family Physicians (AAFP).

[www.aafp.org/online/en/home/cme/aafpcourses/conferences/assembly.html](http://www.aafp.org/online/en/home/cme/aafpcourses/conferences/assembly.html)

**DEC 15–19: SAN FRANCISCO, CALIFORNIA**

American Society for Cell Biology Annual Meeting

[www.ascb.org/meetings](http://www.ascb.org/meetings)

See more events at [www.endosociety.org](http://www.endosociety.org), on the Worldwide Endocrine Events Calendar.

**A. Brian Little, M.D.**

Skillman, New Jersey  
1925–2012

**Dmitrios G. Oreopoulos, M.D., Ph.D.**

Toronto, Canada  
1936–2012

**Philip N. Sambrook, M.D.**

Sydney, Australia  
1953–2012

# CLASSIFIEDS

If you are interested in submitting classified advertising to *Endocrine News*, please contact Christine Whorton at [endocareers@endo-society.org](mailto:endocareers@endo-society.org) or 800-364-3906.

## Endocrinologist Needed in Growing Philadelphia Suburb

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

## Academic Endocrinologist

Department of Veterans Affairs Medical Center and SUNY Upstate Medical University (UMU), Syracuse, New York, has an opening

for a full-time faculty position in Endocrinology, Diabetes and Metabolism. Applicants must be board certified in Internal Medicine and BC/BE in Endocrinology, Diabetes, and Metabolism. The successful candidate must have expertise in patient care and teaching in Endocrinology, as well as experience in clinical research related to Diabetes. Applicants must possess a full and unrestricted license in any state and must qualify for a corresponding academic appointment within the Department of Medicine at SUNY UMU. Interested candidates should fax a cover letter referencing job number 670-05E and a current CV to: 315- 425-2447, attention Linda Zavalas, Human Resources/05, VA Medical Center, 800 Irving Avenue, Syracuse, New York 13210,

or email [Linda.Zavalas@va.gov](mailto:Linda.Zavalas@va.gov). Information on Upstate New York VISN 2 VA Healthcare Network can be found at [www.syracuse.va.gov](http://www.syracuse.va.gov). Position is subject to random drug testing. Equal Opportunity Employer.

## Physician Investigator

Saint Louis University, a catholic, Jesuit institution dedicated to student learning, research, health care, and service is seeking a Physician Investigator for a faculty position in the Department of Internal Medicine, Division of Endocrinology, beginning July 1, 2013. The position can also be for an Assistant or Associate Professor. An M.D. degree and board eligibility in endocrinology are necessary. The physician will be responsible for developing the en-

docrinology division. Primary teaching duties will include medical students, residents, fellows and other health professionals. Send CV and three letters of recommendation to: John E. Morley, M.D., Director of Endocrinology, Saint Louis University, School of Medicine, Division of Endocrinology; 1402 South Grand Boulevard, Room M420; St. Louis, Missouri 63104. Review of applications begins immediately and continues until the position is filled. Saint Louis University is an Affirmative Action, Equal Opportunity Employer and encourages nominations and applications of women and minorities.

## Ohio Endocrinologist

BC/BE Endo to join an established Endo in Toledo, Ohio. 100 percent Endo. Onsite US,

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Board Certified/Board Eligible Endocrinologist



Erin Connell

PHYREC-052

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**We invite you to practice it.**

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Respecting your work/life balance is a big part of the Aspirus culture. We will surround you with a highly qualified nursing and support staff, an extensive network of outstanding specialists, and a medical culture that shares an unyielding commitment to excellence.

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**Contact Dawn Decker at [dawn.decker@aspirus.org](mailto:dawn.decker@aspirus.org) or 800.792.8728.**



# EXPLORE NEW HORIZONS



## ENDOCRINOLOGIST OPPORTUNITY AT THE BEACH

Located in the scenic coastal area where the Atlantic Ocean meets the Delaware Bay, **Beebe Medical Center** is a progressive, 210-bed, not-for-profit-community hospital that serves the growing population of southern Delaware.

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Director of Physician Services, [mhill@bmc.org](mailto:mhill@bmc.org).

## UNIVERSITY OF CALIFORNIA, DAVIS, SCHOOL OF MEDICINE DEPARTMENT OF INTERNAL MEDICINE DIVISION OF ENDOCRINOLOGY, DIABETES & METABOLISM HEALTH SCIENCES CLINICAL PROFESSOR OR CLINICAL X

The Department of Internal Medicine, Division of Endocrinology, Diabetes and Metabolism at the University of California, Davis, School of Medicine, is currently recruiting for two fulltime faculty positions in the Health Sciences Clinical Professor or Clinical X series at the rank of Assistant/Associate Professor. Appointees to the Clinical X series are required to teach, engage in creative activity that can include bench, translational or clinical research, participate in university and public service and provide direct patient care. Appointees to the Health Sciences Clinical series are required to teach, participate in university service and provide direct patient care.

Applicants must have MD or MD, PhD degree(s), be Board Certified/Eligible in Endocrinology, and be eligible for medical licensure in the State of California. Duties include outpatient care in diabetes and general endocrinology, inpatient consultation service, and teaching and supervision of medical students, residents, and fellows.

For full consideration, applications must be received by August 31, 2012. However the position will remain open until filled through January 31, 2013. Applicants should send cover letter, curriculum vitae, and a list of five references (Clinical X applicants should send selected/recent publications) to:

Sidika E. Karakas, MD  
c/o Connie Peters  
University of California, Davis Health System  
Division of Endocrinology, Diabetes & Metabolism  
4150 V Street, Suite G400  
Sacramento, CA 95817

The University of California, Davis is an affirmative action/equal opportunity employer with a strong institutional commitment to the achievement of diversity among its faculty, staff, and students.

### CLASSIFIEDS CONT.

FNA, CGMs, HbA1c. Competitive salary with productivity incentive and full benefits. Buy-in in two years. No J-1. Email CV to [mmoosa61@gmail.com](mailto:mmoosa61@gmail.com).

#### Medical Writer and Editor

Clinical Endocrinologist looking for Ph.D. students or other interested individuals who are literature-search-savvy in the areas of obesity, diabetes, lipids, or hypertension. Tasks involve finding citations for specific assertions made in transcriptions prepared for publications. Writing editor assistant(s) in the same areas listed also desired. No geographical limitations. Generous pay. Would be happy to accommodate internship/externship credit if wished. Contact Brian Fertig, M.D., [fertigkanj@yahoo.com](mailto:fertigkanj@yahoo.com); telephone 732-562-0027; fax 732-562-0041. ■



The Endocrine Society's EndoCareers resources have proven to be very useful for recruiting endocrinologists over the years. I recommend this option to anyone looking for good quality people!

— Physician Recruiter, Tucson, AZ

# EndoCareers®



## The Finest Endocrinology Career Resources Available!

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Contact: Christine Whorton, EndoCareers  
[endocareers@endo-society.org](mailto:endocareers@endo-society.org) | 1 (800) 361-3906 | [www.endocareers.org](http://www.endocareers.org)



## McGILL UNIVERSITY DEPARTMENT OF MEDICINE DIVISION OF ENDOCRINOLOGY



The Department of Medicine at McGill University invites applications for the position of Director of the McGill University Division of Endocrinology and Metabolism and Director of the McGill University Health Centre Division of Endocrinology and Metabolism. The Division of Endocrinology and Metabolism is a highly productive unit, with a cadre of outstanding basic scientific researchers, clinicians and teachers.

Applicants should have strong leadership qualities and a proven track record in basic or clinical research. Demonstrated success in promoting translational research would be considered an asset. Applicants should normally be at the Associate or Full Professor level. This is a tenure-track position.

Applicants will be physicians who have completed subspecialty training in endocrinology and metabolism, be eligible for licensure in Quebec and certification by the Collège des médecins du Québec and have an aptitude for the teaching of medical students, residents and clinical fellows in endocrinology and metabolism.

Candidates would benefit from a working knowledge of French as well as English.

Please submit a CV and covering letter, along with a list of publications and current research interests and the name and coordinates of three references within 30 days from the date of publication to:

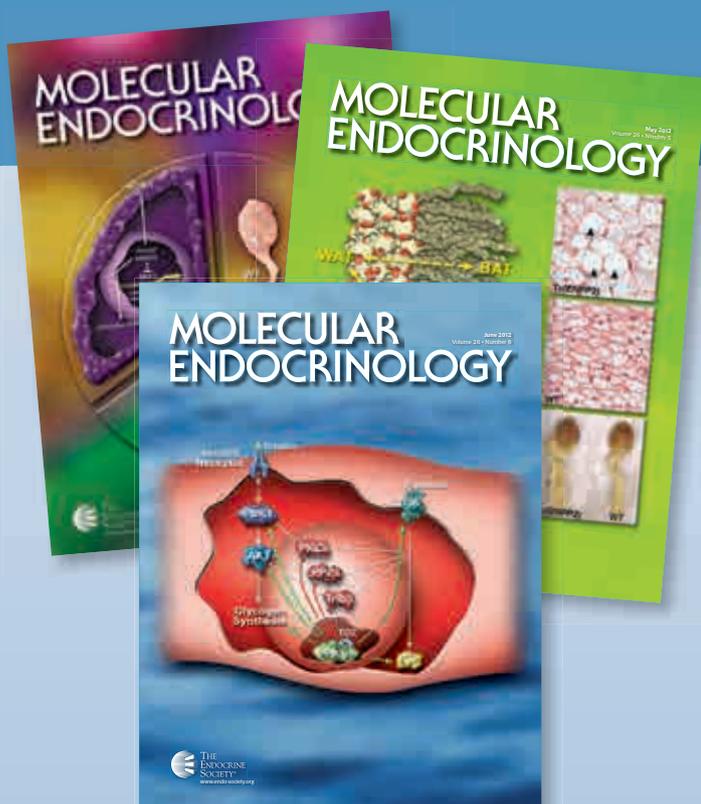
Dr. James Martin, Interim Chair of Medicine  
Department of Medicine, Room A3.09  
Royal Victoria Hospital  
687 Pine Avenue West  
Montreal, Quebec  
H3A 1A1

Fax: (514) 843-8182  
E-Mail: james.martin@mcgill.ca

*McGill University is committed to equity in employment and diversity. It welcomes applications from Aboriginal persons, persons with disabilities, ethnic minorities, persons of minority sexual orientation or gender identity, visible minorities, women, and others who may contribute to diversification. All qualified applicants are encouraged to apply; however, Canadians and permanent residents will be given priority.*

## Call for Nominations and Applications for Editor-in-Chief of

# MOLECULAR ENDOCRINOLOGY



## THE ENDOCRINE SOCIETY

is seeking an Editor-in-Chief for its basic research journal, Molecular Endocrinology. Applicants will have an opportunity to work with an outstanding editorial team to direct a high visibility journal with very rapid communication of cutting-edge science.

### Application deadline is September 28, 2012

For more information and application details, please visit [http://www.endo-society.org/journals/MolecularEndocrinology/mend\\_eic\\_search.cfm](http://www.endo-society.org/journals/MolecularEndocrinology/mend_eic_search.cfm)





## Nobel Prize-Winning Endocrinologists

By Jacqueline Ruttimann, Ph.D.

In the 1920s, when Rita Levi-Montalcini was a young girl in Italy, she aspired to become a scientist, but she had two strikes against her: She is a woman and she is Jewish. Her father believed that a professional career “would interfere with the duties of a wife and mother.” Later, in 1938, Mussolini’s Manifesto of Race banned Jews from academic and professional careers.

### Bedside Laboratory

By the time Levi-Montalcini turned 20, she realized that she “could not possibly adjust to a feminine role” as defined by her father. She appealed to him, finished high school, entered the University of Turin’s Medical School, and graduated summa cum laude in 1936. To circumvent the racist laws, she set up a laboratory in her bedroom, where she studied chick embryo limb formation. Times were so tough that after her experiments, she often ate the eggs.

Heavy Allied bombing in 1941 forced her and her family to leave Turin for a country cottage, where she rebuilt her laboratory. She eventually had to flee to Florence and live underground until the end of World War II. Levi-Montalcini resumed her research at Washing-



Rita Levi-Montalcini

**She studied chick embryo limb formation. Times were so tough that after her experiments, she often ate the eggs.**

ton University in St. Louis. Working jointly with biochemist Stanley Cohen, in 1951, she isolated nerve growth factor (NGF), a neuropeptide important in neurodegenerative diseases, cardiovascular disease, obesity, and type 2 diabetes. She shared the Nobel Prize with Cohen in 1986 for their groundbreaking discovery.

The discovery, in fact, might be personally benefitting Levi-Montalcini. Taking daily eye drop solutions of NGF, she is the oldest living Nobel Laureate at 103 years of age.

Levi-Montalcini is just one of many researchers who have worked against the odds and achieved astounding success in the field of endocrinology. Leonard Wartofsky, editor-in-chief of *The Journal of Clinical Endocrinology & Metabolism*, highlighted a dozen such Nobel Laureates at an **ENDO 2012** presentation.

### From Secretary to Scholar

Among those eminent scholars is American physicist Rosalyn Sussman Yalow, the first female and first Nobel Laureate to become President of The Endocrine Society (1978–1979). Born to parents who never finished high school, Yalow graduated magna cum laude from Hunter College as the school’s first female physics major. She, too, faced anti-semitism and gender discrimination. In her autobiography she recalled how she had to access graduate courses “via the back door,” by taking a job as a typist and stenographer.



Rosalyn Sussman Yalow

Eventually as men vacated universities to enlist in the armed forces during WWII, she landed a position as a teaching assistant in the physics department at the University of Illinois, Urbana-Champaign, where she earned her doctorate in nuclear physics in 1945. Within a few years, Yalow began working the Bronx Veterans Administration Hospital in New York City, transforming a janitor’s closet into a functioning lab. Here



## BACK STORY



she collaborated with physician Solomon Berson in developing the radioimmunoassay technique for measuring insulin and other hormones—work that revolutionized medical research and won Yalow the 1977 Nobel Prize, along with physician and physiologist Roger Guillemin and endocrinologist Andrew Schally, for their work on neuropeptide hormones.

The “tough guy” in this illustrious group of Laureates, according to Wartofsky, was surgeon Frederick Banting. Despite poor vision, Banting served in the Canadian Army



Frederick Banting

Medical Corps in both world wars. He won the Military Cross in 1919 for dressing the wounds of other soldiers for nearly 17 hours despite suffering a severed artery in his own right arm. While serving as a liaison officer between the British and North American medical services during WWII, he was killed

in an airplane crash on a military mission in 1941.

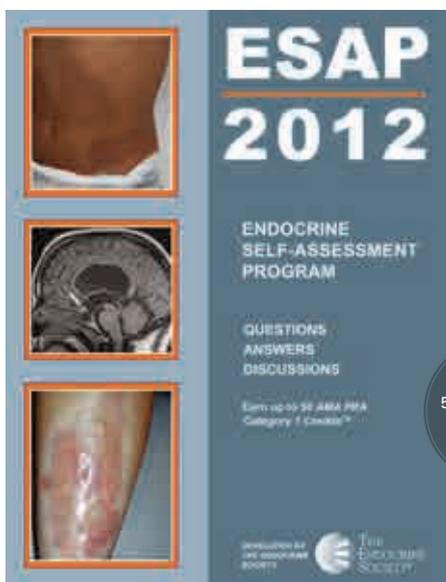
### Of Dogs and Men

In between the wars, Banting worked with medical scientist Charles Best, physician and physi-

ologist John J.R. Macleod, and biochemist James Bertram Collip, to extract insulin from intact islets of Langerhans in dogs. They purified the insulin and, in January 1922, injected it into Leonard Thompson, a 14-year-old boy with diabetes. Leonard survived and lived for many more years. As we know, the discovery was another medical miracle that would save millions of lives. Banting and Macleod received the Nobel Prize in 1923. They then split the award money with Best and Collip.

“There are many achievements in endocrinology recognized by the Nobel Prize,” Wartofsky said. “Who knows what future Laureate attended **ENDO 2012?**” ■

*Ruttimann is the associate editor of Endocrine News.*



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## Victoza® (liraglutide [rDNA origin] injection)

### Rx Only

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

**WARNING: RISK OF THYROID C-CELL TUMORS:** Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors [See Contraindications and Warnings and Precautions].

**INDICATIONS AND USAGE:** Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **Important Limitations of Use:** Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise. In clinical trials of Victoza®, there were more cases of pancreatitis with Victoza® than with comparators. Victoza® has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza®. Use with caution in patients with a history of pancreatitis. Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. The concurrent use of Victoza® and insulin has not been studied.

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

**WARNINGS AND PRECAUTIONS: Risk of Thyroid C-cell Tumors:** Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. It is unknown whether Victoza® will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies [See Boxed Warning, Contraindications]. In the clinical trials, there have been 4 reported cases of thyroid C-cell hyperplasia among Victoza®-treated patients and 1 case in a comparator-treated patient (1.3 vs. 0.6 cases per 1000 patient-years). One additional case of thyroid C-cell hyperplasia in a Victoza®-treated patient and 1 case of MTC in a comparator-treated patient have subsequently been reported. This comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Four of the five liraglutide-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One liraglutide and one non-liraglutide-treated patient developed elevated calcitonin concentrations while on treatment. Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. The serum calcitonin assay used in the Victoza® clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in the clinical trials, adjusted mean serum calcitonin concentrations were higher in Victoza®-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. At these timepoints, the adjusted mean serum calcitonin values (-1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with Victoza® 1.8 mg/day. In trials with on-treatment serum calcitonin measurements out to 5-6 months, 1.9% of patients treated with Victoza® 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of Victoza®. In trials with on-treatment serum calcitonin measurements out to 12 months, 1.3% of patients treated with Victoza® 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated with Victoza® 1.2 mg, placebo and active control, respectively. Otherwise, Victoza® did not produce consistent dose-dependent or time-dependent increases in serum calcitonin. Patients with MTC usually have calcitonin values >50 ng/L. In Victoza® clinical trials, among patients with pre-treatment serum calcitonin <50 ng/L, one Victoza®-treated patient and no comparator-treated patients developed serum calcitonin >50 ng/L. The Victoza®-treated patient who developed serum calcitonin >50 ng/L had an elevated pre-treatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of Victoza®. The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104. Among patients who began with serum calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza®-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients, with an incidence of 1.1% among patients treated with 1.8 mg/day of Victoza®. The clinical significance of these findings is unknown. Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza®, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. **Pancreatitis:** In clinical trials of Victoza®, there were 7 cases of pancreatitis among Victoza®-treated patients and 1 case among comparator-treated patients (2.2 vs. 0.6 cases per 1000 patient-years). Five cases with Victoza® were reported as acute pancreatitis and two cases with Victoza® were reported as chronic pancreatitis. In one case in a Victoza®-treated patient,

pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. One additional case of pancreatitis has subsequently been reported in a Victoza®-treated patient. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. There are no conclusive data establishing a risk of pancreatitis with Victoza® treatment. After initiation of Victoza®, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® and other potentially suspect medications should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Use with caution in patients with a history of pancreatitis. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) may have an increased risk of hypoglycemia. In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza®-treated patients and in two comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea or other insulin secretagogues [See Adverse Reactions]. **Renal Impairment:** Victoza® has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in Victoza®-treated patients [See Adverse Reactions]. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration [See Adverse Reactions]. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including Victoza®. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

**ADVERSE REACTIONS: Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Victoza® was evaluated in a 52-week monotherapy trial and in five 26-week, add-on combination therapy trials. In the monotherapy trial, patients were treated with Victoza® 1.2 mg daily, Victoza® 1.8 mg daily, or glimepiride 8 mg daily. In the add-on to metformin trial, patients were treated with Victoza® 0.6 mg, Victoza® 1.2 mg, Victoza® 1.8 mg, placebo, or glimepiride 4 mg. In the add-on to glimepiride trial, patients were treated with Victoza® 0.6 mg, Victoza® 1.2 mg, Victoza® 1.8 mg, placebo, or rosiglitazone 4 mg. In the add-on to metformin + glimepiride trial, patients were treated with Victoza® 1.8 mg, placebo, or insulin glargine. In the add-on to metformin + rosiglitazone trial, patients were treated with Victoza® 1.2 mg, Victoza® 1.8 mg or placebo. **Withdrawals:** The incidence of withdrawal due to adverse events was 7.8% for Victoza®-treated patients and 3.4% for comparator-treated patients in the five controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza®-treated patients and 0.5% of comparator-treated patients. The most common adverse reactions leading to withdrawal for Victoza®-treated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator). Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials. Tables 1, 2 and 3 summarize the adverse events reported in ≥5% of Victoza®-treated patients in the six controlled trials of 26 weeks duration or longer.

**Table 1: Adverse events reported in ≥5% of Victoza®-treated patients or ≥5% of glimepiride-treated patients: 52-week monotherapy trial**

Adverse Event Term	All Victoza® N = 497 (%)	Glimepiride N = 248 (%)
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
Upper Respiratory Tract Infection	9.5	5.6
Headache	9.1	9.3
Influenza	7.4	3.6
Urinary Tract Infection	6.0	4.0
Dizziness	5.8	5.2
Sinusitis	5.6	6.0
Nasopharyngitis	5.2	5.2
Back Pain	5.0	4.4
Hypertension	3.0	6.0

**Table 2: Adverse events reported in ≥5% of Victoza®-treated patients and occurring more frequently with Victoza® compared to placebo: 26-week combination therapy trials**

Add-on to Metformin Trial			
	All Victoza® + Metformin N = 724 (%)	Placebo + Metformin N = 121 (%)	Glimepiride + Metformin N = 242 (%)
Adverse Event Term	(%)	(%)	(%)
Nausea	15.2	4.1	3.3
Diarrhea	10.9	4.1	3.7
Headache	9.0	6.6	9.5
Vomiting	6.5	0.8	0.4
Add-on to Glimepiride Trial			
	All Victoza® + Glimepiride N = 695 (%)	Placebo + Glimepiride N = 114 (%)	Rosiglitazone + Glimepiride N = 231 (%)
Adverse Event Term	(%)	(%)	(%)
Nausea	7.5	1.8	2.6
Diarrhea	7.2	1.8	2.2

Constipation	5.3	0.9	1.7
Dyspepsia	5.2	0.9	2.6
<b>Add-on to Metformin + Glimepiride</b>			
	Victoza® 1.8 + Metformin + Glimepiride N = 230	Placebo + Metformin + Glimepiride N = 114	Glargine + Metformin + Glimepiride N = 232
<b>Adverse Event Term</b>	(%)	(%)	(%)
Nausea	13.9	3.5	1.3
Diarrhea	10.0	5.3	1.3
Headache	9.6	7.9	5.6
Dyspepsia	6.5	0.9	1.7
Vomiting	6.5	3.5	0.4
<b>Add-on to Metformin + Rosiglitazone</b>			
	All Victoza® + Metformin + Rosiglitazone N = 355	Placebo + Metformin + Rosiglitazone N = 175	
<b>Adverse Event Term</b>	(%)	(%)	
Nausea	34.6	8.6	
Diarrhea	14.1	6.3	
Vomiting	12.4	2.9	
Decreased Appetite	9.3	1.1	
Anorexia	9.0	0.0	
Headache	8.2	4.6	
Constipation	5.1	1.1	
Fatigue	5.1	1.7	

**Table 3: Treatment-Emergent Adverse Events in 26 Week Open-Label Trial versus Exenatide (Adverse events with frequency ≥5% and occurring more frequently with Victoza® compared to exenatide are listed)**

	Victoza® 1.8 mg once daily + metformin and/or sulfonylurea N = 235	Exenatide 10 mcg twice daily + metformin and/or sulfonylurea N = 232
<b>Preferred Term</b>	(%)	(%)
Diarrhea	12.3	12.1
Dyspepsia	8.9	4.7
Constipation	5.1	2.6

**Gastrointestinal adverse events:** In the five clinical trials of 26 weeks duration or longer, gastrointestinal adverse events were reported in 41% of Victoza®-treated patients and were dose-related. Gastrointestinal adverse events occurred in 17% of comparator-treated patients. Events that occurred more commonly among Victoza®-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In a 26-week study of Victoza® versus exenatide, both in combination with metformin and/or sulfonylurea overall gastrointestinal adverse event incidence rates, including nausea, were similar in patients treated with Victoza® and exenatide. In five clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. Approximately 13% of Victoza®-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. In a 26 week study of Victoza® versus exenatide, both in combination with metformin and/or sulfonylurea, the proportion of patients with nausea also declined over time. **Immunogenicity:** Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with Victoza® may develop anti-liraglutide antibodies. Approximately 50-70% of Victoza®-treated patients in the five clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these Victoza®-treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimate of the actual percentage of patients who developed antibodies. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the Victoza®-treated patients in the 52-week monotherapy trial and in 4.8% of the Victoza®-treated patients in the 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the Victoza®-treated patients in the 52-week monotherapy trial and in 1.0% of the Victoza®-treated patients in the 26-week add-on combination therapy trials. Among Victoza®-treated patients who developed anti-liraglutide antibodies, the most common category of adverse events was that of infections, which occurred among 40% of these patients compared to 36%, 34% and 35% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among Victoza®-treated antibody-positive patients were primarily nonserious upper respiratory tract infections, which occurred among 11% of Victoza®-treated antibody-positive patients; and among 7%, 7% and 5% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Among Victoza®-treated antibody-negative patients, the most common category of adverse events was that of gastrointestinal events, which occurred in 43%, 18% and 19% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Antibody formation was not associated with reduced efficacy of Victoza® when comparing mean HbA<sub>1c</sub> of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA<sub>1c</sub> with Victoza® treatment. In clinical trials of Victoza®, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of Victoza®-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza®-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies. **Injection site reactions:** Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of Victoza®-treated patients in the five clinical trials of at least 26 weeks duration. Less than 0.2% of Victoza®-treated patients discontinued due to injection site reactions. **Papillary thyroid carcinoma:** In clinical trials of Victoza®, there were 6 reported cases of papillary thyroid carcinoma in patients treated with Victoza® and 1 case in a comparator-treated patient (1.9 vs. 0.6 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound. **Hypoglycemia:** In the clinical trials of at least 26 weeks

duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza®-treated patients (2.6 cases per 1000 patient-years) and in two comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea. One other patient was taking Victoza® in combination with metformin but had another likely explanation for the hypoglycemia (this event occurred during hospitalization and after insulin infusion) (Table 4). Two additional cases of hypoglycemia requiring the assistance of another person for treatment have subsequently been reported in patients who were not taking a concomitant sulfonylurea. Both patients were receiving Victoza®, one as monotherapy and the other in combination with metformin. Both patients had another likely explanation for the hypoglycemia (one received insulin during a frequently-sampled intravenous glucose tolerance test, and the other had intracranial hemorrhage and uncertain food intake).

**Table 4: Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials**

	Victoza® Treatment (N = 497)	Active Comparator Glimepiride (N = 248)	Placebo Comparator (N = 248)
<b>Monotherapy</b>	<b>Victoza® (N = 497)</b>	<b>Active Comparator Glimepiride (N = 248)</b>	<b>Placebo Comparator (N = 248)</b>
Patient not able to self-treat	0	0	—
Patient able to self-treat	9.7 (0.24)	25.0 (1.66)	—
Not classified	1.2 (0.03)	2.4 (0.04)	—
<b>Add-on to Metformin</b>	<b>Victoza® + Metformin (N = 724)</b>	<b>Glimepiride + Metformin (N = 242)</b>	<b>Placebo + Metformin (N = 121)</b>
Patient not able to self-treat	0.1 (0.001)	0	0
Patient able to self-treat	3.6 (0.05)	22.3 (0.87)	2.5 (0.06)
<b>Add-on to Glimepiride</b>	<b>Victoza® + Glimepiride (N = 695)</b>	<b>Rosiglitazone + Glimepiride (N = 231)</b>	<b>Placebo + Glimepiride (N = 114)</b>
Patient not able to self-treat	0.1 (0.003)	0	0
Patient able to self-treat	7.5 (0.38)	4.3 (0.12)	2.6 (0.17)
Not classified	0.9 (0.05)	0.9 (0.02)	0
<b>Add-on to Metformin + Rosiglitazone</b>	<b>Victoza® + Metformin + Rosiglitazone (N = 355)</b>	<b>None</b>	<b>Placebo + Metformin + Rosiglitazone (N = 175)</b>
Patient not able to self-treat	0	—	0
Patient able to self-treat	7.9 (0.49)	—	4.6 (0.15)
Not classified	0.6 (0.01)	—	1.1 (0.03)
<b>Add-on to Metformin + Glimepiride</b>	<b>Victoza® + Metformin + Glimepiride (N = 230)</b>	<b>Insulin glargine + Metformin + Glimepiride (N = 232)</b>	<b>Placebo + Metformin + Glimepiride (N = 114)</b>
Patient not able to self-treat	2.2 (0.06)	0	0
Patient able to self-treat	27.4 (1.16)	28.9 (1.29)	16.7 (0.95)
Not classified	0	1.7 (0.04)	0

In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza®, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events [see *Adverse Reactions*], no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza®-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established. **Laboratory Tests:** In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of Victoza®-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown. **Post-Marketing Experience:** The following additional adverse reactions have been reported during post-approval use of Victoza®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **Gastrointestinal:** nausea, vomiting and diarrhea sometimes resulting in dehydration [see *Warnings and Precautions*]. **Renal and Urinary Disorders:** increased serum creatinine, acute renal failure or worsening of chronic renal failure, which may sometimes require hemodialysis [see *Warnings and Precautions*].

**OVERDOSAGE:** In a clinical trial, one patient with type 2 diabetes experienced a single overdose of Victoza® 17.4 mg subcutaneous (10 times the maximum recommended dose). Effects of the overdose included severe nausea and vomiting requiring hospitalization. No hypoglycemia was reported. The patient recovered without complications. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

**More detailed information is available upon request.**

For information about Victoza® contact: Novo Nordisk Inc., 100 College Road West, Princeton, New Jersey 08540, 1-877-484-2869

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Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

Victoza® is a registered trademark of Novo Nordisk A/S. Victoza® is covered by US Patent Nos. 6,268,343; 6,458,924; and 7,235,627 and other patents pending. Victoza® Pen is covered by US Patent Nos. 6,004,297; 6,235,004; 6,582,404 and other patents pending.

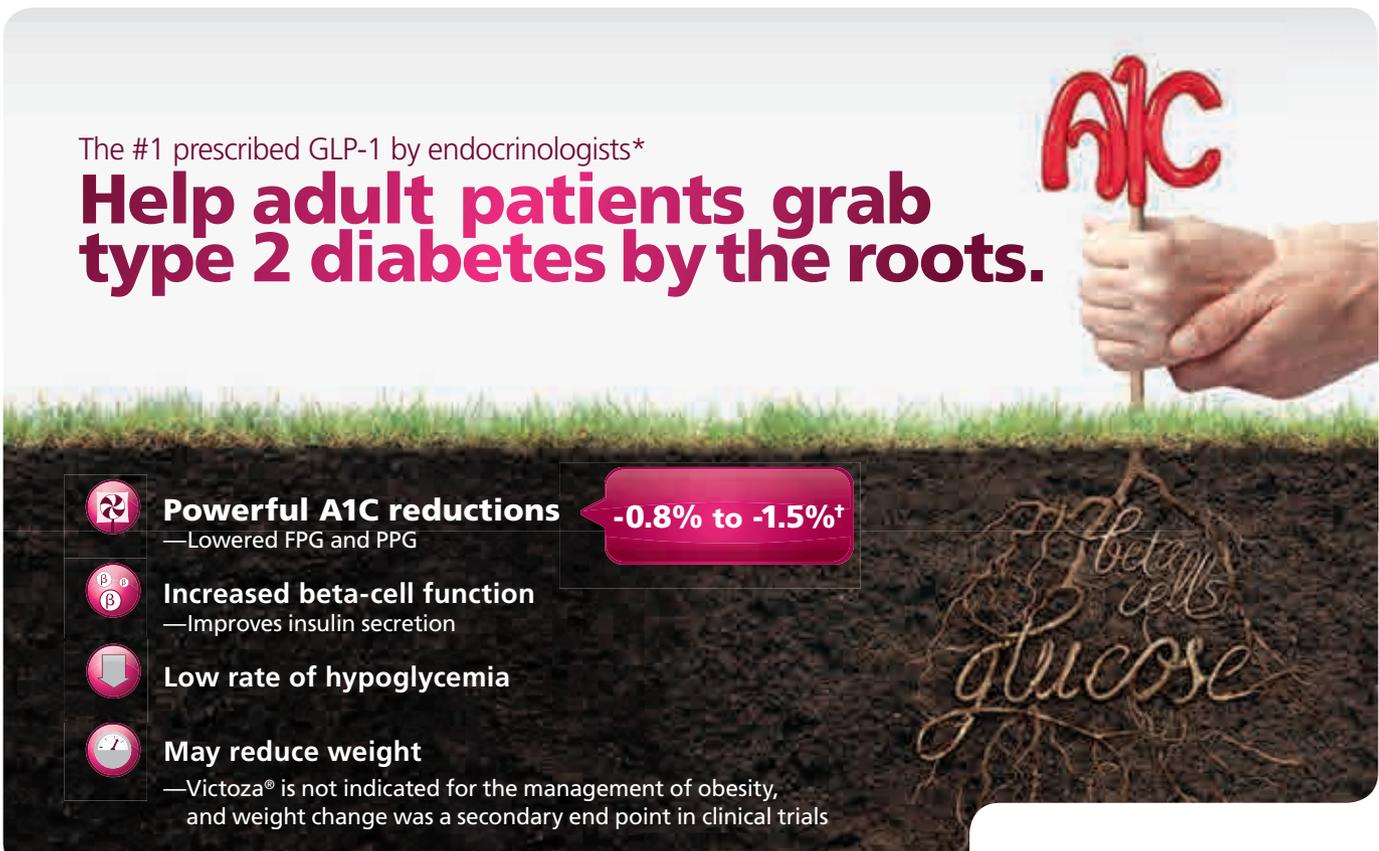
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**VICTOZA®**  
liraglutide (rDNA origin) injection

The #1 prescribed GLP-1 by endocrinologists\*

# Help adult patients grab type 2 diabetes by the roots.



## Powerful A1C reductions

—Lowered FPG and PPG

**-0.8% to -1.5%<sup>†</sup>**



## Increased beta-cell function

—Improves insulin secretion



## Low rate of hypoglycemia



## May reduce weight

—Victoza<sup>®</sup> is not indicated for the management of obesity, and weight change was a secondary end point in clinical trials



90% of subjects found the Victoza<sup>®</sup> pen easy to learn how to use when demonstrating into a pillow.<sup>1‡</sup> Hear from Victoza<sup>®</sup> patients at [VictozaPro.com/Voices](http://VictozaPro.com/Voices).

**VICTOZA<sup>®</sup>**  
liraglutide (rDNA origin) injection



## Indications and usage

Victoza<sup>®</sup> is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza<sup>®</sup> only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza<sup>®</sup> is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

In clinical trials of Victoza<sup>®</sup>, there were more cases of pancreatitis with Victoza<sup>®</sup> than with comparators. Victoza<sup>®</sup> has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza<sup>®</sup>. Use with caution in patients with a history of pancreatitis.

Victoza<sup>®</sup> is not a substitute for insulin. Victoza<sup>®</sup> should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

The concurrent use of Victoza<sup>®</sup> and insulin has not been studied.

## Important safety information

**Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza<sup>®</sup> causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza<sup>®</sup> is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.**

If pancreatitis is suspected, Victoza<sup>®</sup> should be discontinued. Victoza<sup>®</sup> should not be re-initiated if pancreatitis is confirmed.

When Victoza<sup>®</sup> is used with an insulin secretagogue (e.g. a sulfonylurea) serious hypoglycemia can occur. Consider lowering the dose of the insulin secretagogue to reduce the risk of hypoglycemia.

Renal impairment has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration, which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Victoza<sup>®</sup> in patients with renal impairment.

There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza<sup>®</sup> or any other antidiabetic drug.

The most common adverse reactions, reported in  $\geq 5\%$  of patients treated with Victoza<sup>®</sup> and more commonly than in patients treated with placebo, are headache, nausea, diarrhea, and anti-liraglutide antibody formation. Immunogenicity-related events, including urticaria, were more common among Victoza<sup>®</sup>-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

Victoza<sup>®</sup> has not been studied in type 2 diabetes patients below 18 years of age and is not recommended for use in pediatric patients.

Victoza<sup>®</sup> should be used with caution in patients with hepatic impairment.

**Please see brief summary of Prescribing Information on adjacent page.**

**Reference: 1.** Data on file. Novo Nordisk Inc, Princeton, NJ.

\*IMS Health Inc. LifeLink Longitudinal Prescription Database (LRx)<sup>™</sup>, April 2010-March 2011. Patients new to a GLP-1 agonist regimen from a previous regimen without a GLP-1 agonist.

<sup>†</sup>Victoza<sup>®</sup> 1.2 mg and 1.8 mg when used alone or in combination with OADs.

<sup>‡</sup>A randomized, multicenter, open-label, single-visit test to evaluate the usability of 3 Victoza<sup>®</sup> pens following subject review of the Victoza<sup>®</sup> Instructions for Use. Subjects with uncorrected visual impairment, limited manual dexterity, motor impairment, mental incapacity, or psychiatric disorder were excluded. Eligible subjects (N=90) were randomized to 1 of 6 pen/dose combinations and asked to read the Victoza<sup>®</sup> Instructions for Use and independently perform a specified injection into a foam pillow. After reading the Victoza<sup>®</sup> Instructions for Use and completing the task assigned, subjects completed the Victoza<sup>®</sup> Usability Questionnaire. The questionnaire included questions pertaining to how easy or difficult it was to prepare the pen, dial the dose and read the scale, deliver the dose, and learn to use the pen.