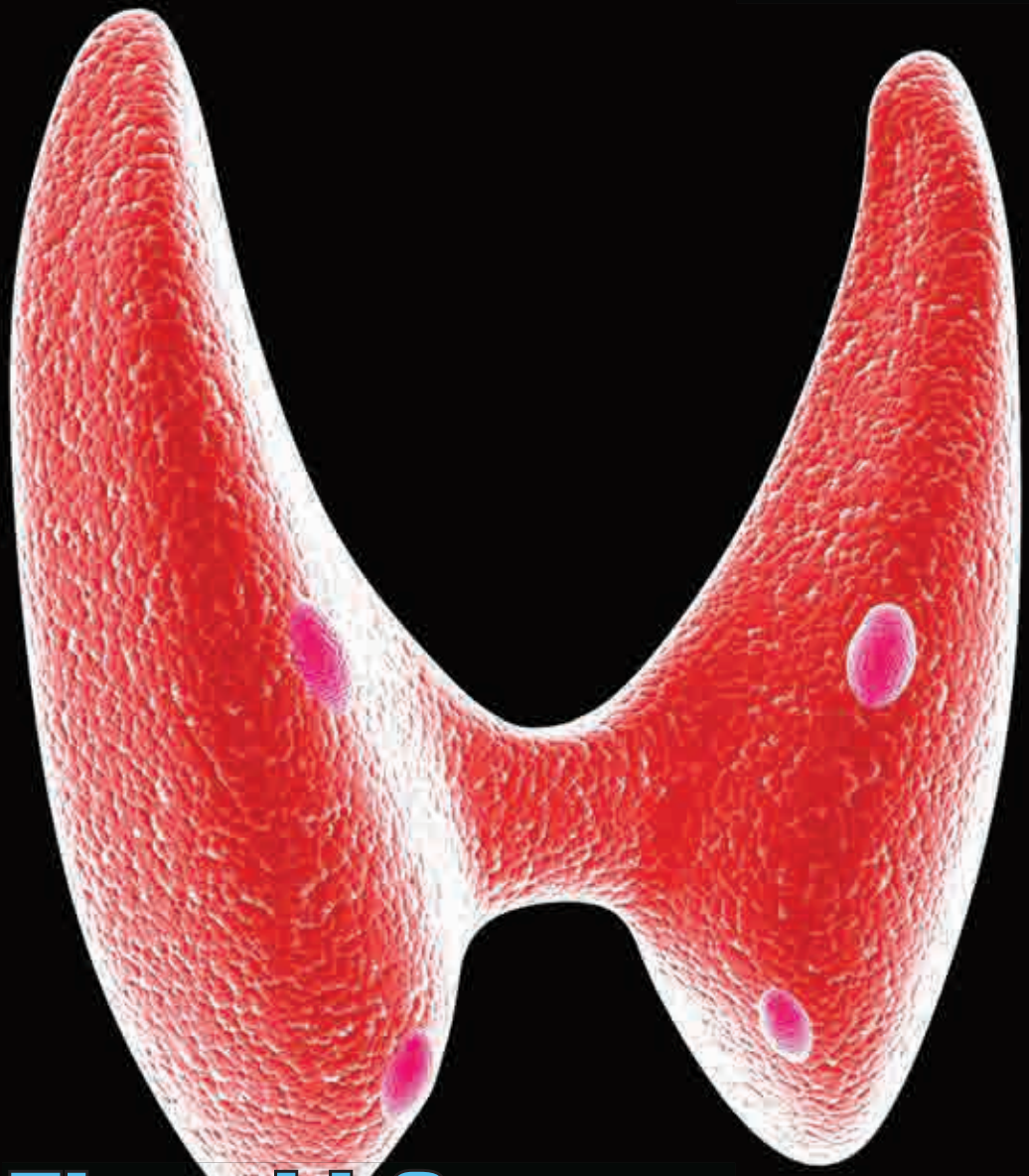
Endocrine news®
OCTOBER 2012



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NEWS & INSIGHTS FOR THE ENDOCRINE COMMUNITY

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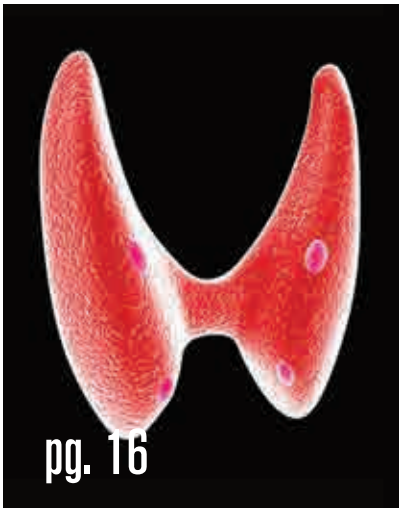
Features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Departments

What is maternal hyperthyroidism?
Read the Hormone Health Network's fact sheet on detecting and treating this thyroid condition (pages 30, 31).

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

Top Issues for the Society's Advocacy Agenda

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

Dear Colleagues:

Membership in The Endocrine Society provides many benefits, including a unified voice on policy issues that affect endocrinologists. We know that members place a high value on the Society's advocacy work, which can influence our professional lives, endocrine research, the practice of endocrinology, and public health. Our advocacy agenda is shaped to address the evolving needs of all of our constituencies.

Biomedical research funding, health disparities, physician reimbursement and access to endocrinologists, endocrinology workforce issues, obesity, and diabetes comprise the 2012 Advocacy Agenda. The Society also focuses on emerging issues including endocrine-disrupting chemicals, clinical research regulation, grant policies, and physician incentive programs.

The Society develops its advocacy tools—*The Value of Endocrine Research*, scientific statements, and position statements, among others—through a rigorous consensus process to ensure that official Society policy represents the consensus of its members and the field of endocrinology. The Society maintains a constant presence on Capitol Hill through the work of its staff and members of the Advocacy and Public Outreach Core Committee. By visiting congressional offices, holding briefings for members of Congress and their staff, and nurturing relationships, the Society has educated legislators and established itself as a leading resource on the issues that affect endocrinology and for those working in the field.

Society Employs Multifaceted Advocacy Approach

Although Congressional impact on policy is clear, many policies affecting endocrinologists are developed through the regulatory process under the President's Administration. The Society is active throughout the development of regulations on many issues and has been proactively approached by the Administration to be a part of the process. Engaging with the Administration is a key component of the Society's advocacy program.

The Society's reputation is strong on Capitol Hill and with the Administration, but there are cases in which many voices speaking together are stronger than the individual. Therefore, the Society is active in numerous advocacy-focused coalitions, including the American Medical Association and the Federation of American Societies for Experimental Biology. The Society has a leading role in these coalitions, and it ensures that the interests of endocrinologists are addressed.

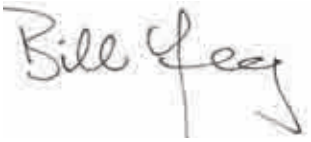
A comprehensive advocacy program uses all of these components to approach a specific issue. For example, the Society is focused on diabetes at all levels, from funding for research to payment for physician services and prevention programs. To this end, the Society's advocacy work has included promoting the renewal of the Type 1 Diabetes Strategic Plan, co-sponsoring Capitol Hill briefings and meeting with members of Congress on diabetes research and prevention programs, funding of the National Diabetes Prevention Program at the level of the Centers for Disease Control and Prevention, maintaining active membership in the Diabetes Advocacy Alliance, developing a position statement on access to affordable diabetes testing supplies, and participating in the development of recommendations on gestational diabetes screening with the United States Preventive Services Task Force. These efforts have resulted in a greater understanding of the diabetes epidemic and the role endocrinology plays in the fight against diabetes, funding for the expansion of the National Diabetes Prevention Program, and renewal of the Type 1 Diabetes Strategic Plan through 2013.

The Society has had many successes in the past year in its advocacy work, but member participation is vital for reaching its goals. I encourage you to become active participants through visits to your members of Congress or by responding to alerts for action from the Society. Together, we can use the tools we have created to have a meaningful impact on issues of concern to you.

New FLARE Program Launched

Finally, I would like to take this opportunity to recognize one of the Society's newest efforts in strengthening the pipeline of biomedical scientists through the Future Leaders Advancing Research in Endocrinology (FLARE) program. Read more about the FLARE program in *Endocrine News* (page 46). If you have any questions or comments, feel free to contact me at *president@endosociety.org*. ■

Sincerely,



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

Dear Readers,

Doctors and researchers debate the cause of the increased incidence of thyroid cancer and bemoan the inconclusive nature of diagnoses, which often requires intrusive surgery to determine if a patient has a malignancy. Fortunately, thyroid cancer is a very treatable cancer, but the treatments can also be controversial. In this issue, four physicians give their perspectives on the use of radioiodine therapy for thyroid cancer patients (page 16).

Broadening our discourse on the disease, freelance science writer Glenda Fauntleroy introduces readers to an innovative molecular diagnostic tool that promises to drastically reduce the number of surgeries associated with thyroid cancer (page 28).

To continue our special focus on thyroid cancer, Fauntleroy also writes about the risks of getting the disease following the Japanese nuclear plant disaster in May 2011. After interviewing a high-level Japanese health official and an American health expert, she reports on the prognosis for millions of Japanese exposed to the plant's radiation (page 22).

There's good news on employment if you want a career in health and medicine. Citing Bureau of Labor statistics, John Bohannon reports on the expected jobs boom in the health industry (page 38).

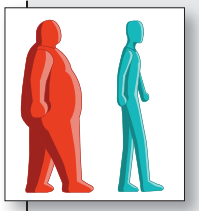
We know that our bodies carry good bacteria as well as bad, but did we know we are inhabited by trillions of microbes and that a lot of them are useful? After a revelatory study by the National Institutes of Health, reports Shannon Fischer, scientists are itching to figure out how to manipulate body bacteria to serve us even better (page 52). ■

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)*.



Beige Fat Fights Obesity
A new type of fat deposit found in adults seems to have calorie-burning properties.

Bequeathing Autism?
A study links mutations in the sperm of older fathers to children with autism and schizophrenia.

Air Pollution and Vitamin D
A pregnant woman's exposure to air pollution may lead to low vitamin D levels in her newborn.

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Endocrine news

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

Print ISSN 2157-2089 Online ISSN 2157-2097

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Binding Protein Plays Key Role in Stress Response and Memory

Stress can cause glucocorticoids to flood the brain and interfere with memory performance and other behaviors. Corticosteroid-binding globulin (CBG), a glycoprotein with high affinity for binding glucocorticoids in blood, is believed to play an important role in this process.

Studies have shown that mice with CBG deficiency react to stressful conditions with lower glucocorticoid signaling, so researchers have hypothesized that plasma CBG plays a crucial role in the amount of corticosterone that gains access to the brain. To test this hypothesis, a research team led by Marie-Pierre Moisan, Ph.D., of the University of Bordeaux, France, investigated the involvement of CBG levels in the stress-induced rise of corticosterone in the hippocampus.

The researchers compared the performance of CBG-deficient mice and controls in a memory retrieval task known to be affected by hippocampal glucocorticoid levels. When the control mice were subjected to acute stress before the test, they suffered from the impaired memory retrieval associated with an increase in corticosterone in the plasma and brain. Stress did not affect the memory retrieval of the CBG-deficient mice; the animals experienced a markedly reduced surge of corticosterone in plasma and no rise in corticosterone in the hippocampus.

To demonstrate that the reduced rise in corticosterone was responsible for the absence of the stress-induced memory change, the researchers infused corticosterone into the hippocampus to mimic a stress-induced increase. Control and CBG-deficient mice reacted with similar memory retrieval impairments. The researchers found that the adrenal glands of the CBG-deficient mice responded normally to stress in increasing corticosterone production, but the lack of CBG binding led to increased clearance, hence the absence of a rise in plasma corticosterone.

In an upcoming ***Endocrinology*** [*endo.endojournals.org*] article, the researchers state that this clear-cut evidence that CBG retains glucocorticoids in plasma, thereby promoting their access to the hippocampus, has important implications for understanding the role of CBG and glucocorticoids in stress-related psychiatric disorders. ■

Eric Seaborg

MicroRNAs Can Be TSH Mediators

Researchers are continually tracing hormone actions back to their most basic levels, including interactions with genes. Although much is known about the pathways by which thyroid-stimulating hormone (TSH) regulates thyroid cell growth and secretion of thyroid hormone, little is known about its interactions with microRNAs (miRNAs), short segments of RNA that bind to target genes and suppress their expression.

To explore the role of miRNAs in TSH activity, Koichi Suzuki, Ph.D., of Japan's National Institute of Infectious Diseases in Tokyo, led a team that performed an miRNA microarray analysis and demonstrated that TSH significantly decreased the expression of 47 miRNAs in thyroid cells. Using miRNA agonists, the researchers identified two miRNAs, miR-16 and miR-195, as mediators of TSH's capacity to induce cell proliferation. High levels of miR-16 and miR-195 suppressed the cell-cycle progression and DNA synthesis that TSH induces.

The target genes suppressed by the two miRNAs were *Mapk8*, *Ccne1*, and *Cdc6*—genes known to be upregulated by TSH as part of cell-cycle regulation in the thyroid. The genes are involved in the phosphatidylinositol 3-kinase (PI3K) and cyclic adenosine monophosphate (cAMP) pathways—activation of these pathways induces a series of transcription factors and cell-cycle regulating proteins that lead to cell proliferation.

An inhibitor of PI3K not only reversed the effect of TSH, but also increased miR-16 and miR-195 expression, and an inhibitor of the cAMP pathway had similar effects. These results led the researchers to suggest that TSH activates the cAMP and P13K signaling cascades to decrease miR-16 and miR-95, which induces the *Mapk8*, *Ccne1*, and *Cdc6* genes to activate cell proliferation. In a paper accepted for publication in ***Molecular Endocrinology*** [*mend.endojournals.org*] the authors write that these findings provide another step toward understanding the physiological regulation of thyroid cell growth and function. ■

Eric Seaborg

Excess Androgen Linked with Fatty Liver in PCOS

➤ Affecting as many as 20 percent of reproductive-age women, polycystic ovary syndrome (PCOS) goes hand in hand with infertility as well as liver disease and obesity. Though multiple studies have shown a higher incidence of nonalcoholic fatty liver disease (NAFLD) in women with PCOS, none has accounted for obesity's possible confounding effects. Does PCOS itself increase risk of NAFLD or is NAFLD in this population purely caused by obesity? Furthermore, does androgen level, a defining trait of PCOS, have anything to do with this dynamic?

Scientists led by Daniel Cuthbertson, M.D., Ph.D., University of Liverpool, United Kingdom, used proton magnetic resonance spectroscopy to measure liver fat in 29 women with PCOS and 22 age-matched controls. In their paper, to be published soon in ***The Journal of Clinical Endocrinology & Metabolism*** [*jcem.endojournals.org*], the researchers report that the hyperandrogenic subgroup of women with PCOS had increased liver fat, a result that held up after adjusting for body mass index. The PCOS subgroup with normal androgen levels showed no significant difference from controls in hepatic steatosis.

The researchers conclude that NAFLD in PCOS is not entirely caused by obesity or insulin resistance, but is instead connected with the hyperandrogenic subtype of PCOS. Knowing that high levels of free androgens in PCOS is a risk factor for developing NAFLD may lead to more aggressive strategies, including lifestyle intervention, in these women. ■

Kelly Horvath

Nursing from Birth Is Important for Cervical Development

➤ Many experts recommend breast-feeding, especially the consumption of "first milk" or colostrum. Although nutritional and immunological benefits of nursing are well recognized, the role of colostrum as a conduit for delivery of milk-borne bioactive factors (MbFs), including hormones and growth factors, to neonates, termed lactocrine signaling, is less well defined. Scientists at Rutgers and Auburn Universities have been conducting research to determine the effect of lactocrine signaling on female reproductive tract (FRT) development. In an upcoming study in ***Endocrinology*** [*endo.endojournals.org*], a team of researchers led by Carol Bagnell and Frank Bartol, sought to determine whether nursing affects the development of neonatal cervical tissues.

As a component of the FRT, the cervix plays an important role in reproduction, serving as a conduit for sperm transport, a protective uterine barrier during gestation and as a dynamic component of the birth canal at parturition. "Earlier studies by our group established that nursing is required to support normal uterine development in the neonate," wrote Carol Bagnell of Rutgers University. "By extension, given the well-established role of relaxin, a prototypical MbF, in cervical growth and remodeling, we hypothesized that aspects of cervical development in the neonate should be both relaxin and lactocrine sensitive."

Using pigs as their model, the researchers found that nursing for two days from birth was required for neonatal expression of cervical proteins important for growth and remodeling including, estrogen receptor-α, vascular endothelial growth factor and matrix metalloproteinase 9. Treatment with relaxin altered expression of these cervical proteins only in pigs that nursed showing that cooperative factors absent in replacer-fed gilts are needed for the cervical response to relaxin.

Returning replacer-fed gilts to nursing two days after birth failed to rescue the lactocrine-null cervical phenotype by postnatal day 14, suggesting that a critical window for lactocrine signaling exists within the first two days after birth. Changes in milk composition and/or development of the gastrointestinal tract may make absorbing MbFs difficult after postnatal day two, the authors suggest.

The researchers conclude that delaying nursing for even two days from birth disrupts cervical development. "This work has significant implications for humans as it pertains to how breast-feeding may support optimal patterns of infant growth and development," Bagnell wrote. "All mammals, including humans, evolved to nurse their young. Consequently, lactocrine signaling is likely to represent a conserved mechanism that extends biochemical communication from mother to offspring into the postnatal period." ■

Dan Kelly

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Reference: 1. Polonsky KS, et al. *N Engl J Med.* 1988;318:1231-1239.

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Hair Provides Cortisol Record for Cyclical Cushing's Syndrome

➤ Hair is being used increasingly as the body's historical record of drug use, environmental exposure, and hormone production. The newest application could be cortisol measurement to identify patients with cyclical Cushing's syndrome.

Cyclical Cushing's is a rare disorder characterized by alternating periods of excess and normal cortisol secretion. The diagnosis is difficult because cycles can be regular or irregular, with normal periods ranging from days to years. The standard screening tests cover only a day, through 24-hour urine collections or midnight saliva tests.

Researchers led by Laura Manenschijn, M.D., of the Erasmus Medical Center in Rotterdam, The Netherlands, collected scalp hair from patients with confirmed Cushing's syndrome, patients suspected of having cyclical Cushing's, and a non-obese control group to test for cortisol.

The cortisol levels were significantly higher in Cushing's patients than controls. The sensitivity and specificity for a Cushing's diagnosis, based on the upper limit of the reference range of healthy individuals, were 86 percent and 98 percent, respectively. These diagnostic percentages compare favorably with those of the commonly used 24-hour urine collections and midnight saliva measurement—tests that had to be performed repeatedly on the patients suspected of having cyclical Cushing's in order to catch them during an episode of excess secretion.

The new technique even offers the possibility of providing a timeline of the disease; the hair samples were measured in 1-cm segments, each corresponding to a period of about a month. The times of high cortisol exposure reconstructed in this way corresponded with the clinical course of the disease, in both patients with Cushing's and cyclical Cushing's. This allowed researchers to create retrospective timelines of cortisol exposure that correlated with symptomatic periods in patients suspected of cyclical Cushing's.

In an article slated for ***The Journal of Clinical Endocrinology & Metabolism*** [*jcem.endojournals.org*], the researchers conclude that this new hair-based diagnostic tool could improve patient care through early recognition cyclic Cushing's syndrome. ■

Eric Seaborg

The "Pill" for Men?

➤ A compound originally synthesized to block a gene that causes cancer may lead to a contraceptive pill for men, say scientists at the Dana-Farber Cancer Institute and the Baylor College of Medicine. Their research in mice suggests that the compound, called JQ1, interferes with the creation and maturation of sperm in the testes.

In a study led by Baylor's Martin M. Matzuk, M.D., Ph.D., and Dana-Farber's James E. Bradner, M.D. that appeared in the August 17 issue of the journal *Cell*, the team compared mice injected with 50 mg/kg of JQ1 daily with untreated mice and found that sperm counts in the treated mice dropped 72 percent after three weeks. By the sixth week, sperm counts in the treated mice had dropped even further, a total of 89 percent. The treatment affected sperm motility, as well. After six weeks, only 5 percent of the few sperm from the treated group were fully motile. Although several treated mice became fathers after 6–10 weeks of treatment with the lower dose of the JQ1, raising the dose to 75 mg/kg or 100 mg/kg per day rendered them sterile by the end of the mating period.

The effects of JQ1 appear to be temporary and limited to fertility; treatment did not affect the animals' testosterone levels and the treated mice continued to mate with female mice as often as before. The mice regained their fertility less than two months after stopping treatment, and offspring conceived afterward were healthy.

The research shows that JQ1 works by binding to a protein called BRDT, which plays a role in chromatin remodeling when the testes generate sperm. During this process, chromatin—the combination of DNA and proteins in the nucleus of a cell—is "remodeled" to give the proteins that regulate genes access to genetic material. BRDT is conserved in mice and men and is related to the cancer-causing gene *BRD4*, for which the compound was originally developed.

Testing in humans is a long way off. Derivatives of JQ1 would have to be developed and optimized for delivery in a pill or implant. However, the compound is a breakthrough because it crosses the difficult barrier that separates blood and sperm. ■

Terri D'Arrigo

Gene Variation Tied to Early Menarche

➤ Divergences in the age at which a woman begins menstruating are associated with many disorders—an early age of menarche is associated with breast and endometrial cancers and a late age increases the risk of Alzheimer's disease and osteoporosis.

Because genetic factors play an important but little-understood role in determining the age of menarche, researchers led by Yao-Zhong Liu, M.D., Ph.D., of Tulane University studied the role of a form of genetic variation called copy number variation (CNV).

In CNV, a DNA segment is repeated (copied) two or more times within a chromosome—and sometimes it is omitted. The repeated segments can range in size from thousands to millions of DNA bases. These gains and losses of large chunks of DNA are believed to account for three times as much genetic variation as is caused by single nucleotide polymorphisms, which have received much more attention. Extra copies of a segment can lead to higher levels of the gene's product, disrupt coding sequences, and affect gene expression even outside the CNV region.

Dr. Liu's team did a genome-wide association study of CNV and age of menarche in 1,654 Caucasian females. They identified a CNV, variation_38399, associated with age of menarche: Test subjects with only one copy of the variant had a mean age of menarche of 14.0 years, more than a year later than the subjects with two copies of the variant, at 12.9 years. The researchers then confirmed the association in a cohort of 752 Chinese women.

The variant is located about 75 kilobases upstream of the diazepam-binding inhibitor gene, a gene known to regulate estrogen levels, a key factor for menarche.

In a paper in ***The Journal of Clinical Endocrinology & Metabolism*** [*jcem.endojournals.org*], the researchers write that this first study of CNV and menarche supports the existence of a mechanism by which variation_38399 modulates the age of menarche by influencing the signaling pathway mediated by the diazepam-binding inhibitor gene. ■

Eric Seaborg

STATS

In 2009–2010, about

1 in 5

Americans age 45 years and older were diagnosed with 2 or more chronic conditions, such as hypertension, heart disease, diabetes, cancer, and stroke.

Source: Centers for Disease Control and Prevention. NCHS Data Brief, Number 100, July 2012, *www.cdc.gov/nchs/data/databriefs/db100.htm.*

Oxytocin Secretion Linked to Eating Disorder

➤ Animal studies have shown that oxytocin is an appetite-regulating hormone. A new study looks at how oxytocin secretion dynamics may differ in anorexia nervosa.

Scientists led by Elizabeth A. Lawson, M.D., M.Sc., at the Harvard Medical School and Massachusetts General Hospital in Boston, studied 13 women with anorexia, 9 women recovered from anorexia, and 13 controls. Participants were given standardized high-protein, high-carbohydrate, low-fat breakfasts, after which serial blood samples were taken. Functional magnetic resonance imaging (fMRI) was also done to assess brain activity in areas involved in appetite, such as the insula, where food intake and emotion related to eating are processed.

In their paper, to be published soon in ***The Journal of Clinical Endocrinology & Metabolism*** [*jcem.endojournals.org*], the researchers report that, as expected, peripheral post-prandial oxytocin levels were highest in women with active disorder and lowest in recovered women and that higher oxytocin levels were associated with greater severity of disordered eating psychopathology. Post-prandial oxytocin secretion was also associated with differences in fMRI activation of brain regions involved in appetite in women with anorexia nervosa, even after recovery.

The researchers conclude that oxytocin may be an independent appetite regulator, and its dysregulation may contribute to symptoms of disordered eating in anorexia nervosa, possibly by desensitizing the anorexic woman to her internal state. "Inherent abnormalities in oxytocin pathways may contribute to underlying deficits that increase susceptibility to developing and sustaining anorexia nervosa," says Dr. Lawson. The next step in unmasking oxytocin's therapeutic possibility is to study its effects when given to humans. ■

Kelly Horvath

Leydig Cell Regenerators Appear to be Stem Cells

➤ Stem cells appear to be the precursors to replacements for Leydig cells, the testosterone-producing cells of the adult testes, and researchers say that they have come up with a new way of studying the regenerative process.

Leydig cells rarely die or divide if left undisturbed but can regenerate if necessary. For example, if Leydig cells are depleted in rats by the injection of the alkylating agent, ethane dimethanesulfonate (EDS), a new generation forms. To better understand this process, Haolin Chen, Ph.D., of Johns Hopkins Bloomberg School of Medicine, led a team to investigate whether the new cells are regenerated by stem cells (which can grow into many forms) or quiescent progenitor cells (cells already in the Leydig cell lineage).

The researchers isolated cells that expressed platelet-derived growth factor α but not 3β-hydroxysteroid dehydrogenase (3β-HSD), a key enzyme in the steroid synthesis pathway. Depending on the culture conditions, these cells, called 3β-HSD-negative, could differentiate into forms that produce testosterone—this ability to differentiate is a characteristic of stem cells.

To determine the cells' location, the researchers separated the seminiferous tubules from the testicular interstitium and cultured both. The seminiferous tubule cells developed 3β-HSD-positive cells capable of producing testosterone, but the interstitial cells did not, which suggested that the tubule surfaces contained stem cells. When the 3β-HSD-positive cells were removed from the seminiferous tubule surfaces with EDS and cultured again, the testosterone-producing cells reappeared—this regenerative ability provided further evidence of the presence of stem cells.

The researchers posit in an article scheduled for ***Endocrinology*** [*endo.endojournals.org*] that the precursors for the newly formed Leydig cells are stem cells, mainly on the surfaces of the seminiferous tubules, showing yet another role for stem cells in regenerative processes. They propose that their tubule culture system, which contains not only the stem cells but also their niche, could provide a valuable example for research into the components and properties of low-turnover adult stem cells, in general, in complex tissues of all mammals. ■

Eric Seaborg

Pancreas Size Shrinks Before Diabetes Onset

➤ Diabetes is presaged by several factors, some not apparent until after diagnosis. Shrinking of the pancreas is common in type 1 diabetes, reducing it by as much as 48 percent in adult patients 10 years after disease onset. Recently, other data show pancreas size shrinking by as much as 31 percent less than 6 months after diagnosis. Researchers led by Alistair Williams, B.Sc., of the University of Bristol have now extended these findings in a larger group of patients.

Twenty adult male diabetes patients and 24 healthy male controls were scanned by MRI. The age of the patients and controls was similar, being centered around 27 years, and each diabetes patient had scans from 1 month to 8 months after being diagnosed. The pancreas size of the patients had decreased by 26 percent compared to their control counterparts.

In the study's findings, to be published in ***The Journal of Clinical Endocrinology and Metabolism*** [*jcem.endojournals.org*], age and disease-duration made no significant contribution to pancreas size. Neither did glucose levels nor the number of autoantibodies. Reduced pancreas size, in turn, did not produce exocrine deficiency, which is common in long-term diabetes.

The study suggests, however, that if pancreas size decreases by 48 percent 10 years after onset and 26 percent just months following diagnosis, then half of that reduction happens in the pre-diabetic period. Furthermore, this atrophy may begin many years before onset, allowing reduction in pancreas size to be useful as a marker of pancreatic β-cell loss before and after diagnosis.

Although the link between β-cell mass and pancreatic size is uncertain, it might provide a measure of disease progression. Coupled with the low risk of non-invasive MRI, this information may give diabetes patients a chance to seek treatment sooner, when effective preventive therapies become available. ■

Dan Kelly

Vitamin D's Effects on Arterial Health

➤ Like most of our body parts, arteries lose their elasticity. Evidence has suggested a link between vitamin D deficiency and arterial stiffening, which would support the notion that vitamin D supplementation reduces the risk for cardiovascular disease. A new study specifically examines the possible connection.

Francesco Giallauria, M.D., Ph.D., at the National Institute on Aging in Baltimore and the University of Naples in Italy, says, "The higher prevalence of hypervitaminosis D is due to several factors that may coexist—low levels of sunlight exposure, sedentary lifestyle, and inadequate consumption of fresh food." His team used pulse-wave velocity (PWV) to test whether low serum levels of 25OHD contribute to carotid–femoral atherosclerosis in 1,288 participants in a multiethnic, cross-sectional analysis as part of the Baltimore Longitudinal Study of Aging.

In their paper, to be published soon in ***The Journal of Clinical Endocrinology & Metabolism*** [*jcem.endojournal.org*], the researchers report that the lowest serum 25OHD levels correlated with the highest PWV measurements, which indicates artery hardening, and that this inverse relationship held up even after adjusting for potential confounders, such as age, sex, ethnicity, and blood-draw timing. Additional adjustments were made for specific cardiovascular factors, such as weight, amount of exercise, and smoking as well as for conditions known to affect the heart such as diabetes.

The researchers conclude that 25OHD level is an independent predictor of arterial stiffness. They are planning to undertake large-scale studies to focus on the underlying mechanism and to determine definitively whether vitamin D supplementation improves arterial elasticity. ■

Kelly Horvath

Body Rhythms Reset Through Site-specific Receptors

➤ Our circadian rhythms are synchronized between the suprachiasmatic nucleus (SCN) in the hypothalamus and peripheral oscillators, the body's ancillary clocks. Glucocorticoids secreted by the adrenal gland, such as corticosterone, provide timing signals so the phases of these clocks act in harmony. Damage to the SCN disrupts the rhythm of these secretions and although peripheral tissues can maintain their oscillations, their phases no longer operate together. The majority of glucocorticoid receptors, however, are outside the SCN.

By removing the adrenal glands of rats, Michael Menaker, Ph.D., Pinar Pezuk, Ph.D., and fellow researchers at the University of Virginia were able to show how important glucocorticoids are to entraining the peripheral oscillators. Following surgery, phase shifts occurred in some tissues but not others. Lungs and the pituitary, pineal, and salivary glands continued normally, although the kidneys, liver, and cornea all lost normal phase relationships with their light-dark cycles.

Hydrocortisone treatments restored the phases of the kidney and cornea but caused dyssynchrony in the liver and the lungs, perhaps attributable to a high-glucocorticoid threshold as seen in responses to stress. Methamphetamine also caused phase shifts in the cornea as did restrictive feeding, which pushes peripheral oscillators to split from the SCN. Animals without adrenal signaling reset faster than intact animals suggesting that glucocorticoids block this uncoupling.

Although adrenalectomy did not cause phase shifts in all tissues, it did advance re-entrainment in almost all peripheral oscillators and the SCN when other phase shifts were induced. Corticosterone itself is slow to adjust to shifts in the light cycle. This may slow recovery of the peripheral tissues for intact animals. In its absence, resynchronization was more rapid.

Circadian rhythms change with our environment. The report of this study in an upcoming article in ***Endocrinology*** [*endo.endojournals.org*] provides a good view of how our organs reset apart from the main body clock through the versatility of glucocorticoids. ■

Dan Kelly

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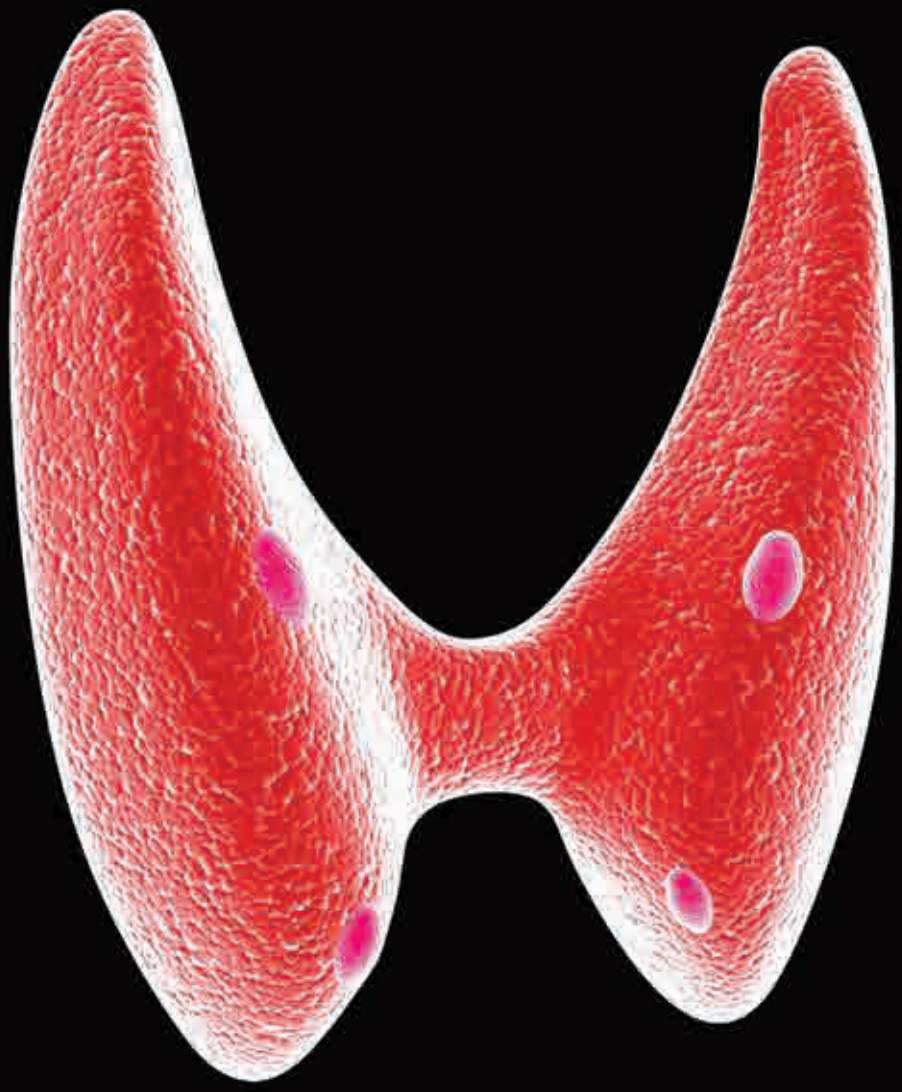


Thyroid Cancer and Radioiodine

Whether due to improved detection or unknown environmental factors, the incidence of thyroid cancer is on the rise. People are twice as susceptible to this cancer today as they were in 1990. The American Cancer Society estimates that more than 56,000 Americans will be diagnosed with thyroid cancer by the end of the year. Three out of four cases will be in women. A common and successful treatment for thyroid cancer is radioactive iodine (RAI), but this therapy is not without its risks and can cause leukemia and impaired fertility. Furthermore, some thyroid cancers are resistant to radioiodine. In this Tri-Point article, a clinical practitioner discusses what factors to consider when selecting patients for radioiodine treatment; a clinical researcher weighs the therapy's general benefits and risks; and two basic researchers unveil possible future therapies to fight resistant thyroid cancers.

Clinical Practitioner Perspective

By Martin Schlumberger, M.D.

Professor Schlumberger is chair of nuclear medicine at Institut Gustave Roussy, Villejuif, France.

Highlights

- In low-risk patients, post-operative radioiodine should be used selectively.
- When indicated, 1.1 GBq following injections of recombinant human TSH (rhTSH) should be used.
- Radioiodine is not routinely used during follow-up.
- Refractory thyroid cancer patients should not be treated with radioiodine.
- New treatment modalities are available for refractory thyroid cancer with documented progression.

Radioiodine is widely used in thyroid cancer patients. Its administration is easy and is usually well tolerated. However, its cost and potential side effects should restrict its use to patients for whom a benefit is expected. When indicated, the lowest effective activity should be administered.

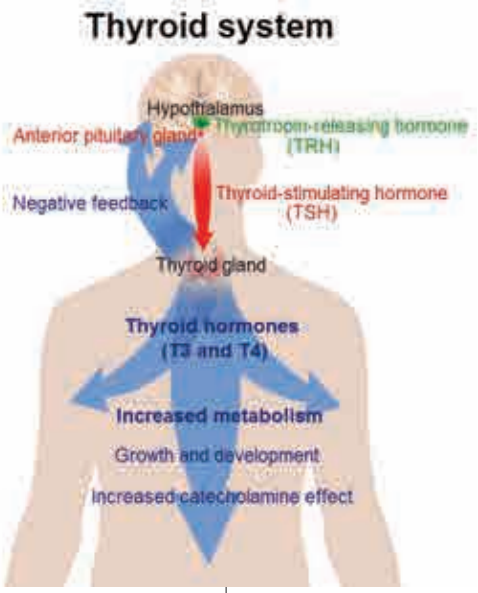
Side effects of radioiodine include swelling of the salivary glands and subsequent dry mouth, lacrimal disturbances, nausea, and loss of taste. Long-term adverse events include the occurrence of secondary cancers and leukemias. However, the risk is significantly increased after the administration of a cumulative activity of 22 GBq or more. No evidence exists of increased risk to pregnancies following radioiodine exposure when conception occurs more than six months after the last exposure. On the other hand, benefits of radioiodine treatment have been shown in only some subgroups of thyroid cancer patients and its use should be selective, after initial surgery, during follow-up, and in patients with persistent or recurrent disease. Indications are well-defined, except after initial surgery, a situation for which prospective trials are needed.

Post-operatively, radioiodine may be administered with three aims: first, to irradiate any persistent neoplastic focus in order to decrease the risk of subsequent recurrence; second, to eradicate normal thyroid remnants in order to obtain an undetectable serum thyroglobulin (Tg) in the absence of anti-Tg antibodies; and third, to perform a whole body scan (WBS) 2–5 days after the

administration of radioiodine to detect metastatic disease. Benefits of radioiodine on outcome have been demonstrated for high-risk patients and for those with persistent disease who are treated with high activities (≥ 100 mCi or 3.7 GBq). Radioiodine is not indicated in very low-risk patients with tumors of less than 1 cm and with no lymph node metastases, and no evidence is currently available that it improves the outcome of low-risk patients (with tumors larger than 1 cm and no or limited lymph node involvement) who have no evidence of disease after total thyroidectomy.[1]

Not All Thyroidectomy Patients Require Radioiodine

Prospective trials are warranted in these latter patients, to identify those who should receive post-operative radioiodine. In the absence of prospective trials, retrospective studies have shown that serum Tg may already be undetectable after total thyroidectomy and before any radioiodine administration, and only 3 percent of such patients had persistent disease on WBS, and all had lymph node metastases.[2] After total thyroidectomy, patients with no lymph node metastases at a prophylactic lymph node dissection or with no evidence of lymph node metastases on neck ultrasonography may not require any radioiodine.[1–4] In these low-risk patients, some questions remain unresolved and, because initial treatment includes several steps that are still not validated, successive prospective randomized trials are needed to answer these questions: (1) What is the optimal protocol for post-operative radioiodine administration? (2) In which low-risk patients should radioiodine be administered? (3) When should prophylactic neck dissection be performed?



To answer the first question, two prospective randomized trials on large series of patients who had been treated with total thyroidectomy have demonstrated that the ablation rate is over 90 percent following either 1.1 GBq or 3.7 GBq and after a preparation using either rhTSH or withdrawal.[5,6] Thus, the use of 1.1 GBq after rhTSH stimulation is recommended when radioiodine ablation is indicated in these low-risk patients: this will avoid any hypothyroidism, maintain the quality of life, and decrease the radiation dose to the body by 5-fold compared to the previous protocol, which used 3.7 GBq following withdrawal. When radioiodine has not been administered, follow-up is based on serum Tg determination on levothyroxine (LT4) treatment and on neck ultrasound at one year. Indeed, with this new standard, we are launching another randomized trial in low-risk thyroid cancer patients after total thyroidectomy, with 1.1 GBq following rhTSH compared to no radioiodine, to define in which patients it may be beneficial.

Diagnostic WBS has no routine indication and ablation is currently assessed by neck ultrasound and serum Tg determination, obtained either using a sensitive method on LT4 treatment[7] or following rhTSH injections. Diagnostic WBS may be performed during follow-up in patients with any abnormality, including an elevated serum Tg, in those with high uptake in large thyroid remnants on post-ablation scan and in those with anti-Tg antibodies.

In patients with persistent or recurrent disease, radioiodine is indicated for the treatment of neoplastic foci in the two-thirds of patients with tumor uptake. In patients with persistent or recurrent disease in the neck, radioiodine may eradicate small neoplastic foci (less than 1 cm in diameter), but rarely larger foci. Radioiodine is useful to localize any neoplastic foci on SPECT/CT in addition to other imaging modalities (neck ultrasonography, CT scan, FDG-PET scan) and to enable their pre-operative localization with a probe. This is the rationale for the administration of a large dose of radioiodine several days before surgery, which enabled the resection of all tumor foci in 92 percent of patients.[8]

Radioiodine Should be Used Only in Selected Cancer Patients

In patients with distant metastases, various treatment dosages are administered depending on the center. However, no evidence exists that any protocol based on dosimetry or using high activities may be more effective than repeated treatments with a standard activity of 3.7 GBq administered following thyroid hormone withdrawal. Complete responses are obtained in 40 percent of distant metastases with radioiodine uptake, and predictive factors for cure are younger age at discovery of the metastases, small size of metastases, well differentiated cancer histotype, and low uptake of FDG on PET scan. Almost all complete responses were obtained with a cumulative activity of 22 GBq or less, and few progressions have been observed after complete remission.[9]

These findings led to the definition of refractory thyroid cancers, which are observed in patients with: (1) at least one target lesion with no detectable iodine uptake, (2) progression during the 12 months following radioiodine treatment, or (3) persistent disease after the administration of 22 GBq. Indeed, radioiodine should not be given to patients who meet one of these criteria. They may be candidates for other treatment modalities in case of documented progression.[10]

In conclusion, the use of radioiodine is easy and is usually well tolerated, but it should be used only in selected thyroid cancer patients for whom benefits have been demonstrated.

Clinical Researcher Perspective

Bryan R Haugen, M.D., F.A.C.P.

Dr. Haugen is a professor of medicine and pathology and head of the Division of Endocrinology at the University of Colorado School of Medicine.

Highlights

- Radioiodine is an excellent targeted therapy for patients with high-risk, radioiodine-avid disease.
- Appropriate risk stratification (AJCC/TNM, recurrence risk stratification, serum thyroglobulin) is important in selecting patients who will most likely benefit from radioiodine therapy.
- The benefits and risks of radioiodine remnant ablation must be carefully weighed in patients with low-to-intermediate risk thyroid cancer.
- Two ways to reduce risks associated with radioiodine therapy are to prepare appropriate patients with recombinant human thyroid-stimulating hormone (euthyroid state) and administer the lowest effective dose (30–50 mCi ^{131}I in many low-risk patients).
- Low-risk patients who do not receive radioiodine can be monitored with exam, serum thyroglobulin, and neck ultrasound.

Consideration in choosing patients to receive radioiodine remnant ablation

The goals of primary therapies, including radioiodine treatment, for any cancers are: (1) to improve cancer-related survival, (2) to minimize the risk of disease recurrence and metastatic spread, (3) to permit accurate long-term surveillance for disease recurrence, (4) to permit accurate staging of disease, and (5) to minimize treatment-related morbidity.[1] In order to choose the appropriate patients who may benefit from radioiodine remnant ablation, we must first stratify these patients by risk. The American Joint Commission Against Cancer/Tumor, Nodes, Metastases (AJCC/TNM) staging system is used to determine overall survival and disease-specific survival. To estimate risk of disease persistence or recurrence, the American Thyroid Association Guidelines classified patients into three risk categories: low, intermediate, and high. These categories appear to be quite good at predicting persistent or recurrent structural disease.[2] Patients in the low-, intermediate-, and high-risk categories have a 2 percent, 19 percent, and 67 percent risk of recurrence. The tumor marker serum thyroglobulin, measured at its nadir under levothyroxine (LT4) suppression therapy, may help further define which low- to intermediate-risk patients may benefit from radioiodine therapy and those who may not.

Radioiodine ablation/therapy is recommended for all patients with thyroid cancer metastases that can concentrate and respond to radioiodine, patients with gross extra thyroidal extension, and patients with tumors greater than 4 cm.[5] Radioiodine ablation is recommended for selected patients with primary tumors between 1 and 4 cm that are confined to the thyroid and who have higher risk features for recurrence (high-risk subtypes of differentiated thyroid cancer, extensive lymph node metastases). Radioiodine remnant ablation is not recommended for patients with unifocal cancer less than 1 cm or for patients with multifocal papillary thyroid carcinoma when each of the foci are less than 1 cm in the absence of other higher risk features.[6, 7]

Benefits and risks of radioiodine remnant ablation

The goals of initial radioiodine therapy are to ablate all residual thyroid cells, both normal and cancerous, remaining after surgery. The results of many retrospective studies looking at the benefit of radioiodine remnant ablation in patients with low- and intermediate-risk thyroid cancer have been mixed. A systematic review of the literature indicates that disease recurrence can be reduced by approximately 50 percent with radioiodine in a large non-risk stratified group of patients.[3] No survival benefit was observed. A prospective multi-center database analysis showed survival benefit of radioiodine therapy for high-risk patients (stage 3 and stage 4) and that radioiodine therapy improved overall survival in stage 2 patients. However, no benefit was observed of radioiodine remnant ablation in the broad group of stage 1 patients.[4]

Multiple risks are associated with radioiodine therapy, including dental caries, watery eyes, gonadal dysfunction, marrow suppression, and secondary malignancies.

Preparation and administered doses of radioiodine for remnant ablation

Many studies have now shown that patients can be adequately prepared for radioiodine remnant ablation using recombinant human TSH.[8, 9] If one is considering withdrawal therapy, many experts suggest three-week withdrawal of LT4 without the addition of liothyronine because this does not appear to improve quality of life. This is a shorter, simpler way to prepare patients for radioiodine remnant ablation.[10]

Two ways to reduce potential risks of radioiodine therapy are to deliver radioiodine in the euthyroid state so that whole body clearance is higher, and administer the lowest dose of ^{131}I that can achieve successful remnant ablation. Two recent prospective randomized trials comparing 30 mCi (1.11 GBq) with 100 mCi (3.7 GBq) of ^{131}I, each in combination with recombinant human TSH, or thyroid hormone withdrawal preparation showed no difference among the subgroups, suggesting that preparation of low-risk patients with recombinant human TSH and 30 mCi of ^{131}I is likely sufficient for remnant ablation in most patients.[11, 12] Older

The 10-year survival of patients with metastatic thyroid cancer that retains RAI avidity is approximately 60% but only 10% if the metastases are refractory to RAI therapy.

studies have shown mixed success in patients receiving doses as low as 30 mCi of ^{131}I. This may be due in part to less complete thyroidectomies performed years ago.

Summary

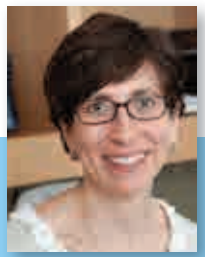
Radioiodine remnant ablation should have limited use in many of our low-risk patients, particularly those with stage 1 disease who are younger, with smaller primary tumors, no lymph node involvement, and no extrathyroidal invasion. We can use a serum thyroglobulin approximately six to eight weeks after thyroidectomy on LT4 suppression to further stratify risk in these patients. We should consider selected use in our low- to intermediate-risk patients and primarily reserve radioiodine remnant ablation for those older patients with larger tumors, more extensive lymph node involvement, and patients with higher risk subtypes of differentiated thyroid cancer (tall cell, insular, etc.). Most low- to intermediate-risk patients who warrant radioiodine remnant ablation can be prepared with recombinant human TSH. Furthermore, the smallest dose possible to achieve successful remnant ablation (30–50 mCi ^{131}I) should be considered.

Basic Researcher Perspective

Determinants of response to RAI in metastatic thyroid cancer

Stephanie Fish, M.D., and James A. Fagin, M.D.

Dr. Fish is an associate member, Endocrinology Service at Memorial Sloan-Kettering Cancer Center in New York, New York. Dr. Fagin is the chief of the Endocrinology Service and a member of the Human Oncology and Pathogenesis Program at Memorial Sloan-Kettering Cancer Center in New York, New York.



Highlights

- Patients with metastatic thyroid cancers that are not RAI avid have greater disease-specific mortality than those that can incorporate iodine.
- Nuclear receptor ligands such as retinoids and PPARγ agonists have not been effective in restoring RAI uptake in patients with metastatic thyroid cancer.
- Clinical trials with histone deacetylase inhibitors and demethylating agents have not increased sensitivity to RAI in patients with metastatic disease.
- Knowledge of the genetic basis of thyroid cancer, and particularly on the role of constitutive MAPK activation by oncogenic effectors in the pathway, has provided novel insights into the mechanisms accounting for loss of RAI uptake in thyroid cancer.
- MAPK kinase pathway inhibitors partially restore sodium-iodide symporter expression and RAI uptake in murine models of thyroid cancer, and hold promise in clinical trials.

Most cases of thyroid cancer can be treated effectively with total thyroidectomy, in some cases followed by adjuvant RAI therapy. Mortality from thyroid cancer is primarily associated with metastatic disease. The 10-year survival of patients with metastatic thyroid cancer that retains RAI avidity is approximately 60 percent, whereas it is only 10 percent if the metastases are refractory to RAI therapy.[1] This has prompted many efforts to develop therapies to restore the ability of RAI-refractory thyroid cancers to trap iodide and respond to this therapy. Iodide uptake and storage in the form of thyroid hormone precursors are complex and highly regulated processes that require the function of key proteins such as the sodium-iodide symporter (NIS), pendrin, the potassium channel subunits KCNQ1 and KCNE2, thyroglobulin (Tg), and thyroid peroxidase (TPO). A subset of thyroid cancers loses expression and function of these genes.[2] The mechanisms that account for this have been extensively investigated and will be discussed here, with particular emphasis on those that have also been tested in the clinic.

Nuclear receptor ligands in RAI refractory thyroid cancer

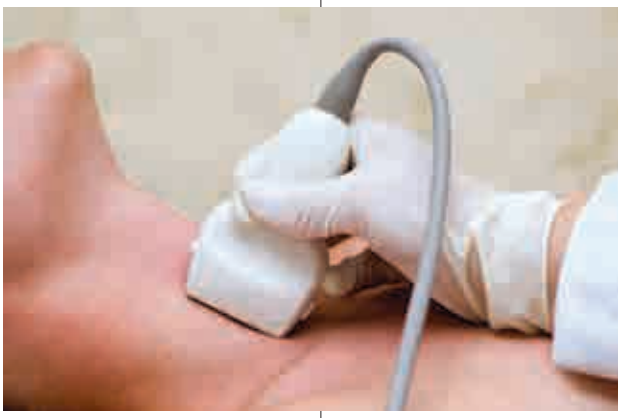
Retinoids act by binding to the retinoic acid (RAR) and the retinoid X (RXR) nuclear receptors, through which they regulate gene transcription by direct interaction with the regulatory regions of a diverse set of genes. Retinoids have key effects on cell differentiation and in development, and are used as cancer therapies. The most notable use of retinoids in cancer is for acute promyelocytic leukemia, more than 95 percent of which are caused by a translocation that juxtaposes the PML gene on chromosome 15 and the RARα gene on chromosome 17. Retinoids induce expression of the type I iodothyronine 5′-deiodinase isoenzymes and *NIS* mRNA in follicular thyroid cancer cell lines.[3] Based on these observations, numerous clinical studies of retinoids in patients with advanced thyroid cancer were initiated, mostly with isotretinoin (13-cis-retinoic acid). About 20–40 percent of patients showed some response to isotretinoin therapy, including reduced tumor size and increased RAI uptake. However, more recent reports have shown that few patients had a clinically meaningful response,[4] suggesting

that retinoid monotherapy is not effective in RAI-resistant metastatic thyroid cancer.

The peroxisome proliferator-activated receptor (PPAR) belongs to the nuclear hormone receptor superfamily. Thiazolidinediones (TZDs), PPARγ agonists that have been used historically and primarily in the treatment of type 2 diabetes, inhibit cell proliferation and induce re-differentiation of different cancer cell types, including follicular thyroid cancer cell lines. Based on these observations, 20 patients with metastatic non-RAI-avid thyroid cancer were treated with the TZD rosiglitazone, but none had significant clinical responses.[5]

Effects of chromatin remodeling and demethylating agents in thyroid cancer

Histone acetylation decreases chromatin compaction, which is permissive for gene transcription. Conversely, when the acetyl groups are removed, electrostatic interactions between DNA and histones compact the chromatin, inhibiting transcription. Histone deacetylase (HDAC) inhibitors, such as depsipeptide, increase *TG* and *NIS* mRNA levels and RAI uptake in poorly differentiated thyroid cancer cells.[6] Unfortunately, these preclinical data did not translate into the clinic, as neither depsipeptide nor vorinostat conferred clinical benefit in patients with RAI-refractory thyroid cancer.[7, 8] The relatively poor record of preclinical studies in predicting the activity of compounds designed to reactivate iodine incorporation in clinical trials of thyroid cancer may be due in part to the fact that some of the in vitro studies used cancer cell lines that were later found to have been misidentified, and were not of thyroid origin.[9] Moreover, the magnitude of the effects in vitro was, in general, quite modest compared to the iodine uptake of well differentiated, non-transformed thyroid cells.



DNA methylation of key gene regulatory elements decreases gene transcription. Cancer cells often exhibit aberrant gene methylation patterns, which accounts for some of the global abnormalities in their gene expression patterns. Many of the key genes required for thyroid hormone biosynthesis have been reported to be silenced through hypermethylation in thyroid cancer.[10] This provided the rationale for a pilot clinical trial of the demethylating agent 5-azacytidine to restore RAI responsiveness, but the results were reportedly negative, according to Kenneth Ain, M.D.

Molecular mechanisms of loss of iodine uptake in thyroid cancer

Recent discoveries on the genetic basis of thyroid cancer have provided novel insights into the mechanisms contributing to loss of RAI uptake in the disease. Papillary thyroid cancers (PTC) are associated with mutually exclusive mutations of oncogenes encoding effectors of the mitogen-activated protein kinase (MAPK) signaling pathway (i.e., *RET*, *NTRK*, *RAS*, and *BRAF*).[11] Oncogenic BRAF signals as a monomer and promotes higher levels of MAPK activity than other lesions in the pathway because normal feedback events controlling MAPK become disabled. Unrestrained MAPK activation in thyroid cells leads to loss of expression of genes required for thyroid hormone biosynthesis, including *NIS* and *TPO*.[12, 13] The activating $BRAF^{V600E}$ mutation is the most frequent genetic alteration in PTC and confers a poor prognosis.[14] BRAF is associated with tumors with lowered *NIS* expression,[2] which likely explains the clinical observation that PTCs with *BRAF* mutations are often particularly resistant to RAI therapy.[15] The mechanisms by which BRAF inhibits differentiated function in thyroid cells, and *NIS* expression and iodide uptake in particular, may involve a BRAF-induced TGFβ1 autocrine loop.[16]

Loss of *NIS* expression is restored in vitro by treatment with MAPK kinase (MEK) inhibitors.[12, 17] Mice with doxycycline-inducible expression of $BRAF^{V600E}$ in thyroid cells develop invasive lesions that are histologically consistent with papillary thyroid cancers, showing profound decreases in expression of thyroid-specific genes and of radioactive iodide uptake in vivo. Iodide uptake is restored when doxycycline is discontinued, and when the mice are treated with RAF or MEK inhibitors.[18] Based on these results, drugs of this class are currently being tested in phase 2 clinical trials of patients with RAI-refractory thyroid cancer.

Conclusion

The prognosis of patients with metastatic RAI-refractory thyroid cancer is poor. A better understanding of the basic mechanisms accounting for the loss of iodine incorporation in cancer cells points to ways by which this process can be reversed, at least in a subset of patients. MAPK activation in thyroid cells leads to loss of thyroid-specific gene expression. Agents that can effectively block this pathway in a sustained manner have had promising results in mouse models of thyroid cancer, and are now being tested in clinical trials. ■

This article was reviewed by Daniel Bernard, Ph.D., and Cecilia Wang, M.D., of The Endocrine Society's Research Affairs Core Committee.

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Assessing the RISK of Thyroid Cancer

By Glenda Fauntleroy

In the year and a half since the Fukushima Daiichi Nuclear Power Plant disaster following the March 2011 earthquake and tsunami in Japan, residents near the site have become increasingly concerned about the potential long-term effects to their health from radioactive contamination.

More than 100,000 people were evacuated after the meltdown, and significant radiation spread across 700 square miles of land, prompting health officials to make care and treatment of those exposed to radiation a top priority.

Monitoring such residents is "an unprecedented health management program for a two-million population for almost a whole lifespan," said Shunichi Yamashita, M.D., vice president of Fukushima Medical University, during a presentation at **ENDO 2012**.

The organ most at risk from radioactive iodine is the thyroid gland, according to the American Thyroid Association (ATA). The thyroid absorbs iodine from the bloodstream and uses it to create energy-regulating hormones. The gland cannot, however, distinguish between regular iodine and the radioactive type and will absorb whatever it can. When thyroid cells absorb too much radioactive iodine, it can cause DNA damage, leading to the development of thyroid cancer several years after the exposure. Babies and young children are at highest risk.

Valuable lessons have been learned from past nuclear accidents, such as the 1986 disaster at Chernobyl in Ukraine that led to huge

after Fukushima Crisis

releases of radioactive materials into the atmosphere, Yamashita said in his lecture. The average thyroid "effective dose"— the amount of risk—to children at Chernobyl was 490 mSv (millisieverts), whereas children in Fukushima averaged a thyroid effective dose of less than 50 mSv, he said. A typical CT head scan delivers 2 mSv. The effective dose of radiation exposure takes into account the amount of ionizing radiation energy absorbed, the type of radiation, and the likelihood of organ damage.

"The dose of thyroid exposure in children in Fukushima is much lower compared to those in Chernobyl," Yamashita told ***Endocrine News***. "We do not expect any significant increase of childhood thyroid cancer, but it is our responsibility to pay special attention and care to those suffering from the Fukushima nuclear disaster for a long time."

Yamashita reported that medical surveys have been shipped to more than two million people to determine the whereabouts of every resident from the time of the March 11 accident onward. So far, about 430,000 surveys have been returned (21 percent response rate). In an effort to examine target populations, more than 360,000 thyroid ultrasound exams have been conducted on residents under age 18 in the last year. Residents' mental health and lifestyle will also require lifelong monitoring.

Reports of the lasting health damage to Chernobyl residents spurred some of the concern in Fukushima. According the World Health Organization (WHO), nearly 5,000 cases of thyroid cancer have been diagnosed to date among children who were 18 years old or younger at the time of the accident and lived in the most contaminated areas of Belarus, the Russian Federation, and Ukraine. A lot of the exposure occurred from the radioactive iodine deposited in pastures where cows grazed; children later consumed the contaminated milk. The health risks from the two disasters, however, are far apart, experts said.

"Comparing the health consequences of Fukushima to Chernobyl is a bit like comparing a mouse to an elephant," said Thomas McKone, Ph.D., deputy for research at the Lawrence Berkeley National Laboratory and adjunct professor in the School of Public Health at the University of California, Berkeley.

Unlike Chernobyl, there were fewer radioactive elements and significantly less total radiation released at Fukushima, he said.

"Residents near Fukushima were monitored, evacuated, and given potassium iodide to minimize doses from iodine isotopes, while in Chernobyl the authorities delayed evacuations for many days and didn't use potassium iodide, which resulted in significant population exposures and health consequences," McKone explained.

Potassium iodide floods the thyroid with iodine thus preventing radioactive iodine from being absorbed. According to the ATA, if taken at the proper time, the potassium iodide can protect the thyroid from radioactive iodine from all sources, including air, food, milk, and water.

Despite these optimistic reports, the Japanese government and the nuclear operator Tokyo Electric Power Co. (Tepco) were recently criticized harshly for the Fukushima Daiichi plant disaster. A 641-page report released in July by an independent parliamentary panel found that regulators and nuclear operators disregarded warnings that the plant was a safety risk because of its vulnerability to earthquake damage. The panel further accused Tepco and government officials of slow and faulty communication after the disaster, which hindered emergency response.

The officials, the report said, "effectively betrayed the nation's right to be safe from nuclear accidents." ■

Fauntleroy is a freelance writer in Carmel, Indiana.

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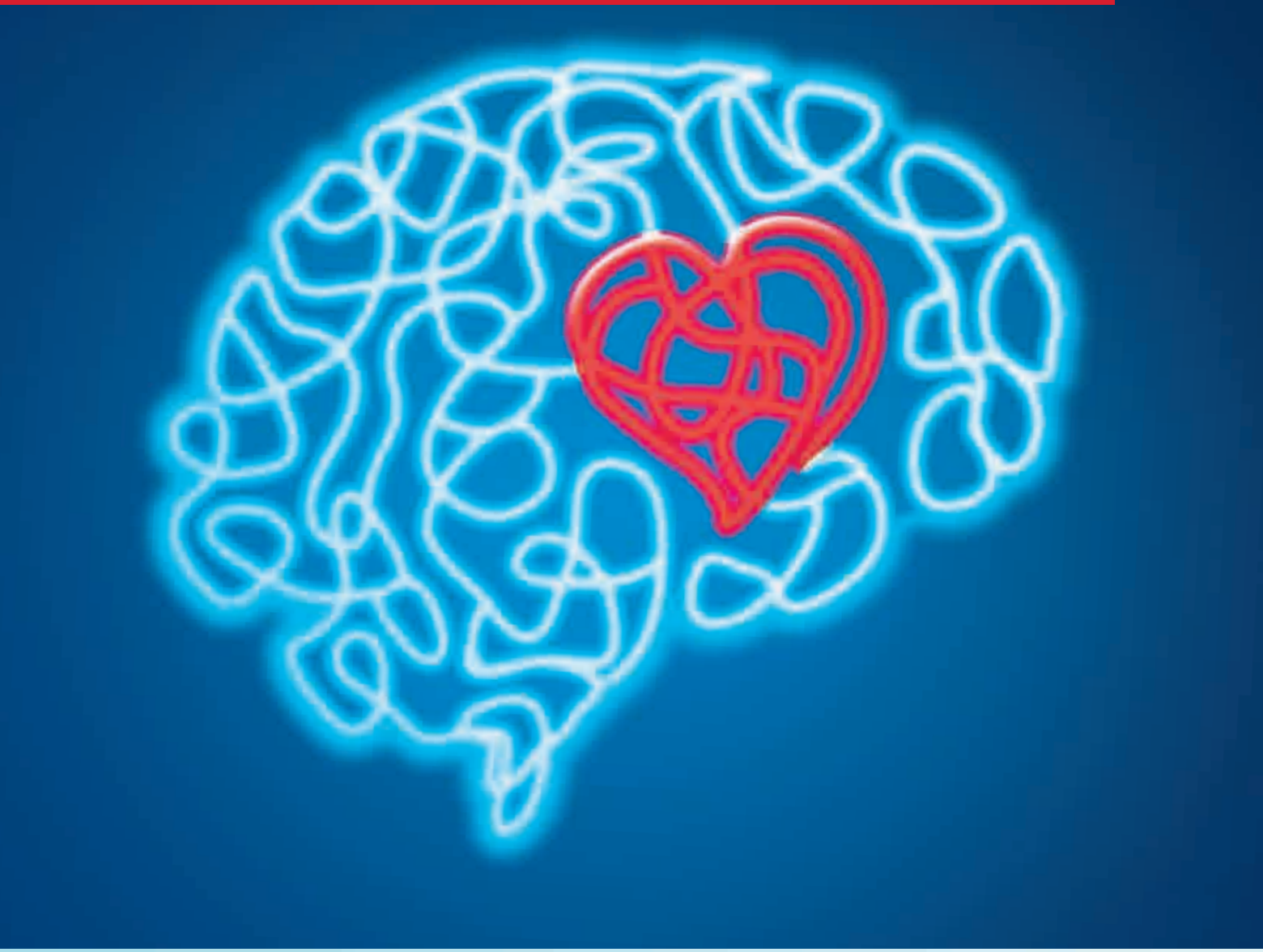

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CYCLOSET is contraindicated in patients with hypersensitivity to ergot-related drugs, bromocriptine, or any of the excipients in CYCLOSET. Do not use in patients with syncopal migraines. It may precipitate hypotension. Do not use in nursing women.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

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

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

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

Safety and effectiveness have not been established in pediatric patients.

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

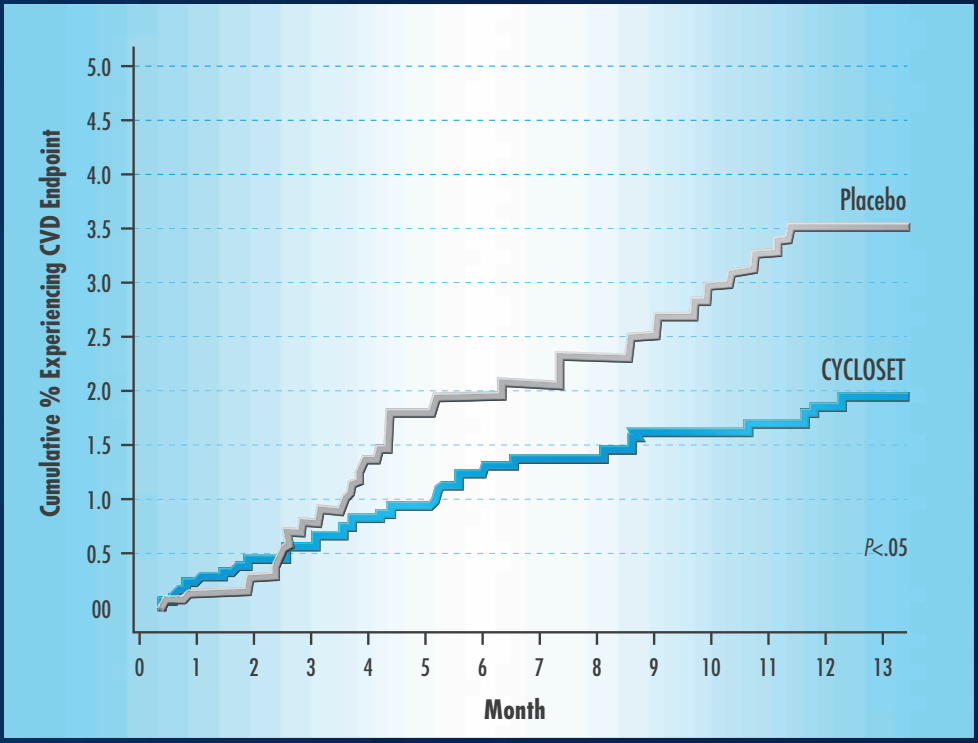
Please see adjacent Brief Summary of Prescribing Information.
Full Prescribing Information available at www.cycloset.com.

Improved glycemic control*

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

Demonstrated CV safety profile‡

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



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

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

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

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

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

Reference: Data on File. Santarus, Inc.

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

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

SANTARUS, INC.®

CYCLOSET®
bromocriptine mesylate tablets

CYCLOSET®
bromocriptine mesylate tablets

Brief Summary of Prescribing Information

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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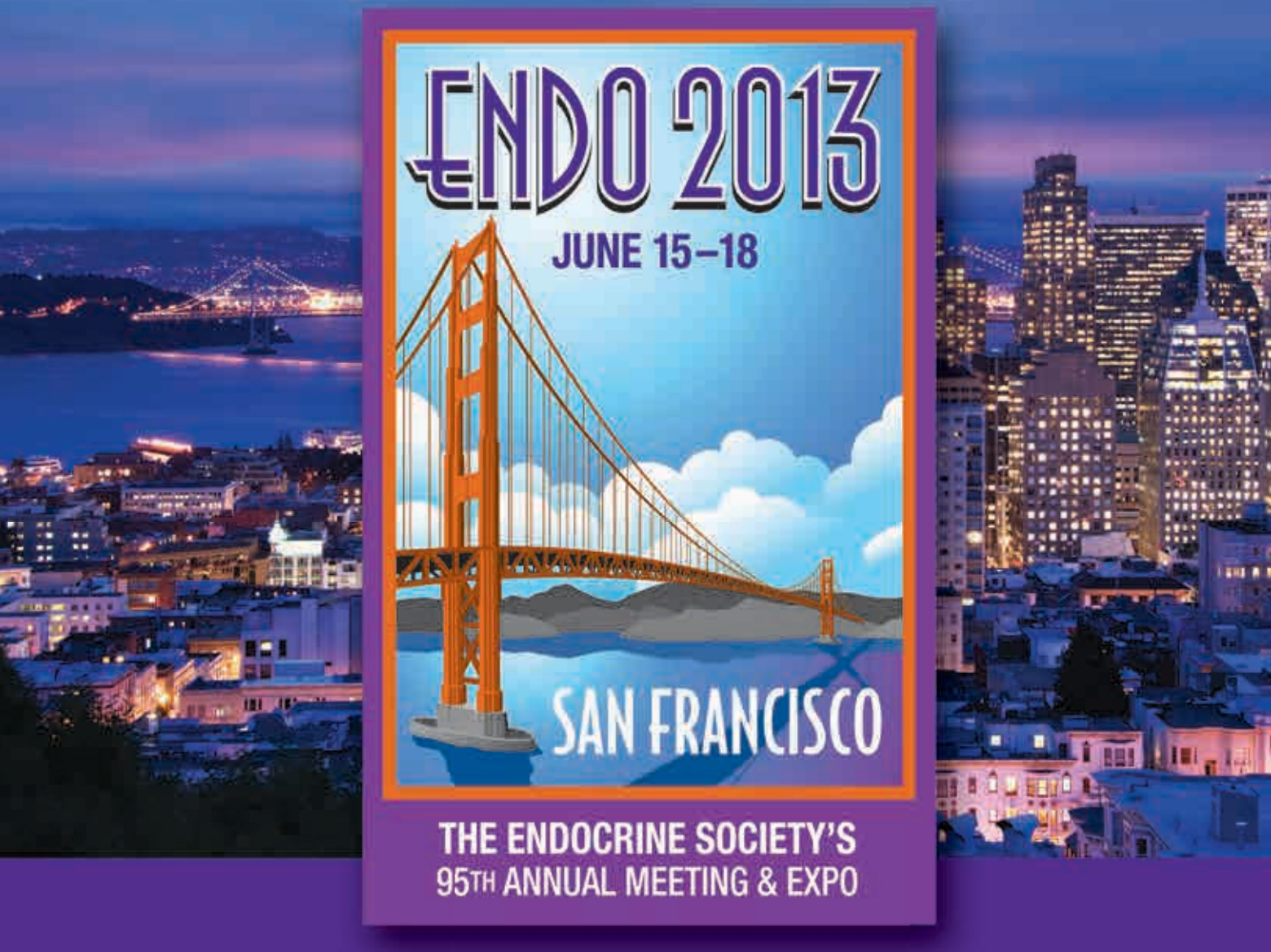

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New Diagnostic Test Promises Huge Reduction in Thyroid Surgeries

By Glenda Fauntleroy

A new test designed to identify benign thyroid nodules that were originally diagnosed inconclusive might spare tens of thousands of patients unnecessary invasive surgery each year, according to two recent research studies.

The studies published in the *New England Journal of Medicine* (*NEJM*) and *Thyroid* investigated a diagnostic test known as the Afirma Gene Expression Classifier (GEC), a genomic test developed by Veracyte, Inc. located in South San Francisco, California. Both studies were funded by research grants from the molecular diagnostics company.

The American Cancer Society (ACS) estimates that 56,460 new cases of thyroid cancer will be diagnosed in the United States in 2012, and the chance of being diagnosed is more than twice what it was in 1990. According to the ACS, most thyroid nodules that develop in patients are benign, but 1 in 20 is cancerous.

The simplest way to diagnose whether or not a thyroid nodule is malignant is with a fine-needle aspiration (FNA), and about 450,000 nodule FNAs are performed each year in the U.S. In about 30 percent of cases, the results are ambiguous and current guidelines recommend surgery for most of these patients to remove all or part of their thyroid for final diagnosis—an invasive option that may result in lifelong thyroid hormone therapy for the patient.

The goal of the new gene-expression test, which became available to endocrinologists in early 2011, is to help reduce thyroid surgeries due to inconclusive nodules by using cutting-edge diagnostic techniques. The Afirma procedure begins with a cytopathology review of thyroid nodule FNA samples. If the results are inconclusive, Veracyte follows up with its gene expression classifier. At the company's laboratory, technicians extract RNA from the sample. The RNA is then affixed to a microarray embedded with 142 genes known to be specifically expressed in either benign or malignant thyroid tissue. The gene chip also includes another 25 genes expressed in rare cancers. A computer scan of the microarray shows which genes the sample RNA binds to; a proprietary algorithm then classifies the sample as either benign or suspicious for cancer. Doctors typically receive genomic test results within two weeks.

265 Indeterminate Samples

In the *NEJM* study published in the August issue, researchers enrolled 3,789 patients and collected 4,812 thyroid FNA samples from nodules at least 1.0 cm in size over a two-year period. Forty-nine academic and community sites participated around the country. Samples were simultaneously collected for local cytopathology analysis and for the study. If the local cytopathology result was indeterminate, the study sample was then analyzed using the GEC test. Researchers analyzed 265 cytologically indeterminate thyroid FNA samples from patients who had undergone surgical thyroidectomy. The findings showed that the genomic test could reclassify the inconclusive samples as "benign" with a high degree of accuracy.

When applied to the major categories of indeterminate samples (those with cytology labeled: "atypical of an undetermined significance"

Technicians at Veracyte's laboratory in California use the gene expression classifier to process thyroid FNA samples.

Photographs by Kent Clemenco.

or "follicular neoplasm"), the genomic test reclassified most as benign and demonstrated a negative predictive value (NPV) of 95 percent and 94 percent, respectively, for a population that demonstrated a 32 percent prevalence of malignancy. Overall, the NPV was 93 percent, based on the study's cancer prevalence rate of 32 percent.

"Presently, patients with cytologically indeterminate thyroid nodules are usually referred for thyroid surgery to ensure that thyroid cancer is not present," said co-author Erik K. Alexander, M.D., of Brigham and Women's Hospital and Harvard Medical School. "The gene expression test, when benign, should now enable physicians to consider recommending against surgery, given the low risk of carcinoma conveyed by a negative GEC results, and confidently monitor patients in a more conservative fashion."

Surgery Rates Plummet

In the second study, appearing online in July in *Thyroid,* investigators aimed to answer whether endocrinologists would accept the GEC results and avoid surgery for their patients.

Researchers collected data from 51 endocrinologists at 21 community practices and academic settings on 368 adult patients (ages 21–86 years) who underwent a combined total of 395 biopsies. The participating practices all had three or more benign GEC readings in nodules of at least 1.0 cm with indeterminate FNA cytology readings. Information about the patients' conditions and the decision to operate was obtained from the practice records.

The study's findings showed that the surgery rate for patients with indeterminate thyroid cytology fell from the previously reported rate of 74 percent to 7.6 percent among patients whose GEC test results were classified as benign. The results illustrated that the use of the GEC reduced surgery rates by 90 percent—a drop that was larger than expected, even to investigators.

"We anticipated that the use of the test would lead to a significant reduction in surgery, though not to the extent that we actually found," said co-author Bryan McIver, M.B., Ph.D., in the Division of Endocrinology at Mayo Clinic in Rochester, Minnesota.

Were any of the physicians participating in the study hesitant about trusting the classifier's results?

"It is important to emphasize that the study, by its nature, included physicians who were 'early adopters' of this new technology," explained McIver. "That level of enthusiasm could, of course, mean that these physicians were more likely to be 'true believers' in the technology, so more likely to encourage their patients to avoid surgery."

> 'Longer term follow-up of these patients will be important in regard to how many ultimately went to surgery irrespective of the GEC result,' Wartofsky said.

McIver added that the *NEJM* study would likely "cement" substantial trust in the GEC and lead more physicians to adopt the test, thereby, expanding the number of patients who are recommended to avoid surgery.

In an accompanying editorial in *NEJM,* J. Larry Jameson, M.D., Ph.D., pointed out that "5 to 10 % of nodules classified as benign (false negative) are likely to be malignant." For such high-risk patients, "it might be reasonable to repeat the fine-needle aspiration biopsy or perform a diagnostic hemithyroidectomy even when the gene expression classifier indicates a benign profile," he suggested.

Study Projects Big Savings

Leonard Wartofsky, M.D., chairman of the Department of Medicine at Washington Hospital Center in Washington, D.C. has taken a wait-and-see stance regarding the GEC's impressive results. "Longer term follow-up of these patients will be important in regard to how many ultimately went to surgery irrespective of the GEC result," he said. "It is important to stress that non-operated patients still need to be followed long-term and monitored.

"The cost savings of not doing surgery needs to be balanced against the costs of follow-up for the patient, physician visits, potential repeat ultrasonography, and fine needle aspiration cytology," he cautioned.

A team of researchers from Johns Hopkins University conducted a statistical modeling study of the cost-effectiveness of routine use of the GEC. In results published last November in ***The Journal of Clinical Endocrinology & Metabolism,*** the researchers demonstrated that mean discounted-cost estimates were $12,172 for current practice and $10,719 with the molecular test during a modeled five-year follow-up for an average per-person savings of more than $1,400. Afirma GEC's developer, Veracyte, reported that these numbers would create a savings to the U.S. health care system of more than $600 million in direct costs over five years.

McIver added that he hopes the detailed cost-effectiveness analysis, based on real-world experience rather than a statistical model, will ultimately confirm the expectation that a reduced number of surgeries leads both to improved quality of life for patients and a reduction in overall health care expenditures. ■

Fauntleroy is a freelance writer based in Carmel, Indiana.

Hormone Health Network's

Patient Guide to Detecting and Treating Hyperthyroidism Before, During, and After Pregnancy

Thyroid dysfunction—changes in how well your thyroid gland works—can start during or after pregnancy in women who never had thyroid problems before. This occurs because pregnancy causes major changes in the levels of hormones made in the thyroid gland.

When the thyroid makes too much of the thyroid hormones T3 and T4, it is called overactive thyroid or hyperthyroidism. This problem also causes very low levels of thyroid stimulating hormone (TSH), a hormone that tells the thyroid to make T3 and T4. This is because too much T3 and T4 in the body causes TSH production to shut down. An overactive thyroid greatly increases metabolism (how your body uses energy). It most often affects women ages 20 to 40, in their childbearing years.

Fortunately, hyperthyroidism during pregnancy is not common. However, the symptoms may be overlooked because some can mimic the hormonal changes a woman has in a normal pregnancy: for instance, feeling too warm, tired, or anxious. If left untreated, maternal hyperthyroidism poses a risk for both mother and baby. Pregnant women with uncontrolled hyperthyroidism can develop high blood pressure. There is also an increased risk of miscarriage, premature birth, and having a baby with a low birth weight.

This guide for patients comes from The Endocrine Society's 2012 practice guidelines for physicians about the detection and treatment of thyroid dysfunction during and after pregnancy.

What causes maternal hyperthyroidism?

A common cause of overactive thyroid in pregnant women is Graves' disease. This disease occurs when your immune system becomes overactive and forms antibodies (immune proteins) that attack the thyroid. This causes the gland to enlarge and make too much thyroid hormone. Most women with Graves' disease find out they have it and get treatment before they become pregnant.

Women with severe nausea and vomiting or those expecting twins may develop temporary hyperthyroidism. Called transient gestational thyrotoxicosis, this hyperthyroidism is due to high levels of a pregnancy hormone called human chorionic gonadotropin or hCG. Because it resolves by week 14 to 18 of pregnancy, women do not need antithyroid drugs to treat this condition.

Sometimes, hyperthyroidism starts during pregnancy because of nodules (small lumps) in the thyroid. These nodules make too much thyroid hormone.

The thyroid also can become overactive after childbirth. In the first year after giving birth, about 7 percent of women get postpartum thyroiditis (inflammation of the thyroid). This problem starts with hyperthyroidism. Most often, it clears up without treatment in a few weeks or months. But sometimes the inflammation leads to hypothyroidism, the opposite condition in which the thyroid gland doesn't make enough thyroid hormone. In most cases, this hypothyroidism goes away on its own.

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

What are the symptoms of maternal hyperthyroidism?

Symptoms of hyperthyroidism include

- Feeling too hot when others are comfortable
- Rapid heartbeat
- Trembling hands
- Weight loss even though you eat enough
- Tiredness and/or trouble sleeping
- Feeling irritable and anxious

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How is hyperthyroidism found?

Most often, women find out they are hyperthyroid before they become pregnant. To detect hyperthyroidism, your doctor does a physical exam and orders blood tests to measure your thyroid hormone levels. Low TSH levels plus high levels of T4 (also called thyroxine) indicate hyperthyroidism.

Another test for hyperthyroidism is the radioactive iodine uptake test. Pregnant and breastfeeding women should not have this test, so tell your doctor if you are expecting or nursing. (This test measures how much iodine your thyroid absorbs. The thyroid uses iodine to make thyroid hormone.)

It is important to find out the cause of your overactive thyroid so your doctor knows if you need treatment or not.

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

What is the treatment for maternal hyperthyroidism?

During pregnancy. The preferred treatment for pregnant women with hyperthyroidism due to Graves' disease is antithyroid medication. These drugs prevent the thyroid from making too much thyroid hormone. Temporary (gestational) hyperthyroidism does not need this treatment.

Pregnant women with Graves' hyperthyroidism or thyroid nodules should start antithyroid drug treatment or, if already taking this medication, see their doctor about the dose. Hyperthyroidism due to Graves' disease most often improves as pregnancy advances but may worsen during the first six months after birth. Therefore, your doctor may need to change your dose of antithyroid medicine both during and after pregnancy.

In the first trimester of pregnancy, the preferred drug to treat hyperthyroidism is propylthiouracil (PTU). Another antithyroid drug, methimazole, may cause birth defects if taken during early in pregnancy. Women may need to take methimazole in the first three months of pregnancy if they cannot tolerate PTU.

After the first trimester, experts recommend switching from PTU to methimazole. This is because in rare cases PTU can cause severe liver injury. Both drugs are equally effective. Talk to your doctor about the benefits and risks of these medicines, and which is the best choice for you.

Antithyroid medication can treat most cases of Graves' disease in pregnancy. Rarely, some women may need surgery to remove part of the thyroid. The best time for this surgery during pregnancy is the second trimester (months 4 through 6).

Women who are or may be pregnant should not receive treatment with radioactive iodine. This radioactive drug usually destroys the patient's thyroid gland to stop it from being overactive, and also can harm the unborn baby's thyroid.

While breastfeeding. Women who are breastfeeding should not get radioactive iodine treatment. They may continue antithyroid drug therapy if they take their medicine as prescribed.

Will your baby need special care?

Most people with Graves' disease have measurable antibodies in their blood known as thyroid stimulating immunoglobulins. In pregnant women with Graves' disease, these antibodies can pass across the placenta to the baby. Though it does not occur often, this can cause thyroid disease and other medical problems for the newborn. All newborns of mothers with Graves' disease who are positive for these antibodies should be checked for signs of thyroid problems and treated if necessary.

What can you do to help have a healthy baby?

You can help ensure both your baby's health and your own health. Work with your pregnancy care provider and your endocrinologist, a specialist who treats hormone-related conditions, to receive proper medical care before, during, and after pregnancy. Take your medication as prescribed.

Your doctor can advise you on pregnancy planning. If you have active Graves' disease, delay pregnancy until your disease is well controlled. Also, if you had radioactive iodine treatment, wait 6 to 12 months before trying to become pregnant.

EDITORS

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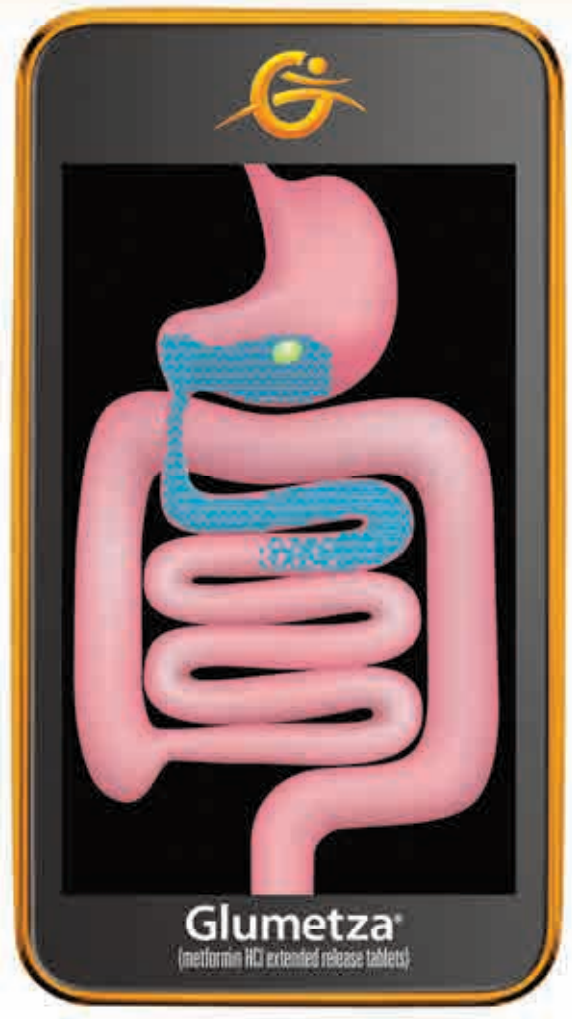
August 2012

This patient guide is the first of three guides based on The Endocrine Society's revised clinical guidelines on thyroid dysfunction in pregnancy. Part 2 addresses maternal hypothyroidism, and part 3 deals with thyroid nodules and thyroid cancer.

GLUMETZA®: Unique, controlled delivery may improve



IMPORTANT SAFETY INFORMATION ABOUT GLUMETZA

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning

- Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. (5.1)
- Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. (5.1)
- If acidosis is suspected, discontinue GLUMETZA and hospitalize the patient immediately. (5.1)

GLUMETZA is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see **WARNINGS and PRECAUTIONS** (5) of the Full Prescribing Information).
- Known hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those

tolerability and help more patients get to A1C goal

TECHNOLOGY

GLUMETZA provides a unique, advanced polymer technology* that may help reduce GI adverse events in your patients

- GLUMETZA targets the upper GI tract for slow delivery over 8-9 hours,[1] providing consistent 24-hour control

TOLERABILITY

Well tolerated, with no significant increase in adverse events at higher doses

- <1% of GLUMETZA patients discontinued due to GI adverse events in Week 1[2†]; starting dose was 1000 mg

A1C CONTROL

Improved tolerability‡ may help more patients reach A1C goal

- More patients reached goal with GLUMETZA 2000 mg QD versus Glucophage® 1500 mg/day[1,3§]

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with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

In clinical trials, the most common side effects with GLUMETZA monotherapy were diarrhea, nausea, dyspepsia, and upper abdominal pain. In clinical trials of GLUMETZA combined with a sulfonylurea, the most common side effects included hypoglycemia, diarrhea, and nausea.

*GLUMETZA 500 mg utilizes patented AcuForm® gastric retention technology. GLUMETZA 1000 mg utilizes patented Smartcoat® gastric retention technology.[4]

†Findings from a 24-week, noninferiority clinical trial comparing different GLUMETZA dosing regimens vs Glucophage® (metformin hydrochloride tablets). GLUMETZA patients were initiated with 1000 mg (2 X 500 mg QD) for 1 week, then titrated to their randomly assigned dose over 2 to 3 weeks, and remained on this dose for the remainder of the study unless discontinuation was warranted.

‡The overall incidence of drug-related adverse events was similar with GLUMETZA dosed up to 2000 mg/day vs Glucophage 1500 mg/day: 33% vs 35%, respectively.[2§]

§From a supplementary analysis of the findings from a 24-week, 4-arm, noninferiority trial comparing different GLUMETZA dosing regimens vs Glucophage. Note: 40.6% of patients (n=182) reached A1C goal with GLUMETZA 1500 mg BID (dosed 500 mg AM; 1000 mg PM).

‖Some restrictions apply. Please see the eVoucherRx™ and Savings Card Program Brochure for Terms and Conditions. Santarus reserves the right to modify or cancel these offerings at any time.

References: 1. Foster RH, Keam SJ. Metformin extended release. *Am J Drug Deliv.* 2006;4(3):1-11. **2.** Schwartz S, Fonseca V, Berner B, Cramer M, Chiang YK, Lewin A. Efficacy, tolerability, and safety of a novel once-daily extended-release metformin in patients with type 2 diabetes. *Diabetes Care.* 2006;29(4):759-764. **3.** Glumetza [package insert]. San Diego, CA. Santarus, Inc. 2011. **4.** Data on file. Santarus, Inc.

Glumetza®
(metformin HCl extended release tablets)

SANTARUS, INC.®

1-GLM12199 08/2012

GLUMETZA®
(metformin hydrochloride extended release tablets)
BRIEF SUMMARY OF PRESCRIBING INFORMATION

BEFORE PRESCRIBING, CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USE—GLUMETZA (metformin hydrochloride extended release tablets) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS—

GLUMETZA is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia. (See **WARNINGS AND PRECAUTIONS**)
- Known hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.

WARNINGS AND PRECAUTIONS

Lactic Acidosis

Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUMETZA and is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate concentrations (> 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years. In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, particularly when accompanied by hypoperfusion and hypoxemia due to unstable or acute failure, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking GLUMETZA. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. GLUMETZA treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, GLUMETZA should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUMETZA should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking GLUMETZA, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, GLUMETZA should be temporarily discontinued prior to any intra vascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may frequently cause dose-dependent metabolic acidosis (In controlled trials, 32% and 67% for adjunctive treatment in adults and pediatric patients, respectively, and 15 to 25% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 20 mEq/L; 3% and 11% for adjunctive treatment in adults and pediatric patients, respectively, and 1 to 7% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 17 mEq/L) and may exacerbate the risk of metformin-induced lactic acidosis. (See Drug Interactions and Clinical Pharmacology) The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis.

Patients should be educated to promptly report these symptoms should they occur. If present, GLUMETZA should be withdrawn until lactic acidosis is ruled out. Serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Once a patient is stabilized on any dose level of GLUMETZA, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUMETZA do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly-controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUMETZA, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See CONTRAINDICATIONS)

Monitoring of Renal Function

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Therefore GLUMETZA is contraindicated in patients with renal impairment.

Before initiation of GLUMETZA and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (e.g., elderly), renal function should be assessed more frequently and GLUMETZA discontinued if evidence of renal impairment is present. Metformin treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis.

Use of concomitant medications that may affect renal function or metformin disposition — Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **DRUG INTERACTIONS**), should be used with caution.

Radiological studies and surgical procedures:

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, GLUMETZA should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

GLUMETZA therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Hypoxic States

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUMETZA therapy, the drug should be promptly discontinued

Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake while receiving GLUMETZA

Impaired Hepatic Function

Because impaired hepatic function has been associated with some cases of lactic acidosis GLUMETZA should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels

In controlled, 29-week clinical trials of immediate release metformin, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUMETZA or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUMETZA and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at two- to three-year intervals may be useful.

Hypoglycemia

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with GLUMETZA or any other oral anti-diabetic 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 clinical practice.

In clinical trials conducted in the U.S., over 1000 patients with type 2 diabetes mellitus have been treated with GLUMETZA 1500-2000 mg/day in active-controlled and placebo-controlled studies with the 500 mg dosage form.

In the 24-week monotherapy trial comparing GLUMETZA to immediate-release metformin, serious adverse reactions were reported in 3.6% (19/528) of the GLUMETZA-treated patients compared to 2.9% (5/174) of the patients treated with immediate-release metformin. In the add-on to sulfonylurea study, patients receiving background glyburide therapy were randomized to receive add-on treatment of either one of three different regimens of GLUMETZA or placebo. In total, 431 patients received GLUMETZA and glyburide and 144 patients received placebo and glyburide. A serious adverse reaction was reported in 2.1% (9/431) of the GLUMETZA and glyburide-treated patients compared to 1.4% (2/144) of the placebo and glyburide-treated patients. When the data from the monotherapy and add-on to sulfonylurea clinical trials were combined, the most frequently (incidence ≥ 0.5%) reported serious adverse reactions classified by system organ class were gastrointestinal disorders (1.0% of GLUMETZA-treated patients compared to 0% of patients not treated with GLUMETZA) and cardiac disorders (0.4% of GLUMETZA-treated patients compared to 0.5% of patients not treated with GLUMETZA). Only 2 serious adverse reactions (unstable angina [n=2] and pancreatitis [n=2]) were reported in more than one GLUMETZA-treated patient.

Adverse reactions reported in greater than 5% of patients treated with GLUMETZA that were more common in the combined GLUMETZA and glyburide group than in the placebo and glyburide group are shown in Table 1.

In 0.7% of patients treated with GLUMETZA and glyburide, diarrhea was responsible for discontinuation of study medication compared to no patients in the placebo and glyburide group. Table 1: Adverse Reactions Occurring in 1% or More of Patients on Omeprazole Therapy from U.S. Studies

Table 1: Treatment-Emergent Adverse Reactions Reported By >5%* of Patients for the Combined GLUMETZA Group Versus Placebo Group

Adverse Reaction	GLUMETZA + Glyburide (n = 431)	Placebo + Glyburide (n = 144)
Hypoglycemia	13.7%	4.9%
Diarrhea	12.5%	5.6%
Nausea	6.7%	4.2%

*AE's that were more common in the GLUMETZA-treated than in the placebo-treated patients.

Laboratory Tests

Vitamin B_{12} concentrations

Metformin may lower serum vitamin B_{12} concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on GLUMETZA and any apparent abnormalities should be appropriately investigated and managed. (See **WARNINGS AND PRECAUTIONS**)

DRUG INTERACTIONS

Carbonic Anhydrase Inhibitors—

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with metformin, as the risk of lactic acidosis may increase.

Cationic Drugs—

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GLUMETZA and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Drugs Affecting Glycemic Control—

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered to a patient receiving GLUMETZA, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving GLUMETZA, the patient should be observed closely for hypoglycemia.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category B

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, which represent 3 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparison for rats and rabbits, respectively. However, because animal reproduction studies are not always predictive of human response, Metformin HCl should not be used during pregnancy unless clearly needed.

Labor and Delivery

The safety and effectiveness of GLUMETZA used during labor and delivery has not been evaluated in human studies.

Nursing Mothers

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Thus, the potential for hypoglycemia in nursing infants after Metformin HCl Oral Solution may exist.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. GLUMETZA is not recommended in pediatric patients below the age of 18 years.

Geriatric Use

Clinical studies of GLUMETZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. (See **WARNINGS AND PRECAUTIONS**)

OVERDOSAGE

No cases of overdose were reported during GLUMETZA clinical trials. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea, and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded.

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. (See **WARNINGS AND PRECAUTIONS**) Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

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RESEARCH BRIEFS

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

Endocrinology

➤ **In mice fed a low-fat diet, angiotensin II regulates adipocyte differentiation and morphology via the AT1aR; this finding could be useful in diseases associated with cachexia.**
Putnam K, Batifoulier-Yiannikouris F, Bharadwaj KG, et al. *Deficiency of angiotensin type 1a receptors in adipocytes reduces differentiation and promotes hypertrophy of adipocytes in lean mice.*

➤ **The actin regulatory protein, filamin A, is involved in rat BTB assembly.**
Su W-h, Mruk DD, Lie PPY, Lui W-y, Cheng Y. *Filamin A is a regulator of blood-testis barrier assembly during postnatal development in the rat testis.*

➤ **Chemerin levels are elevated in a 5α-dihydrotestosterone–induced rat PCOS model.**
Wang Q, Kim JY, Xue K, Liu J-y, Leader A, Tsang BK. *Chemerin, a novel regulator of follicular steroidogenesis and its potential involvement in polycystic ovarian syndrome.*

➤ **Elephant shark MC2R is the first vertebrate MC2R that does not require MRAP1 for functional activation and can use either ACTH or MSH-sized ligands, these characteristics help separate cartilaginous fishes from bony fishes.**
Reinick CL, Liang L, Angleson JK, Dores RM. *Identification of an MRAP-independent melanocortin-2 receptor: Functional expression of the cartilaginous fish,* Callorhinchus milii, *melanocortin-2 receptor in CHO cells.*

The Journal of Clinical Endocrinology & Metabolism

➤ **ALL treatment in childhood without cranial radiation may not result in long-term bone deficits.**
Mostoufi-Moab S, Brodsky J, Isaacoff EJ, et al. *Longitudinal assessment of bone density and structure in childhood survivors of acute lymphoblastic leukemia without cranial radiation.*

➤ **Endometrial S100A11 plays an important role in intracellular Ca^{+2} homeostasis, embryo implantation, and pregnancy outcomes.**
Liu X-M, Ding G-L, Jiang Y, et al. *Down regulation of S100A11, a calcium-binding protein, in human endometrium may cause reproductive failure.*

➤ **Visceral adipose tissue and bone marrow fat are detrimental to bone, whereas muscle mass, testosterone, estradiol, and growth hormone are beneficial.**
Bredella MA, Lin E, Gerweck AV, et al. *Determinants of bone microarchitecture and mechanical properties in obese men.*

➤ **Lower vitamin D levels in offspring may occur if the child was exposed in utero to ambient urban air pollution.**
Baïz N, Dargent-Molina P, Wark JD, et al. *Gestational exposure to urban air pollution related to a decrease in cord blood vitamin D levels.*

➤ **Subclinical hyperthyroidism in the elderly is linked to dementia.**
Gan EH, Pearce SHS. *The thyroid in mind: Cognitive function and low thyrotropin in older people.*

Molecular Endocrinology

➤ **A negative feedback mechanism for glucose-stimulated insulin secretion involving dopamine might explain the increased adiposity seen with antipsychotics and the recurrence of type 2 diabetes following sleeve gastrectomy.**
Simpson N, Maffei A, Freeby M, et al. *Dopamine mediated autocrine inihibitory circuit regulating human insulin secretion in vitro.*

➤ **AR is involved in the crosstalk between macrophages and prostate epithelial cells.**
Lu T, Lin W-J, Izumi K, et al. *Targeting androgen receptor to suppress macrophage-induced EMT and benign prostatic hyperplasia (BPH) development.*

➤ **A ghrelin-glucagon axis is activated to control glycemia under fasting conditions.**
Chuang J-C, Sakata I, Kohno D, et al. *Ghrelin directly stimulates glucagon secretion from pancreatic alpha-cells.*

➤ **In mice, macrophages suppress the renin-angiotensin system, and thus atherosclerosis, through vitamin D receptor signaling.**
Szeto FL, Reardon CA, Yoon D, et al. *The vitamin D receptor signaling inhibits atherosclerosis in mice.*

October 2012 issue of *Endocrine Reviews*

Randeva HS, Tan BK, Weickert MO, et al. *Cardiometabolic aspects of the polycystic ovary syndrome.*

Limonta P, Marelli MM, Mai S, Motta M, Martini L, Moretti RM. *GnRH receptors in cancer: From cell biology to novel targeted therapeutic strategies.*

Kang J, Rivest S. *Lipid metabolism and neuroinflammation in Alzheimer's disease: A role for liver X receptors.*

Ke HZ, Richards WG, Li X, Ominsky MS. *Sclerostin and dickkopf-1 as therapeutic targets in bone diseases.*

Mortensen KH, Andersen NH, Gravholt CH. *Cardiovascular phenotype in Turner syndrome—integrating cardiology, genetics, and endocrinology.* ■

TRAINEE CORNER

Communication Is Key to Good Mentoring

Dr. Steven Anderson, professor of pathology and vice chair for research in the Department of Pathology at the University of Colorado Anschutz Medical Campus, is a long-standing member of The Endocrine Society who has been actively involved in mentoring minority students and fellows with an interest in biomedical research. He currently serves as a member of the Advocacy and Public Outreach Core Committee (APOCC) and as principal investigator of the Society's Minority Access Program (MAP). Prior to joining APOCC, he served on the Minority Affairs Committee for six years and the Training Development Committee for two years. He has participated in career development events such as the Endocrine Trainee Day and the Minority Mentoring and Poster Reception at the Society's annual meeting. Dr. Anderson talked with ***Endocrine News*** about his experiences as a mentor.

Q: ***How did you get started in The Endocrine Society and what advice do you have for young people wanting to get involved?***

A: I joined the Society about 15 years after moving to Colorado in 1993. There are many active members of the Society in Denver who encourage you to join and become active. Getting involved in the activities allows you to meet people and extend your network of colleagues. Most importantly, you make the Society yours instead of it being a group that is run by others in which you have no part.

Q: ***What areas do you specialize in and what initiated your interest in these areas?***

A: My lab is interested in mammary gland development and tumorigenesis. I was trained as a cancer biologist and over time became interested in both normal and abnormal mammary gland development because they represent opposite sides of the same coin.

Q: What is an average day like in your life?

A: I review my schedule and priorities for the day before leaving the house. Answering e-mails then is the next priority, especially if they involve actions that have to be coordinated with others. Meetings usually start about 9 each day. In addition to my weekly lab meeting, I have weekly meetings with my trainees and collaborators on important projects, papers, and grants. I have an open-door policy so there are frequent interruptions. I close the door when I need to write in a focused manner. Ideally I go to the gym around 6:30 a.m. in order to get some regular exercise, although some days the evening is the only alternative.

Q: ***What is your most effective time-management skill?***

A: I strictly adhere to a schedule of weekly meetings and hold myself and others accountable to make the best use of this time. Meetings can be shortened, but I do not cancel them unless I am travelling. Rapid follow-up on these meetings keeps me from forgetting important tasks that need to be accomplished. The second most import time-management skill is to delegate. Asking for help is a critical survival skill.

Q: ***What have been some of the most rewarding or challenging moments of your career?***

A: Transitions from industry to academics or to a new institution are both the most challenging and rewarding. With each transition comes new expectations. The challenge of rejection—whether a grant or a paper—is clearly difficult, and yet finally succeeding in getting that grant funded is very rewarding.

Q: ***What is the riskiest career move you've ever made?***

A: My postdoctoral advisor moved to a pharmaceutical company during my first year in his lab, and I chose to go with him. Ultimately I chose to leave that company after four years and go to an academic institution. It was big jump to make without an active research program that I could move with me, and it meant starting everything from scratch. Grants were hard to get at that time, and I was fortunate to get my first NIH grant on its

Good mentors should challenge their trainees to be their best and to excel in their profession. Good communication is essential, as is a common set of goals for success. Trainees should communicate in an open and honest manner about what they want.

first submission. It was risky because I was not well prepared to run my own lab and everything required hard work on my behalf. There were supportive faculty members who helped me with the transition and provided important advice to me in the first few years.

Q: ***What do you consider the most important aspect of the mentor and trainee relationship?***

A: Good mentors should challenge their trainees to be their best and to excel in their profession. Good communication is essential, as is a common set of goals for success. Trainees should communicate in an open and honest manner about what they want. Frustrations in the lab or with one's career path are easier to address when there is open line of communication. This also requires being honest with one's self and open to criticism and change.

Q: ***Any other advice for trainees?***

A: The Society offers a terrific forum for expanding your network of colleagues and friends. At every ENDO meeting I look forward to renewing friendships, exploring new collaborations, and meeting new people. Despite the huge increase in electronic means to communicate, I am still a firm believer in face-to-face contact as the best and most meaningful way to meet people. ■

VISIT THE ENDOCRINE SOCIETY AT THE FOLLOWING CONFERENCES

SOCIETY FOR THE ADVANCEMENT OF CHICANOS AND NATIVE AMERICANS IN SCIENCE (SACNAS) 2012 ANNUAL CONFERENCE, SEATTLE
- Meeting Dates—October 11–14, 2012
- *www.sacnas.org*

ANNUAL BIOMEDICAL CONFERENCE FOR MINORITY STUDENTS (ABRCMS), SAN JOSE, CALIFORNIA
- Meeting Dates—November 7–10, 2012
- *www.abrcms.org*

FUTURE LEADERS ADVANCING RESEARCH IN ENDOCRINOLOGY (FLARE) WORKSHOP, SAN DIEGO
- Meeting Dates—January 25–26, 2013
- Program Application Deadline—November 14, 2012
- *www.endo-society.org/FLARE*

U.S. Labor Dept. Predicts a Surge in Health Industry Jobs

By John Bohannon

The future looks bleak for many Americans trying to launch a career. Recent college graduates have spent their entire adult life in a recession. About 1 in 10 won't find a job at all, let alone the job they want. That is, unless that job is related to health and medicine. According to a recent forecast by the U.S. Bureau of Labor Statistics, opportunities in health care fields are brighter than ever. The industry, which includes hospitals, family services, nursing and residential care facilities, is expected to increase overall by 33 percent, producing nearly six million new jobs.

Depending on the specific jobs, which encompass everything from physical therapy and personal care to surgery and biomedical engineering, the labor department projection of growth ranges from 20 to 70 percent by 2020. Jobs for physicians specializing in endocrinology stand to gain 22 percent. Even receptionist jobs at medical practices are expected to grow by 43 percent. Of the 30 fastest-growing jobs in the United States, half of them are in health care.

What's driving the boom? The baby boomers, in part. "People are getting older," says Sandra Raehl, president of allied staffing at CompHealth in Grand Rapids, Michigan. When a hospital or home care service provider runs short on staff, CompHealth finds health care experts to fill the gap. "Over the last couple of years, we've seen more need for therapists to go into the home," she says. "It's increased by double digits." As America grays, the health care industry will have to keep expanding to meet the need.

New Technology Creates Jobs

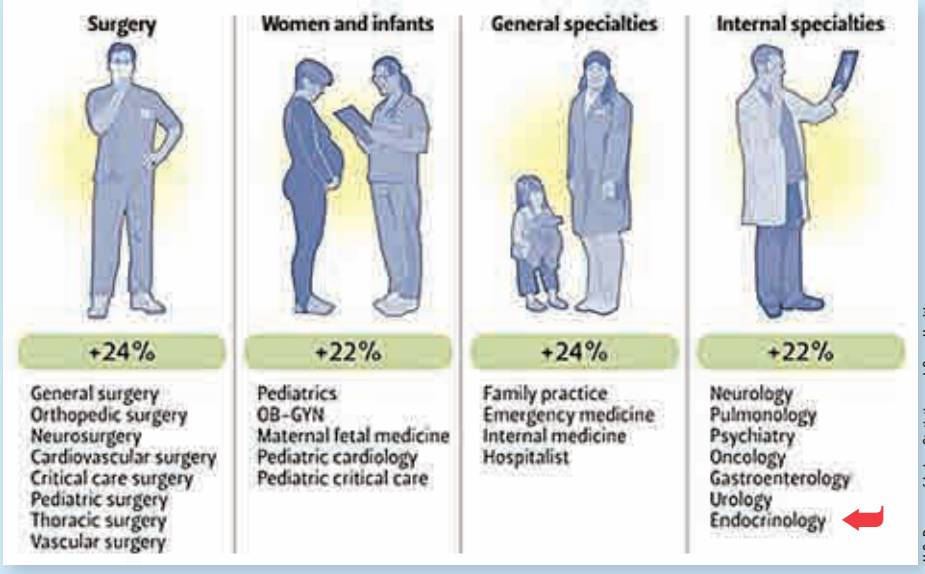
Beyond elderly care, the job explosion in health and medicine offers careers in such fields as dentistry, audiology, health care education, occupational and physical therapy, and mental health counseling.

"It's also advancements in medical technology," says Raehl. Diagnostic procedures that once took 10 minutes in the doctor's office now require a separate trip to a specialist. That trend is often cited as a reason for the staggering cost and inefficiency of U.S. health care, but there is no doubt that it drives growth in medical jobs. For every new medical device and technique, new jobs are created. The Bureau of Labor projects that jobs for medical diagnostic sonographers will almost double in the next decade.

Another reason for the job boom is the Affordable Care Act, President Obama's health insurance plan, experts say. "That's going to have a big impact," says Jorge Alberto Girotti, associate dean at the University of Illinois College of Medicine (UIC), in Chicago. "There are 30 million people who currently have no access to health care who will get it starting in 2014." And that influx is independent of the baby boomers because Medicare covers the elderly. "There's going to be a wave of people coming into the system," he says, "needing help with acute problems but also long-term chronic illness."

Girotti worries that

Projected Growth in Physician Specialties



U.S. Bureau of Labor Statistics and CompHealth.com

Although physician specialties are not among the Labor Department's list of fastest-growing health industry jobs, they are expected to experience a healthy bounce in the next decade.

the U.S. health care system will not be able to handle it. "That's going to be a lot of pressure and the system is already buckling," he says, noting a prediction by the Association of American Medical Colleges that the United States could see a shortfall of nearly 100,000 doctors by 2020.

"It takes a long time to train doctors, typically 11 to 13 years, and even more for professions like neurosurgery," he adds. Until medical schools expand, he predicts that non-physician professionals will be picking up the slack. "Nurses and physician assistants will have to take over many of the routine tasks that doctors currently do."

Whatever the future may hold, the health care industry is already throwing its weight around. "There's a ton of money to be made," says Natasha Mott, an endocrinology Ph.D. student at Loyola University in Maywood, Illinois. She hopes to defend her thesis in December, and for the next step, she has chosen to stay in academic research. "I feel kind of crazy for the decision," she admits.

"It takes a long time to train doctors," Girotti adds. "Nurses and physician assistants will have to take over many of the tasks that doctors currently do."

Another soon-to-be endocrinologist, Joanna Spencer, took the other path. She is now an endocrinology resident at the University of Michigan in Ann Arbor. Spencer says her employment outlook is undeniably rosy. "My job security is above and beyond that of any of my classmates. I was aware of that the whole time." But she adds that she is mostly driven by a passion for the field. "I like the mystery of endocrinology," she says. "You take a constellation of unrelated symptoms and try to make sense of them. It's a riddle." ■

Bohannon is a freelance writer in Boston.

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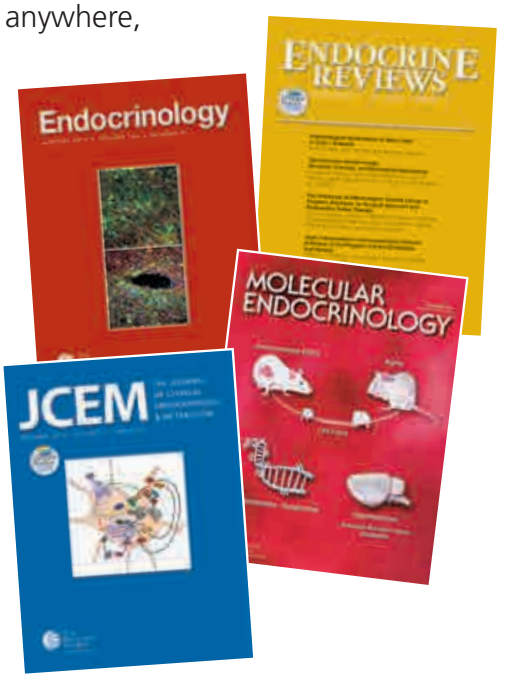

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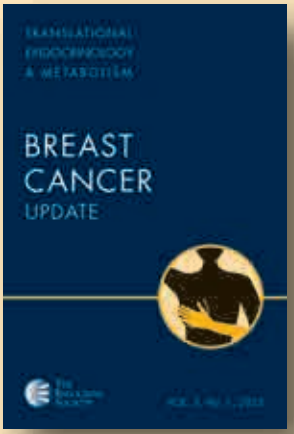

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Automatic Funding Cuts Imminent for Health Organizations

By Stephanie Kutler

Endocrine Society members who receive research grants from the federal government or care for Medicare patients face uncertainty in the near future regarding their funding due to an impending deficit cutting process known as sequestration. The Endocrine Society has taken an aggressive stance against these cuts, and is working directly with members of Congress to illustrate the impact of these cuts on researchers, physicians, and patients.

In 2011, Congress passed the Budget Control Act (BCA), which established caps on defense and nondefense discretionary (NDD) programs, including research funding and Medicare, that will reduce this funding by $1 trillion over 10 years. The BCA also created the Joint Select Committee on Deficit Reduction to develop a plan to reduce the deficit by another $1.2 trillion over the same period. In the event the Committee failed to come up with a viable plan, the BCA established "sequestration" as an incentive to force bipartisan compromise. A rigid budgetary tool, sequestration will force automatic, across-the-board cuts of another $1 trillion to nearly all government programs, including public health. Because the Committee has failed to produce an agreement, sequestration is scheduled to begin on January 2, 2013.

Estimates of the impact on individual federal agencies vary from 7.8 percent to 9.1 percent. The Federation of American Societies for Experimental Biology (FASEB), of which the Society is a member, offers an illustration of the impact to the National Institutes of Health based on fiscal year 2012 levels if a 9.1 percent cut were to be implemented. With a fiscal year 2012 budget of $30.8 billion, a 9.1 percent reduction to NIH's budget would be $2.8 billion. Cutting this amount from the NIH budget would be difficult and highly disruptive to ongoing efforts.

Moreover, not every activity can be reduced by 9.1 percent. For example, salary costs for federal employees cannot be reduced with the speed mandated by BCA. Some NIH activities, such as the intramural program ($3.4 billion), research management and support ($1.5 billion), and the Office of the Director ($0.6 billion), consist largely of salary expenses. If these activities (totaling $5.5 billion) are not subject to immediate reduction, then NIH would have to take $2.8 billion from the remaining extramural budget ($25.3 billion), which will require a reduction of 11.1 percent of extramural programs. Other organizations of which the Society is a member, including United for Medical Research and Research!America, have completed similar analyses with equally stark results. The Office of Management and Budget has estimated that NIH would issue 700 fewer grants in fiscal year 2013 than in the previous year.

The Medicare program would also be impacted by spending cuts resulting from the sequestration process. While Medicare benefits to patients would not be subject to budgetary cuts, healthcare professionals, including endocrinologists, would receive a 2 percent annual payment reduction from 2013 to 2021 in addition to an almost 30 percent reduction in reimbursement if Congress fails to pass a solution to the flawed sustainable growth rate formula by January 1, 2013. It is anticipated that a short-term fix will be passed to prevent the SGR cuts from taking effect.

The Society, however, will continue to actively engage lawmakers on Capitol Hill to pass a permanent solution that will address the needs of endocrinologists and other medical specialists. The organizations representing the interests of agencies funded through discretionary spending are working together to stop additional cuts to these programs. The Society is engaged in this large effort that extends beyond biomedical research and Medicare, and is meeting with members of Congress to advocate for a balanced approach to deficit reduction. ■

Kutler is Director of Government Affairs at The Endocrine Society.

Society update

Members of the Annual Meeting Steering Committee met recently to begin planning **ENDO 2013,** which will be held June 15–18, 2013, in San Francisco.

FLARE: Lighting the Way for Minority Scientists

As principal investigator of the Future Leaders Advancing Research in Endocrinology (FLARE) program, I am honored to share my thoughts on The Endocrine Society's newest endeavor to foster the development of the next generation of endocrine scientists. The FLARE program aims to provide research fellows and senior graduate students from underrepresented minority communities with necessary knowledge and skills to help them make the transition to independence and to have successful, rewarding careers in endocrine research. Underrepresented minorities in the biomedical sciences include African Americans, Hispanic Americans, Native Americans, Native Alaskan Eskimo or Inuit, and U.S. Pacific Islanders.

E. Dale Abel, M.D., Ph.D.
Professor of Medicine, Biochemistry and Human Genetics; Senior Investigator, Program in Molecular Medicine; Chief, Division of Endocrinology, Metabolism and Diabetes; University of Utah School of Medicine

Through a structured series of activities, FLARE participants will gain leadership skills and knowledge from expert Society mentors, will participate in meaningful mentoring activities, and will learn how to excel within a professional society through a governance internship program.

FLARE was developed in response to a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) request for grant proposals from professional societies for programs promoting diversity. The Society received a five-year, $733,000 grant from NIDDK to support the program, which started in August 2012.

Leadership development training is key to sustained success in any field. The FLARE program will distinguish itself as a key resource for positive and fundamental development of underrepresented minority scientists. This program will be especially valuable to endocrinology because it will strengthen the pipeline of minority scientists who will impact the research and treatment of endocrine disorders that disproportionately affect underserved communities. Accomplishing these goals requires involvement from everyone. The application deadline for fellows is mid-November. Whether you are a trainee or a senior member, the success of this program depends on you. If you are interested in applying or in learning more about how you can become a part of FLARE, please visit us at *www.endo-society.org/FLARE*.

FLARE
FUTURE LEADERS ADVANCING RESEARCH IN ENDOCRINOLOGY

2012 Endocrine Trainee Class

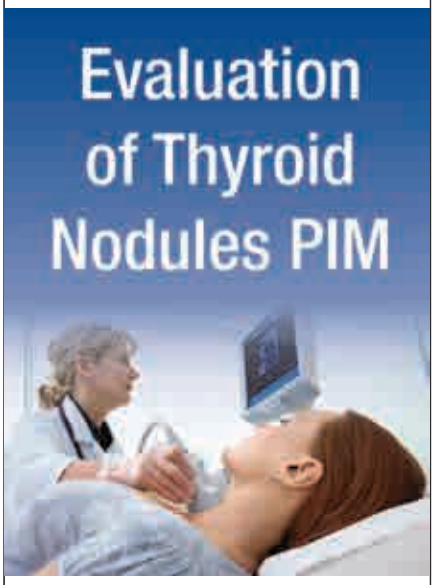
The Endocrine Trainee Day Class of 2012 gathered in Houston on Friday, June 22, 2012, the day prior to the start of ENDO 2012. The Society hosted more than 210 graduate and medical students, postdoctoral, and clinical fellows interested in learning about careers in endocrinology, developing essential career skills, and connecting with expert faculty. The Endocrine Trainee Day is co-sponsored by the Society's Trainee and Career Development Core Committee and Women in Endocrinology. Participants included 150 Trainee Day travel award winners and 60 paid attendees.

Sawin Library Books Available for Loan

The Clark T. Sawin Memorial Library has more than 4,500 books in its collection, and many of them are available for

loan as a free member benefit for Society members. Members may also schedule a time to visit the library to explore our collection of rare and historical texts from the founders of endocrinology. Learn more about the Sawin Library and search the library's online catalogue by visiting *www.endo-society.org/about/sawin* or to request that one of our thousands of books be sent by mail, contact the Endocrine Society's librarian at *librarian@endo-society.org*.

Thyroid Nodules: Targeted Education to Improve Patient Care



Thyroid cancer is generally a curable illness if detected and effectively managed. The recommended evaluation of thyroid nodules involves clinical examination, ultrasound, and other modalities. Research, however, suggests a high variability in practitioners' care of thyroid patients.

To increase awareness of "best practices," The Endocrine Society has released its first practice improvement module (PIM), The Evaluation of Thyroid Nodules PIM. PIMs are Web-based quality improvement tools that measure data and information from an individual practitioner or group practice against clinical performance measures. The thyroid-based PIM measures the national guidelines for thyroid nodule treatment developed by the American Thyroid Association and the American Association of Clinical Endocrinologists.

The module also provides a centralized list of resources and a measurement of practice change upon implementation of improvements.

For more information about this PIM and obtaining Maintenance of Certification credits for it, visit *endoselfassessment.org*.

Type 1 Transition of Care Resources Now Available

The Endocrine Society recognizes a significant need for better care coordination to ensure that pediatric and adult providers—and their patients—are fully prepared for transitions of care. Because every disease has a specific need in this regard, and especially those of a chronic and complex nature, the Society recently spearheaded an initiative to develop transition of care resources specific to type 1 diabetes. Developed by a working group comprising physician representatives from the Society, Hormone Health Network, American Academy of Pediatrics, American Diabetes Association, Pediatric Endocrine Society, American College of Physicians, Juvenile Diabetes Research Foundation, International Society for Pediatric and Adolescent Diabetes, and American Association of Diabetes Educators, the resources include: 1. a patient self-assessment for diabetes concerns; 2. a recommended approach to planning for pediatric practices; 3. a welcome to the practice guide; 4. a patient skill set; 5. a visitor information form; 6. a clinical summary; 7. an approach to the adolescent transitioning to the adult practice; and 8. educational fact sheets on issues faced by emerging adults with type 1 diabetes.

To access copies of these resources, please go to *www.endo-society.org/clinicalpractice/transition_of_care.cfm*. The Society plans to develop similar tools for congenital adrenal hyperplasia, Turner syndrome, and growth hormone deficiency and will alert its members once these resources become available.

Society Weighs in on Pediatric Obesity

Two weeks before all the sugary treats from Halloween come trickling in, in mid-October, The Endocrine Society will broadcast a Webinar on pediatric obesity, tackling such topics as the health effects of high-fructose corn syrup and diet soft drinks. See *www.endo-society.org/media/index.cfm* for more details. ■

In Memoriam

William Thomas Griffin, M.D.
Columbia, Missouri
1932–2012

Richard P. Levy, M.D.
Quechee, Vermont
d. 2012

Charles Robert Meloni, M.D.
Harrisburg, Pennsylvania
1927–2012

Hilton A. Salhanick, M.D., Ph.D.
Brookline, Massachusetts
1924–2012

James Claris Wright, Jr., M.D.
Indianapolis, Indiana
1930–2012

calendar

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

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

OCT 20: KANSAS CITY, MISSOURI
OCT 27: INDIANAPOLIS
NOV 10: NEW YORK CITY
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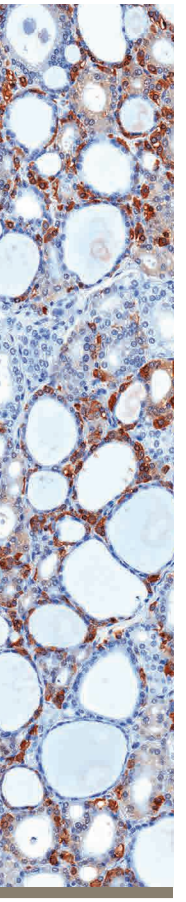
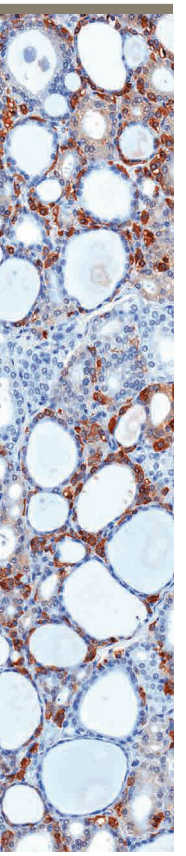


THE EVALUATION OF THYROID MODULE
Practice Improvement Module (PIM)



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

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

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

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

For more information visit endoselfassessment.org.

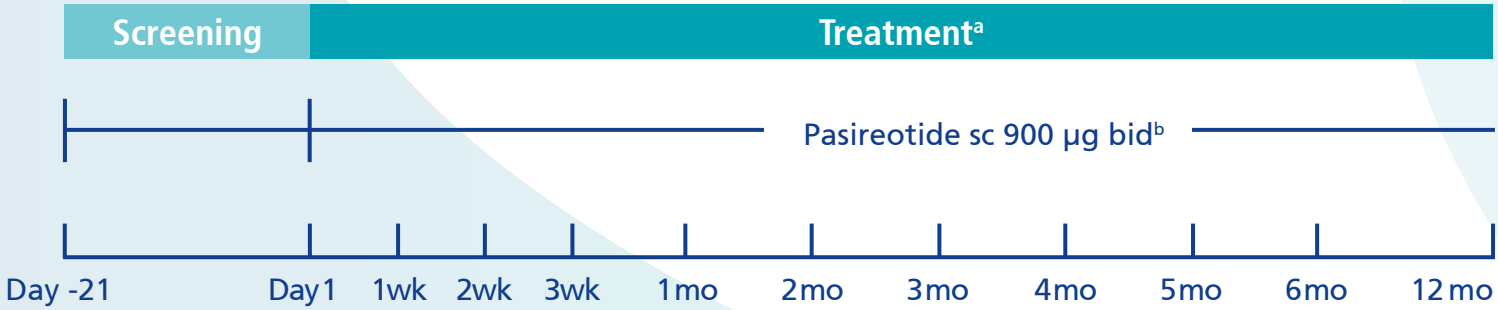
The Endocrine Society®

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

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

Enrolling now.

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



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

ELIGIBLE PATIENTS:

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

PRIMARY END POINT:

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

PASPORT

The PASPORT Research Program

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

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

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

ClinicalTrials.gov Identifier: NCT01582061

Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936-1080

6/12
SOM-1045462

Classifieds

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

Endocrinologist Needed in Growing Philadelphia Suburb

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

Endocrinologist

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

Pennsylvania Endocrinologist

Well respected endocrinology group with offices in upscale suburban Philadelphia seeks BE/BC endocrinologist for their successful practice. The group has two office locations and one of the offices will be expanding. The group is involved in both inpatient and outpatient care and the patient mix is heavily weighted toward diabetes and thyroid management. The practice has approximately 50–60 new patients weekly. A nurse educator is being added to the practice in the near future. Call will be l:5. Local residents in training rotate through the practice. The group is employed by a local hospital which will be moving to a new facility in October of this year. The offices are very near to the new facility. A competitive compensation package will be available to appropriate candidates along with excellent benefits. For further information please contact Malinda D. Hale, CMSR, President, Physician Options, Inc., 800-208-6088, e-mail: *malinda@VONL.com.* ■

ENDOCRINOLOGIST

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

Ochsner Baptist Medical Center, with a deep-rooted history in Uptown New Orleans, is a fully accredited, full-service hospital staffed by more than 390 physicians. We have all private rooms, an ICU, 13 operating rooms, and a state-of-the art imaging center. We are proud to be distinguished by our excellence in specialty care and high patient satisfaction scores. Our newly renovated 24-hour full-service emergency department is staffed by a team of board-certified ER physicians.

Ochsner Health System

The Ochsner Health System comprises 8 hospitals and more than 38 clinics across southeast Louisiana with over 1.5 million clinic patient visits annually. Ochsner is a major provider of graduate medical education with 23 ACGME-accredited residency and fellowship programs, including our Endocrinology Fellowship Program. Please visit our Web site at www.ochsner.org.

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

Please email CV to: profrecruiting@ochsner.org, Ref. # ABENDO1 or call 800-488-2240 for more information. EOE.

Sorry, no J-1 visa opportunities available.

University of Michigan
Medical School

Tenure Track Faculty Position
Division of Metabolism, Endocrinology & Diabetes
Department of Internal Medicine
University of Michigan

The Division of Metabolism, Endocrinology & Diabetes, Department of Internal Medicine at the University of Michigan, Ann Arbor, seeks applicants for tenure track faculty positions in clinical and translational research in diabetes. Candidates should have sufficient experience to establish cutting-edge, independently funded research programs. All candidates will be evaluated but those applying at the level of Assistant/Early Associate Professor and who are board certified/eligible in endocrinology are preferred.

The Division of Metabolism, Endocrinology & Diabetes currently has 45 primary faculty, including 9 with active clinical and translational research programs in the areas of diabetes, diabetic complications, and obesity. The University is home to vigorous research centers, including the Michigan Diabetes Research Center, the Michigan Center for Diabetes Translational Research, and the Michigan Nutrition Obesity Research Center.

Applicants should forward curriculum vitae and contact information for three references to:

MEND Search Committee
c/o Dr. William H. Herman
University of Michigan
6108 Brehm/SPC5714, 1000 Wall Street
Ann Arbor MI 48105-1912.

The University of Michigan is an equal opportunity/affirmative action employer and encourages nominations and applications from women and minority candidates.

Florida Hospital | Translational Research Institute for Metabolism and Diabetes | Florida Hospital • Burnham Institute | Sanford|Burnham Medical Research Institute

Clinical Research Faculty—
Translational Research Institute for Metabolism and Diabetes, Orlando, Florida

The Florida Hospital, Sanford-Burnham, Translational Research Institute for Metabolism and Diabetes (TRI) seeks outstanding clinical scientists (M.D. and/or Ph.D.) in the areas of obesity, diabetes (both type 1 and 2) and metabolic cardiovascular disease.

TRI is the product of an innovative affiliation between Florida Hospital and Sanford-Burnham Medical Research Institute. By linking one of the largest not-for-profit hospitals in the country with a nationally renowned basic science leader, the TRI bridges the gap between the research bench and the patient's bedside. The mission of the TRI is to extend and improve the quality of lives through the conduct of world-class, innovative translational research that leads to discoveries—and ultimately cures—for metabolic diseases. For additional information, please visit *www.TRI-MD.org* or our TRI Discovery iPad App.

Sanford-Burnham Medical Research Institute is dedicated to discovering the fundamental molecular causes of disease and devising the innovative therapies of tomorrow. The Institute consistently ranks among the top five organizations worldwide for its scientific impact in the fields of biology and biochemistry (defined by citations per publication) and currently ranks third in the nation in NIH funding among all laboratory-based research institutes. For additional information, please visit *www.sanfordburnham.org.*

Faculty members in the new institute will be based at a new 54,000 square feet, state-of-the-art clinical translational research building located on the Florida Hospital campus. The institute has developed outstanding core technologies including on-site research dedicated imaging (3T MRI), room calorimetry, and a clinical research unit including overnight rooms, laboratory/biorepository, recruiting, clinical operations, and biostatistics/bioinformatics. The Institute is adjacent to and supported by the Florida Hospital Diabetes Institute, a pre-eminent diabetes practice in the Orlando area. Faculty may seek joint appointments at the Florida Hospital Diabetes Institute and/or Sanford-Burnham where appropriate.

Applicants for the position must have a record of accomplishments in clinical translational biomedical research, a proven track record of external research funding, and a demonstrated commitment to excellence in metabolism or related fields.

Target areas include but are not limited to:

- Diabetes (both type 1 and 2)
- Obesity and ingestive behavior
- Metabolic liver disease
- Polycystic ovary syndrome
- Muscle metabolism and exercise in metabolic disease
- Metabolic aspects of cardiovascular diseases
- Imaging in metabolic disease
- Bioinformatics
- Complications of diabetes
- Metabolism and cancer
- GI/Metabolism

Applications will be accepted until these positions are filled. Applications should include a cover letter and current curriculum vitae. Applicants can address questions to the Scientific Director of TRI: Steven R. Smith, M.D., (*steven.r.smith.md@flhosp.org*).

Harnessing the Human Microbiome

By Shannon Fischer

Your body is not your own. It's also the walking, talking home of tens of trillions of bacteria, viruses, mites, and fungi, which collectively outnumber your human cells by at least 10 to 1. They help you digest your foods, metabolize your drugs, maintain your weight (or not), keep pathogens at bay—even prepare your children for their new world.

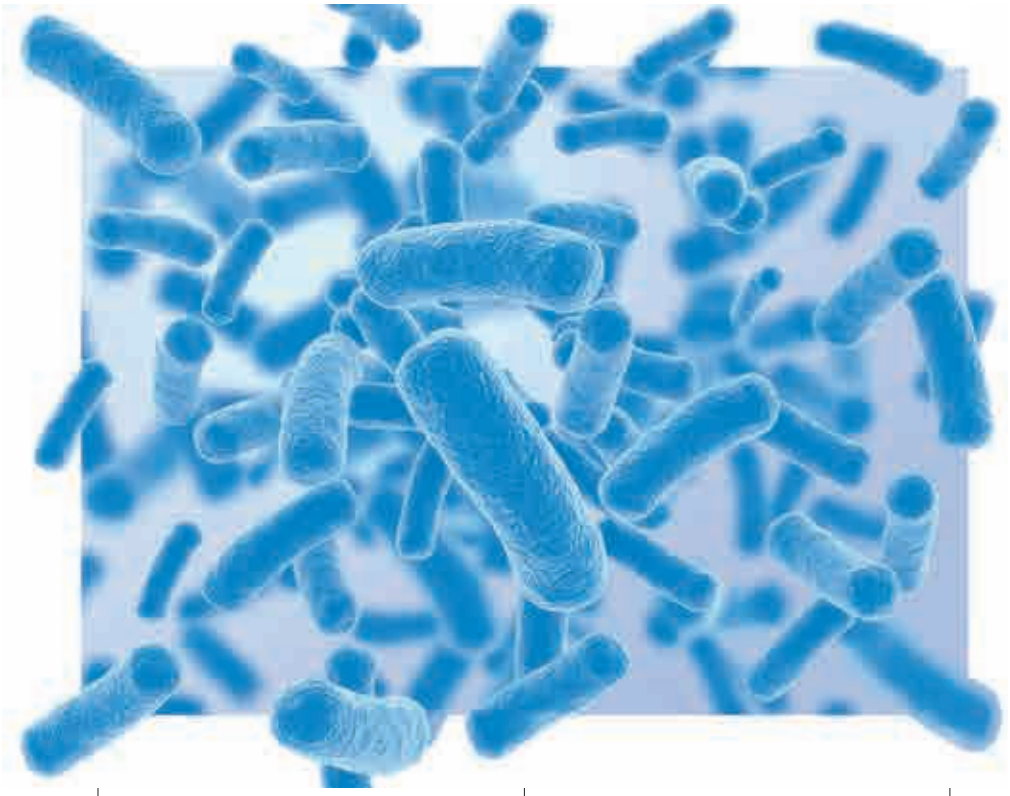
We've known of some of these microbes for more than a century—even suspected a few of them might be benefitting us. Not until the last decade, however, did we have the tools needed to get an honest census of exactly what our microbial shadow—our microbiome—*really* looked like. That shift happened when researchers realized that the DNA sequencing advances and computational techniques being used by environmental microbiologists to analyze bacterial genomes could also be applied to the human body. A few years later, in 2007, the National Institutes of Health launched the Human Microbiome Project (HMP), pouring more than $170 million into a study of nearly 250 healthy adults to create a reference snapshot of a healthy human microbial community. What the microbe-mapping project turned up when the study concluded this June astounded everyone.

Not only do our microbes wildly outnumber us—showing up behind our ears, between our teeth, even in our lungs—but no two populations are quite alike. In fact, more than 10,000 different microbial species may call the human body home. The microbe community between your toes differs from that on your heel, which in turn differs from your neighbor's heel—although his may still perform many of the same functions.

"It's been surprising," says Ruth Ley, a microbiologist at Cornell University. "One reaction was, 'Oh gosh, it's so *complicated*, we'll never get a handle on what's important. Now we are starting to home in on what are actually going to be the important bits in terms of interactions with the hosts in various contexts."

In one of her most recent studies, for instance, she tracked the transformation of women's guts over the course of pregnancy, finding that near the end of gestation, the women's normal microbiotic populations dropped in diversity and began favoring a pro-inflammatory microbial profile almost indistinguishable from that of a person with metabolic syndrome. Ordinarily, the changes would be dangerous—implanted into mice, the microbes caused weight gain and insulin resistance—but in a pregnancy, hypothesizes Ley, they might be helping keep the mother from rejecting the fetus while preparing her body for breastfeeding.

Pregnancy isn't the only time these microbe populations shift. The community of intestinal helpers, easily the richest in our bodies, also evolves with age, diet, and metabolic state. Tantalizing



Scientists also suspect links between our microbiota and diseases ranging from diabetes and cancer to COPD and asthma. If these circuits can be mapped out, the therapeutic potential could be revolutionary.

studies hint that changes to the gut biota could have enormous implications in modern health problems like obesity. Obese mice and humans both show different gut microbe profiles than their lean counterparts, for instance, and germ-free mice given a transplant of gut microbes promptly gain weight. High-fat diets also appear to alter gastrointestinal populations in mice, favoring the animals' ability to extract more energy from their food. What's alarming, says microbiologist Martin Blaser of New York University, is that our overuse of antibiotics may be killing off bacteria involved in regulating key metabolic circuits, such as those using leptin and the ghrelin hunger hormone.

Scientists also suspect links between our microbiota and diseases ranging from diabetes and cancer to COPD and asthma. If these circuits can be mapped out not just in form—where the bulk of the research has focused to date—but in *function*, so that scientists can learn how to harness the microbes, the therapeutic potential could be revolutionary.

"We know that microbes manipulate immunity, and we know that microbes manipulate metabolism," says Blaser. "If we could figure out the right ones, or figure out the right principles, then we may be able to treat [these disorders]."

The possibilities, he adds, are "at least equal to the potential of stem cells for changing health and disease." ■

Fischer is a freelance science writer based in Boston.

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 prandial insulin has not been studied.

CONTRAINDICATIONS: Do not use 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). Do not use in patients with a prior serious hypersensitivity reaction to Victoza or to any of the product components.

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 6 reported cases of thyroid C-cell hyperplasia among Victoza®-treated patients and 2 cases in comparator-treated patients (1.3 vs. 1.0 cases per 1000 patient-years). One 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. Five of the six Victoza®-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One Victoza® and one non-Victoza®-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 have been 13 cases of pancreatitis among Victoza®-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with Victoza® were reported as acute pancreatitis and four 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. 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) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin *[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. **Hypersensitivity Reactions:** There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with Victoza®. If a hypersensitivity reaction occurs, the patient should discontinue Victoza® and other suspect medications and promptly seek medical advice. Angioedema has also been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Victoza®. **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® has been evaluated in 8 clinical trials: A double-blind 52-week monotherapy trial compared Victoza® 1.2 mg daily, Victoza® 1.8 mg daily, and glimepiride 8 mg daily; A double-blind 26 week add-on to metformin trial compared Victoza® 0.6 mg once-daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and glimepiride 4 mg once-daily; A double-blind 26 week add-on to glimepiride trial compared Victoza® 0.6 mg daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and rosiglitazone 4 mg once-daily; A 26 week add-on to metformin + glimepiride trial, compared double-blind Victoza® 1.8 mg once-daily, double-blind placebo, and open-label insulin glargine once-daily; A double-blind 26-week add-on to metformin + rosiglitazone trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily and placebo; An open-label 26-week add-on to metformin and/or sulfonylurea trial compared Victoza® 1.8 mg once-daily and exenatide 10 mcg twice-daily; An open-label 26-week add-on to metformin trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, and sitagliptin 100 mg once-daily; An open-label 26-week trial compared insulin detemir as add-on to Victoza® 1.8 mg + metformin to continued treatment with Victoza® + metformin alone. *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 double-blind 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. In these five trials, 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. *Common adverse reactions:* Tables 1, 2, 3 and 4 summarize common adverse reactions (hypoglycemia is discussed separately) reported in seven of the eight controlled trials of 26 weeks duration or longer. Most of these adverse reactions were gastrointestinal in nature. In the five double-blind clinical trials of 26 weeks duration or longer, gastrointestinal adverse reactions were reported in 41% of Victoza®-treated patients and were dose-related. Gastrointestinal adverse reactions occurred in 17% of comparator-treated patients. Common adverse reactions that occurred at a higher incidence among Victoza®-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In the five double-blind and three open-label clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. In the five double-blind trials approximately 13% of Victoza®-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. In the 26-week open-label trial comparing Victoza® to exenatide, both in combination with metformin and/or sulfonylurea, gastrointestinal adverse reactions were reported at a similar incidence in the Victoza® and exenatide treatment groups (Table 3). In the 26-week open-label trial comparing Victoza® 1.2 mg, Victoza® 1.8 mg and sitagliptin 100 mg, all in combination with metformin, gastrointestinal adverse reactions were reported at a higher incidence with Victoza® than sitagliptin (Table 4). In the remaining 26-week trial, all patients received Victoza® 1.8 mg + metformin during a 12-week run-in period. During the run-in period, 167 patients (17% of enrolled total) withdrew from the trial: 76 (46% of withdrawals) of these patients doing so because of gastrointestinal adverse reactions and 15 (9% of withdrawals) doing so due to other adverse events. Only those patients who completed the run-in period with inadequate glycemic control were randomized to 26 weeks of add-on therapy with insulin detemir or continued, unchanged treatment with Victoza® 1.8 mg + metformin. During this randomized 26-week period, diarrhea was the only adverse reaction reported in ≥5% of patients treated with Victoza® 1.8 mg + metformin + insulin detemir (11.7%) and greater than in patients treated with Victoza® 1.8 mg and metformin alone (6.9%).

Table 1: Adverse reactions reported in ≥5% of Victoza®-treated patients in a 52-week monotherapy trial

	All Victoza® N = 497	Glimepiride N = 248
Adverse Reaction	(%)	(%)
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
Headache	9.1	9.3

Table 2: Adverse reactions 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 Reaction	(%)	(%)	(%)
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 Reaction	(%)	(%)	(%)
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

Add-on to Metformin + Glimepiride			
	Victoza® 1.8 + Metformin + Glimepiride N = 230	Placebo + Metformin + Glimepiride N = 114	Glargine + Metformin + Glimepiride N = 232
Adverse Reaction	(%)	(%)	(%)
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

Add-on to Metformin + Rosiglitazone		
	All Victoza® + Metformin + Rosiglitazone N = 355	Placebo + Metformin + Rosiglitazone N = 175
Adverse Reaction	(%)	(%)
Nausea	34.6	8.6
Diarrhea	14.1	6.3
Vomiting	12.4	2.9
Headache	8.2	4.6
Constipation	5.1	1.1

Table 3: Adverse Reactions reported in ≥5% of Victoza®-treated patients in a 26-Week Open-Label Trial versus Exenatide

	Victoza® 1.8 mg once daily + metformin and/or sulfonylurea N = 235	**Exenatide 10 mcg twice daily + metformin and/or sulfonylurea** N = 232
Adverse Reaction	(%)	(%)
Nausea	25.5	28.0
Diarrhea	12.3	12.1
Headache	8.9	10.3
Dyspepsia	8.9	4.7
Vomiting	6.0	9.9
Constipation	5.1	2.6

Table 4: Adverse Reactions in ≥5% of Victoza®-treated patients in a 26-Week Open-Label Trial versus Sitagliptin

	All Victoza® + metformin N = 439	**Sitagliptin 100 mg/day + metformin** N = 219
Adverse Reaction	(%)	(%)
Nausea	23.9	4.6
Headache	10.3	10.0
Diarrhea	9.3	4.6
Vomiting	8.7	4.1

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 double-blind 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 double-blind 52-week monotherapy trial and in 4.8% of the Victoza®-treated patients in the double-blind 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 double-blind 52-week monotherapy trial and in 1.0% of the Victoza®-treated patients in the double-blind 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_{1c} 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_{1c} with Victoza® treatment. In the five double-blind 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 double-blind 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 7 reported cases of papillary thyroid carcinoma in patients treated with Victoza® and 1 case in a comparator-treated patient (1.5 vs. 0.5 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 eight clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 11 Victoza®-treated patients (2.3 cases per 1000 patient-years) and in two exenatide-treated patients. Of these 11 Victoza®-treated patients, six patients were concomitantly using metformin and a sulfonylurea, one was concomitantly using a sulfonylurea, two were concomitantly using metformin (blood glucose values were 65 and 94 mg/dL) and two were using Victoza® as monotherapy (one of these patients was undergoing an intravenous glucose tolerance test and the other was receiving insulin as treatment during a hospital stay). For these two patients on Victoza® monotherapy, the insulin treatment was the likely explanation for the hypoglycemia. In the 26-week open-label trial comparing Victoza® to sitagliptin, the incidence of hypoglycemic events defined as symptoms accompanied by a fingerstick glucose <56 mg/dL was comparable among the treatment groups (approximately 5%).

Table 5: Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials

	Victoza® Treatment	**Active Comparator**	**Placebo Comparator**
Monotherapy	**Victoza®** (N = 497)	**Glimepiride** (N = 248)	**None**
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)	—
Add-on to Metformin	**Victoza® + Metformin** (N = 724)	**Glimepiride + Metformin** (N = 242)	**Placebo + Metformin** (N = 121)
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)
Add-on to Victoza® + Metformin	**Insulin detemir + Victoza® + Metformin** (N = 163)	**Continued Victoza® + Metformin alone** (N = 158*)	**None**
Patient not able to self–treat	0	0	—
Patient able to self–treat	9.2 (0.29)	1.3 (0.03)	—
Add-on to Glimepiride	**Victoza® + Glimepiride** (N = 695)	**Rosiglitazone + Glimepiride** (N = 231)	**Placebo + Glimepiride** (N = 114)
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
Add-on to Metformin + Rosiglitazone	**Victoza® + Metformin + Rosiglitazone** (N = 355)	**None**	**Placebo + Metformin + Rosiglitazone** (N = 175)
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)
Add-on to Metformin + Glimepiride	**Victoza® + Metformin + Glimepiride** (N = 230)	**Insulin glargine + Metformin + Glimepiride** (N = 232)	**Placebo + Metformin + Glimepiride** (N = 114)
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

*One patient is an outlier and was excluded due to 25 hypoglycemic episodes that the patient was able to self-treat. This patient had a history of frequent hypoglycemia prior to the study.

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. **Vital signs:** Victoza® did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with Victoza® compared to placebo. The long-term clinical effects of the increase in pulse rate have not been established *[see Warnings and Precautions]*. **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: Dehydration resulting from nausea, vomiting and diarrhea *[see Warnings and Precautions]*; Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis *[see Warnings and Precautions]*; Angioedema and anaphylactic reactions *[see Contraindications, 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 overdosage, 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

Date of Issue: April 6, 2012

Version: 4

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

novo nordisk®

ViCTOZA®
liraglutide (rDNA origin) injection

When measuring glycemic control
in adult patients with type 2 diabetes

Victoza®—proven superior efficacy versus Januvia®.

Discover more updates and data at **VictozaPro.com.**

Victoza® delivered superior A1C reductions of 1.2%-1.5% vs 0.9%,* with additional benefits:

	Victoza®	Januvia
MORE THAN TWICE AS MANY PATIENTS TO A1C <7%	44% and 56%	22%
GREATER FPG REDUCTIONS	-34 mg/dL to -39 mg/dL	-15 mg/dL
GREATER WEIGHT LOSS	-5.9 lb to -7.3 lb	-1.8 lb

Victoza® is not indicated for the management of obesity, and weight change was a secondary end point in clinical trials.

*A 26-week, open-label, active-comparator, 3-armed, parallel-group trial to compare the efficacy and safety of Victoza® with sitagliptin for the treatment of type 2 diabetes. Patients with type 2 diabetes inadequately controlled on metformin (n=665) were randomized to receive once-daily Victoza® (1.2 mg or 1.8 mg) or Januvia (100 mg). The primary outcome was change in A1C.[1]

Safety and tolerability versus Januvia.

Most common adverse reactions	Victoza® + metformin (n=439)		Januvia 100 mg + metformin (n=219)
NAUSEA	23.9%	VS	4.6%
HEADACHE	10.3%	VS	10.0%
DIARRHEA	9.3%	VS	4.6%
VOMITING	8.7%	VS	4.1%
MINOR HYPOGLYCEMIA	5.0%	VS	5.0%

Indications and Usage

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

Victoza® has not been studied in combination with prandial insulin.

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® 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.

Do not use in patients with a prior serious hypersensitivity reaction to Victoza® or to any of the product components.

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

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

Renal impairment has been reported post-marketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Victoza® (liraglutide [rDNA origin] injection) in patients with renal impairment.

Serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) have been reported during post marketing use of Victoza®. If symptoms of hypersensitivity reactions occur, patients must stop taking Victoza® and seek medical advice promptly.

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

The most common adverse reactions, reported in ≥5% of patients treated with Victoza® 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®-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

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

There is limited data in patients with renal or hepatic impairment.

Reference: 1. Pratley RE, Nauck M, Bailey T, et al; for the 1860-LIRA-DPP-4 Study Group. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet.* 2010;375(9724):1447-1456.

Please see brief summary of Prescribing Information on adjacent page.

0512-00009509-1 September 2012

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VICTOZA®
liraglutide (rDNA origin) injection