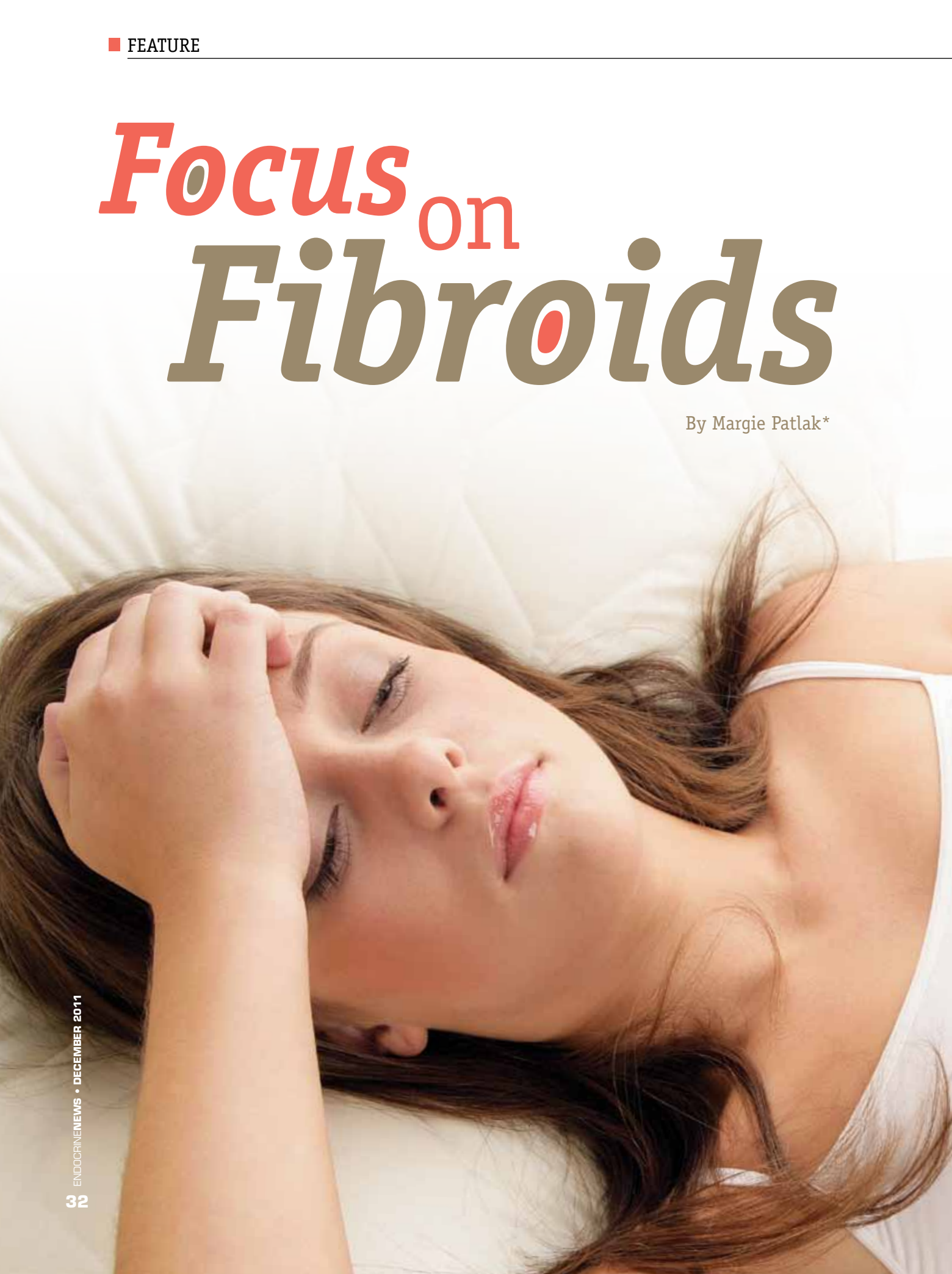
Focus on Fibroids

By Margie Patlak*



Three-quarters of women develop uterine fibroids in their lifetime, and as many as one-fourth suffer from them. Yet what causes these common outcroppings in the womb has largely remained a mystery. That is unfortunate, given that the excessive bleeding, pain, constipation, and difficulty urinating caused by these noncancerous tumors prompt nearly 200,000 women in the United States each year to have hysterectomies—and risk infection, adhesions, and damage to nearby organs. For women not done bearing children, hysterectomies are obviously not an option.

"For women a generation or so ago, hysterectomy was acceptable because they had completed their families at a younger age. But times have changed and women tend to delay starting a family, so there's a demand for nonsurgical alternatives," gynecologist Ayman Al-Hendy, M.D, Ph.D., who directs the Center for Women's Health Research at Meharry Medical College in Nashville, Tenn., told ***Endocrine News***. Also commenting was molecular biologist Julie Kim, Ph.D., of Northwestern University in Evanston, Ill. "I'm sure if you were to ask a woman whether she would prefer to take a pill for the treatment of fibroids or have surgery, the pill would win hands down."

Rising to meet that demand for medical therapy is a cadre of committed researchers who are rapidly uncovering the molecular mechanisms behind uterine fibroids. Their research has turned up numerous drug targets, some of which are currently being tested in the clinic. "There has been an exponential increase recently in the number of publications on the topic," Dr. Al-Hendy noted. The research has revealed the importance of progesterone in fostering fibroids and has teased apart some of the molecular threads in the extensive web of overactive cell signaling. This altered signaling results in the tangled mess of collagen and other fibers in uterine cells that is the hallmark of fibroids.

Steroid Suspects

Experts have suspected for a while that steroid hormones play an important role in uterine fibroids, given that the longer a woman menstruates, the greater the likelihood she'll develop fibroids and that they often diminish in size and symptoms once a woman hits menopause. Although a lot of the blame for fibroids in the past has been heaped on estradiol, recent findings suggest it should not bear the brunt of the blame—estradiol acts as the trigger, but progesterone plays the predominant role in fostering uterine leiomyomas.

Estradiol is required for fibroid cells to sprout progesterone receptors, studies show, but both the progesterone derivative P4 and estradiol are needed to prompt fibroid growth—neither hormone will by itself do this. When both hormones are withdrawn, fibroids shrink in size. These findings are bolstered by the clinical observation that the growth of these tumors is stimulated in postmenopausal women by hormone therapy that includes progestin, but no boost in growth occurs when only supplemental estrogens are taken.

Acting Locally

Circulating levels of both estradiol and progesterone are similar in women with or without fibroids, suggesting that it's all about location. Studies support this notion, finding more up-regulation of estrogen and progesterone receptors in uterine fibroids than in normal myometrium, as well as greater amounts of estradiol in fibroids, whose cells can produce the hormone.

The burning question is what is churning up this localized production of steroid hormones and their receptors? Some evidence suggests that for select women, the heightened hormonal environment in their wombs is due to too much aromatase, which converts testosterone to estrogens. Studies also find that certain variants of the estradiol-metabolizing enzyme catechol-*O*-methyltransferase (COMT) can shift the balance so more active estrogen metabolites are produced locally. Growth factors, such as insulin-like growth factor-I (IGF-I), may also be responsible in part, although it's hard to tell which comes first. For example, IGF-I can indirectly activate estrogen receptor α, but estrogens can also up-regulate IGF-I expression. As Dr. Kim summed up, "It's more complex than the amount of circulating or local hormones." Dr. Al-Hendy added, "These tumors seem to be self-sustaining—they produce their own steroids and probably many other growth factors as well."

Crosstalk Chatter

The complexity becomes apparent when you consider all the chemical chatting estradiol and progesterone do with a number of growth factors known to promote growth and inhibit cell death, including platelet-derived growth factor (PDGF), transforming growth factor (TGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and IGF-I. A large and diverse group of these compounds is apparently needed to support fibroids. A study found that 39 of 42 of the scrutinized tyrosine kinase receptors necessary for activating growth factors were expressed in human uterine fibroid tissues more than in normal myometrium tissue. One of the implicated growth factors, TGFβ, is especially known for promoting the growth of the collagen fiber tendrils that make up the bulk of these growths, whereas others specialize in promoting the growth of blood vessel cells that are probably needed to support fibroids, and might contribute to the excessive bleeding they cause.

Although the sheer number of growth factors involved can be overwhelming, only some make especially desirable therapeutic targets. As Dr. Kim pointed out, "A lot of these growth factors have common pathways, and it's really the pathways that are dictating what goes on, in terms of a physiological response." Some of the same molecular pathways active in tumor growth, such as the notorious PI3K/AKT and its affiliated mTOR pathway, are also overly active in uterine fibroids.

Dr. Kim noted, however, that unlike for malignant tumors, many growth-regulating pathways are still likely to be operational in fibroids. It is thus possible that relatively minor molecular tweaking may be all that's needed to limit their growth. For that tweaking, Dr. Al-Hendy suggested focusing on a few master checkpoints or regulators of the molecular pathways involved in these growths, most notably progesterone receptor, mTOR, aromatase, and COMT.

Hitting Hormones

Anti-fibroid compounds that are furthest along in the testing process are selective progesterone receptor modulators (SPRMs). Several have been tested in clinical trials, and these compounds have reduced related symptoms such as bleeding and/or uterine fibroid volume. Despite these promising results, one SPRM called asoprisnil caused endometrial changes similar to, but not exactly the same as, hyperplasia. The concern that asoprisnil might precipitate cancer led one company to discontinue its phase II testing of this SPRM, but clinical testing of others continues in women with fibroids.

In contrast, selective estrogen receptor modulators (SERMs) such as raloxifene have not proven exceptionally effective in stemming fibroid growth. There's some hope that aromatase inhibitors, e.g., letrozole or anastrozole, might reduce estrogen production enough to shrink these tumors, but not enough to cause bone problems or hot flashes. Pilot studies have found that aromatase inhibitors can decrease fibroid size and symptoms.

Clinical studies have shown that the progesterone receptor antagonist RU486 (mifepristone) also reduces fibroid volume and symptoms, but this drug is currently approved only for abortion. The doses for this use are much higher than daily doses to reduce fibroids in these clinical studies. Apparently daily fibroid treatment is needed, because the masses returned when treatment stopped.

Intriguingly, progestin-releasing intrauterine devices have been reported by some researchers to significantly reduce uterine fibroid symptoms in some women, although other findings conflict. Some experts speculate that such localized release of progestin might stem fibroids by curbing the expression of endometrial progesterone receptors in the uterus. Researchers also report that low-dose birth control pills can help stem the heavy bleeding experienced by some women with this condition.

Natural Agents

Compounds currently being tested for reducing uterine fibroids include natural compounds that target TGF or COMT. These include vitamin D_3 and such nutritional stars as resveratrol, which is found in grape skins, and EGCG, the anti-oxidant found in green tea. A recent in vitro study revealed that resveratrol not only inhibited cell proliferation and induced human fibroid cell death in vitro, it also reduced the production of two types of collagen in a dose-dependent manner, apparently by blocking the action of TGFβ. Gregory M. Christman, M.D., reported the unpublished study last year at "Advances in Uterine Leiomyoma Research: 3rd NIH International Congress."

Dr. Al-Hendy showed in animal and in vitro studies that both vitamin D_3 and EGCG inhibit proliferation of fibroid cells by affecting COMT, which ultimately caused progesterone receptor levels to drop. A pilot clinical trial of EGCG is under way and another is planned for vitamin D_3 in subjects with uterine fibroids, according to Dr. Al-Hendy. "I'm very excited about this new direction, because these compounds are well tolerated with little to no side effects, so we can entertain the concept of using them for fibroid prevention," he said.

This paradigm shift in thinking about prevention is possible, Dr. Al-Hendy pointed out, now that he has found, and Donna Baird, Ph.D., at the University of North Carolina at Chapel Hill has confirmed in a larger study, that insufficient serum vitamin D_3 is a risk factor for fibroids. These researchers found that the lower the serum vitamin D_3 levels in women with symptomatic fibroids, the greater their tumor burden. Interestingly, vitamin D deficiency is 10 times more prevalent in African Americans than in other populations and may explain why they experience uterine fibroids much more than Caucasians. According to Dr. Al-Hendy, it's conceivable that vitamin D supplements taken regularly might prevent fibroids in some women, if not relieve their burden once it has become established.

Hope is palpable that preventives and treatments will soon develop from the flurry of current research in fibroids, and those therapies surely will be welcomed by the millions of women plagued by the condition. As Elizabeth Stewart, M.D., of the Mayo Clinic in Rochester, Minn., pointed out at the 2010 NIH fibroids meeting, "Fibroids cause significant impairment of health for millions of women—[having fibroids] affects them during the years when they have the most demands on their time, both from raising families and establishing careers."

With scientists on the charge, although fibroids may still claim a lot of victims, their days are numbered. ■

---

* Margie Patlak is a free-lance science writer, living in the Philadelphia area.

Resources:

- Kim JJ, Sefton EC. The role of progesterone signaling in the pathogenesis of uterine leiomyoma. *Mol Cell Endocrinol,* 2011, doi:10.1016/j.mce.2011.05.044.
- Zhang D, Al-Hendy M, Richard-Davis G, et al. Green tea extract inhibits proliferation of uterine leiomyoma cells in vitro and in nude mice. *American Journal of Obstetrics and Gynecology,* 2010, March;202(3):289.
- Halder SK, Goodwin JS, Al-Hendy A. 1,25-dihydroxyvitamin D_3 reduces TGF-Beta3-induced fibrosis-related gene expression in human uterine leiomyoma. *J Clin Endocrinol Metab,* April 2011;96(4):E754–E762.
- More links at *www.endo-society.org/endo_news.*

Introducing a smart partnership

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

Indication and usage

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

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

Important Safety Information

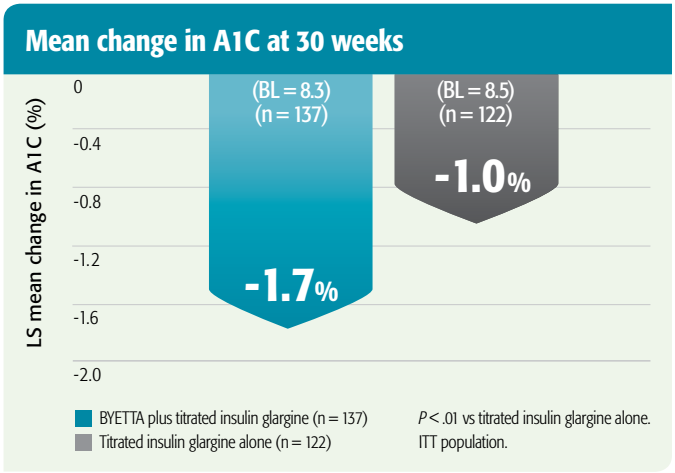
Contraindications

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

Warnings and precautions

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

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



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

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

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

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

Warnings and precautions (cont'd)

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

Adverse reactions

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

Drug interactions

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

Use in specific populations

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

To learn more, visit www.ByettaHCP.com.

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

BYETTA® HAS A
Over **6 years** on the market
Over **1 million** patients†
Over **8.5 years** of clinical experience
PROVEN HISTORY

†SDI data, December 2009.

Byetta®
exenatide injection

AMYLIN
SOLUTIONS THROUGH SYNERGY
Lilly

BYETTA® (exenatide) injection

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

INDICATIONS AND USAGE

Type 2 Diabetes Mellitus

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

Important Limitations of Use

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

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

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

DOSAGE AND ADMINISTRATION

Recommended Dosing

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

CONTRAINDICATIONS

Hypersensitivity

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

WARNINGS AND PRECAUTIONS

Acute Pancreatitis

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

Use with Medications Known to Cause Hypoglycemia

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

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

Renal Impairment

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

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

Gastrointestinal Disease

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

Immunogenicity

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

Hypersensitivity

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

Macrovascular Outcomes

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

ADVERSE REACTIONS

Clinical Trial Experience

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

Hypoglycemia

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

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

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

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

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

Immunogenicity

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

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

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

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

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

Other Adverse Reactions

Monotherapy

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

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

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

Combination Therapy

Add-on to metformin and/or sulfonylurea

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

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

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

Add-on to thiazolidinedione with or without metformin

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

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

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

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

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

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

Post-Marketing Experience

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

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

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

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

Neurologic: dysgeusia; somnolence

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

Skin and Subcutaneous Tissue Disorders: alopecia

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

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

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

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

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

Pregnancy Registry

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

OVERDOSAGE

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

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

Marketed by Amylin Pharmaceuticals, Inc. and Eli Lilly and Company

1-800-868-1190

http://www.BYETTA.com

Literature Revised October 2011

822015-EE
02-09-9300-D