

Byetta: Fit or Not Fit? by Rhea E. Coquia, Pharm.D.

Innovative hypoglycemic agents continue to be developed in order to alleviate the challenge of achieving normoglycemia in patients with type 2 diabetes. According to the American Diabetes Association (ADA), the total annual cost of diabetes was estimated to be \$174 billion in 2007.¹ Despite the availability of many effective nonpharmacologic and pharmacologic interventions, patients continue to have suboptimal control of their disease. It has been estimated that less than 40% of patients with diabetes achieve the ADA's goal of a hemoglobin A1c of less than 7%.² It has been projected that by 2025, 36.2 million people in North America will have diabetes. This is a sharp increase from the estimated 23 million people with diabetes in 2003.³ An extensive range of oral hypoglycemic agents are available for patients with type 2 diabetes. The main classes of medications include agents that stimulate insulin secretion from the pancreas (sulfonylureas and rapid acting secretagogues), agents that reduce hepatic glucose production (biguanides), agents that delay digestion and absorption of intestinal carbohydrate (alpha-glucosidase inhibitors), and those that improve insulin action (thiazolidiones).⁴ Exenatide is a relatively new agent for the treatment of type 2 diabetes and enhances glucose-dependent insulin secretion by mimicking the actions of glucagon-like peptide-1 (GLP-1). Exenatide was recently approved as adjunctive therapy in diabetic patients failing sulfonylureas and/or metformin. The aim of this article is to review exenatide's mechanism of action, discuss risks and benefits, as well as examine its role as a treatment strategy for patients with type 2 diabetes.

Clinical practice guidelines suggest a target hemoglobin A1c of less than 7% to minimize the risk of long-term consequences associated with diabetes, such as cardiovascular and microvascular complications. This recommendation is based on the findings of the Diabetes Control & Complication Trial in type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes.^{5,6} There are insufficient data at this time to support a recommendation of one class of glucose-lowering agents, or one combination of medications, over others with regard to effects on long-term therapy. To assist the clinician, however, the ADA and the European Association for the Study of Diabetes have endorsed a four-step treatment algorithm for the initiation and adjustment of diabetes therapy (Table 2).⁷ The diabetes treatment algorithm is a consensus statement based on the percent reduction in hemoglobin A1c expected with each agent, incidence of adverse effects, tolerability, and cost. When a single oral anti-hyperglycemic agent no longer provides adequate glycemic control, combination therapy may become necessary. Step one of the algorithm focuses on lifestyle modification, and each subsequent step adds therapy to the preceding step. The next step in the consensus algorithm recommends adding a second agent if glycemic control is not maintained despite an adequate trial of the previous step. The algorithm for the management of type 2 diabetes is outlined in Table 1, which lists first-line agents for each step in italics with alternatives listed below the first-line agent. Exenatide is indicated in the 3rd step of the algorithm as an alternative to metformin and thiazolidinediones when target glycemic goals are not achieved or sustained. The rationale for its use is based on the unique pharmacology of incretins.

The role of incretin hormones in the maintenance of glucose homeostasis is a relatively new area of research. The incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), derive from the enteroendocrine cells of the gastrointestinal (GI) tract. They potentiate insulin secretion following the intake of food.⁴ In addition, they decrease postprandial hepatic glucose production, slowing gastric emptying and promoting the sensation of satiety.⁴ The incretins have a short duration of action, half-life ($t_{1/2}$) <2 min, due to rapid degradation by dipeptidyl peptidases. Clinical use of exogenously administered human GLP-1, therefore, is impractical.

continued

Advances in the understanding of the natural history and pathophysiology of type 2 diabetes have resulted in the development of new treatment options that enhance the activity of GI hormones. Exenatide, Byetta[®], is an injectable GLP-1 agonist derived from Gila monster venom and is the first commercially available incretin mimetic in the United States. Exenatide contains a glycine at position 2, which makes the molecule resistant to dipeptidyl peptidase cleavage; the result is a molecule with a longer $t_{1/2}$ and duration of effect, making it a clinically viable treatment modality. Binding of exenatide to the GLP-1 receptor on pancreatic β -cells leads to increased insulin synthesis and secretion. A key difference between exenatide and other agents that stimulate insulin secretion is the glucose-dependent nature of insulin secretion. Exenatide stimulates insulin secretion only in the presence of elevated glucose levels and is thus theoretically a “smart” insulin secretagogue. In addition to its direct effects on insulin secretion, exenatide mimics the other actions of GLP-1, such as slowing gastric emptying and suppressing glucagon secretion, which contributes to its antihyperglycemic effects. It has emerged as an efficacious adjunctive therapy when used concomitantly with one or more oral hyperglycemic agents. The efficacy of exenatide 10 mcg twice daily as add-on therapy to metformin, a sulfonylurea, or both has been evaluated in three placebo-controlled trials of 30 weeks duration, and the mean reduction in hemoglobin A1c was 0.9% ($p < 0.005$).^{8,9} A trial of exenatide as add-on therapy to metformin and/or a thiazolidinedione reported a similar reduction in hemoglobin A1c.¹⁰

One of the clinical challenges for patients and healthcare providers in managing type 2 diabetes is the potential for weight gain, which can significantly and ultimately worsen long-term glycemic control. A significant advantage of exenatide compared to other therapies is the potential for weight loss.^{8,11,12} In the above-mentioned efficacy trials, exenatide resulted in progressive weight loss over the duration of follow-up, with a mean weight loss of 2.8 ± 0.5 kg at 30 weeks.⁸ Weight loss is theorized to be associated with GLP-1's ability to cause satiety and slow gastric emptying.

An association between exenatide and acute pancreatitis has been suggested in clinical trials and post-marketing reports. Several new cases of pancreatitis with serious complications, some with a fatal outcome, have been reported to the Food and Drug Administration (FDA). The FDA advisors are requesting “a stronger, more prominent warning” about the risks of developing acute hemorrhagic or necrotizing pancreatitis. Healthcare providers should be watchful of the signs and symptoms of acute pancreatitis, such as severe abdominal pain that may or may not be accompanied by nausea and vomiting. The FDA has recommended that patients immediately discontinue exenatide if signs of acute pancreatitis develop. Another antidiabetic agent should be considered in patients with a history of pancreatitis.¹⁴

Exenatide is generally well tolerated; however, a potential barrier to the use of exenatide is its relatively high incidence of GI adverse effects. Robert et al. reported 30-45% of patients treated with exenatide experienced nausea and/or vomiting early in therapy.¹¹ A meta-analysis revealed that the incidence of nausea and vomiting was greatest during the first 8 weeks of exenatide therapy and decreased in frequency with continued treatment. Diarrhea is also an early, dose-related adverse effect of exenatide.^{4,8} To minimize these GI adverse effects and improve tolerability, exenatide is initiated at 5mcg twice daily prior to the morning and evening meals. It can be titrated up to 10 mcg twice daily after 4-8 weeks of therapy, if tolerated. Exenatide is also associated with an indirect risk of hypoglycemia. Clinical trials using exenatide with a sulfonylurea have reported an increase in incidence of hypoglycemia with the combination. The combination of metformin with exenatide, however, is not associated with hypoglycemia.¹³ Providers should consider reducing the dose of the sulfonylurea when adding exenatide to existing therapy in patients who are closer to their goal hemoglobin A1c.¹⁰

The requirement of twice daily subcutaneous injections, as well as cost (approximately \$225/mo), are other significant obstacles to the use of exenatide. Exenatide is considerably more expensive than metformin, sulfonylureas, and insulin, but comparable to other alternative therapies such as thiazolidinediones (Table 1). Given the recent concerns with the cardiovascular safety of the thiazolidinediones, however, exenatide may be a more attractive alternative.

The development of GLP-1-based antidiabetic agents is a novel and promising strategy to treat diabetes. Exenatide, with its unique mechanism of action, has been shown to be effective in providing additional glucose control as a third-line agent in patients with type 2 diabetes who are already receiving therapy with metformin, a sulfonylurea, or both, but continue to have suboptimal glycemic control. The first available incretin mimetic, exenatide favorably causes progressive weight loss but is associated with some unfavorable side effects as well. Nausea and vomiting are significant side effects that unquestionably limit its use. Equally important are the inconvenience of subcutaneous injections and cost associated with the use of this agent. Availability of new treatment options, however, allow earlier, more aggressive treatment of diabetes with a higher likelihood of improving β -cell function and maintaining glycemic control. Indeed, future investigation will be necessary to confirm the significance of the efficacy as well as the safety of exenatide in patients with diabetes.

The author and editor are grateful for the comments provided by Janet Kelly, Pharm.D. and Jennifer Beach, Pharm.D., CDE, during their review of this document.

TABLE 1: A Four-Step Treatment Algorithm for the Management of type 2 diabetes.^{7,13}

STEP	INTERVENTION	MAXIMAL EXPECTED DECREASE IN HEMOGLOBIN A1c	ADVANTAGES	DISADVANTAGES	APPROXIMATE MONTHLY COST*
1 Initial therapy	Lifestyle modifications: diet and exercise	1-2%	Provides additional health benefits, minimal adverse effects	Difficult to sustain	N/A
2 Add an oral agent	<i>Metformin</i>	1.5%	Does not cause hypoglycemia when used as monotherapy, weight neutral, low cost	Gastrointestinal adverse effects, rare cases of lactic acidosis	\$30
	Sulfonylurea	1.5%	Low cost and extensive clinical experience	Potential for hypoglycemia weight gain	\$15
	Thiazolidinedione	0.5-1.4%	Does not cause hypoglycemia when used as monotherapy, improved lipid profile	Weight gain, fluid retention, adverse cardiac effects	\$115-\$220
3 Add a 2nd agent	<i>Metformin/Sulfonylurea</i> (whichever not previously on)	~2-2.5%	Extensive clinical experience with this combination, low cost	Potential for hypoglycemia weight gain	\$45
	Thiazolidinedione	~2%		Weight gain, fluid retention, adverse cardiac effects	\$130-\$250
	Exenatide	0.5-1%	Weight neutral or loss, no increase in hypoglycemia if added to metformin.	Subcutaneous injections, gastrointestinal adverse effects, cost, increased risk of hypoglycemia if added to sulfonylurea	\$215-\$255
4 Add insulin	Insulin	No upper limit	Effective, extensive clinical experience, improved lipid profile	Hypoglycemia, weight gain, increased blood glucose monitoring needs	Glargine \$61.90 (10mL) NPH \$17.25 (10mL)

students write

Don't Foster Zoster!

Brock Taylor • UW Pharmacy Student • Class of 2010

Herpes zoster, commonly known as "shingles," can lead to significant morbidity in older individuals who have been previously exposed to chickenpox. Approximately 33% of patients will experience varicella zoster virus (VZV) reactivation in their lifetime, translating into 1 million cases of herpes zoster per year in the United States (U.S.).¹ Immunization levels for VZV throughout the U.S. are low, averaging 2% for the elderly population in 2007.² Current CDC guidelines recommend all people ≥ 60 years old be vaccinated for the prevention of herpes zoster. Nearly 100% of the population in the U.S. carries or has been exposed to VZV.³ Complications of herpes zoster typically occur in adults aged ≥ 50 years as a result of the reactivation of latent VZV years after initial VZV infection is established.¹ The presenting symptoms of herpes zoster include a prodrome of headache, photophobia, and malaise, followed by painful, vesicular, cutaneous eruptions, which appear unilaterally along the thoracic, cervical, and abdominal dermatomes without crossing the midline.⁴ Serious complications that may result from secondary infection of VZV include post-herpetic neuralgia (PHN), (a debilitating and painful condition involving neuronal degeneration), pneumonia, encephalitis, ophthalmic involvement resulting in blindness, and death. Zoster rash typically lasts 7-10 days, with complete healing within 2-4 weeks. Scarring and pigmentation changes may be permanent, however. The duration of PHN has been observed to last from 30 days to more than 6 months. Pathological observations that distinguish PHN from uncomplicated zoster include extensive tissue damage involving the dorsal root ganglia, atrophy of the spinal dorsal horn, and eventual loss of epidermal innervation. Current definitions and clinical diagnosis of PHN is difficult given the wide variation in intensity and duration of pain in these patients.

The current vaccine, Zostavax[®], is a single-dose, live, attenuated vaccine that reduces the risk of reactivation of VZV in patients ≥ 60 years old by up to 64% with the highest efficacy in those 60-69 years old.¹ Vaccine efficacy has not been established in patients < 60 years old.¹ The vaccine has been studied up to 4 years post-vaccination for prophylaxis of VZV, but analysis of protection beyond this period has not been investigated; therefore, duration and efficacy of immunity remain unknown.¹ At the present time, booster doses are not recommended, although an unpublished clinical study for 10-year vaccine follow-up may soon alter current booster guidelines.¹ Vaccination with Zostavax[®] is not recommended in those having received a varicella vaccine. Most patients within the recommended age groups, however, will not have received any varicella immunization due to the routine vaccination of patients beginning in 1995.¹ Patients with unknown varicella immunization history or those with a history of varicella infection should be administered the vaccine due

to waning immunity from initial VZV infection and the increased risk for zoster reactivation. Zostavax[®] should not be used for the following: treatment of acute herpes zoster, to prevent persons with acute zoster from developing PHN, to treat current PHN, or for the prevention of varicella (chickenpox).¹ Patients with a previous history of zoster can be administered the vaccine, provided there is no acute zoster eruption.¹

Concomitant administration of zoster vaccine and other live, attenuated and inactivated vaccines has not resulted in impaired immune response or an increase in rate of adverse events.¹ If simultaneous administration of other vaccines is not possible during the same visit, the zoster vaccine can be given at any time before or after another inactivated vaccine; a 4-week minimum interval should separate any other live, attenuated vaccine to avoid immune inactivation, however.⁵ Patients taking herpes antiviral agents should discontinue use 24 hours prior to receiving the zoster vaccination and abstain from antiviral use 14 days after receiving the zoster vaccine.

Common adverse reactions after administration include injection site erythema (36%), pain (35%), swelling (26%), and headache (1.4%), with approximately 50% of patients experiencing one or more of these adverse events.¹ The vaccine is contraindicated in pregnant women, teens, children, those with immunodeficiency, and patients anaphylactic to gelatin, neomycin, or any other component of the vaccine. Caution is warranted in patients who are breastfeeding and those with active, untreated TB cases.¹ Delayed-type immune responses (non-anaphylactic), impaired humoral immunity (dysgammaglobulinemia), fever, or other short-term illnesses are not valid contraindications for vaccination. If immunosuppressive agents must be used, zoster vaccine should be given 4 weeks prior to initiating therapy.¹ No evidence was seen of transmission of the vaccine virus from vaccine recipients to contacts.¹ As with administration of any vaccine, anaphylactic reactions may occur, often within minutes to several hours of administration, and 25% of vaccine recipients may have an anaphylactic recurrence within several hours of the first anaphylactic episode (biphasic anaphylaxis).⁶ If the patient experiences anaphylaxis to the vaccine, an adult (0.3 mg) epinephrine auto-injector should be administered immediately. Zostavax[®] must be stored frozen, at $\leq 5^{\circ}\text{C}$, and should be used within 30 minutes of reconstitution.⁷

Most Medicare Part D plans now reimburse for both the cost and administration of the vaccine as Zostavax[®] is not billable under Medicare Part B for 2008, unlike other common clinic-administered vaccinations. Increasing vaccination rates can greatly assist in improving quality of life and reduce the disease burden in these vulnerable populations. Don't Foster Zoster!

REFERENCES**BYETTA: FIT OR NOT FIT?**

1. American Diabetes Association (ADA) statement. Economic costs of diabetes in the U.S. in 2007. *Diabetes Care* 2008; 31(3):1-20.
2. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004; 291:335-42.
3. International Diabetes Federation (IDF). *Diabetes Atlas 2003*. Available at: <http://www.atlas.idf.org/prevalence>. Accessed January 16, 2008.
4. Richard EP & Afshin S. Inhibition of DPP-4: a new therapeutic approach for the treatment of type 2 diabetes. *Curr Med Res Opin* 2007; 23(4):919-931.
5. UKPDS Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352:837-53.
6. DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *NEJM* 1998; 329:977-985.
7. Nathan DM, Buse JB, Davidson MB et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care* 2006; 29:1963-72.
8. Ralph AD et al. Effects of exenatide on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005; 28(5):1092-1100.
9. Mark SF et al. Effects of glycemic control of exenatide additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. *Diabetes Care* 2003; 26(8):2370-2377.
10. Byetta® [package insert]. San Diego (CA). Amylin Pharmaceuticals Inc; 2008.
11. Robert JH et al. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes. *Ann Intern Med* 2005; 143:559-569.
12. Kjeld H & Lene SM. Bodyweight changes associated with antihyperglycaemic agents in type 2 diabetes mellitus. *Drug safety* 2007; 30(12):1127-1142.
13. Iltz J et al. Exenatide: an incretin mimetic for the treatment of type 2 diabetes mellitus. *Clin Ther* 2006; 28(5):652-665.
14. Information for Healthcare Professionals Exenatide (marketed as Byetta®). Rockville, MD: Food and Drug Administration, August 18, 2008. (Accessed August 18, 2008 at <http://www.fda.gov/cder/drug/InfoSheets/HCP/exenatide2008HCP.htm>).
15. Todd JF & Bloom SR. Incretins and other peptides in the treatment of diabetes. *Diabet Med* 2007; 24:223-232.

DON'T FOSTER ZOSTER!

1. CDC. Prevention of herpes zoster: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2008; RR-57.
2. Hampton T. Research reveals low immunization rates and vaccination awareness among adults. *JAMA* 2008; 299(9):1007.
3. Kilgore PE et al. Varicella in Americans from NHANES III: implications for control through routine immunization. *J Med Virol* 2003; 70:S111-S118.
4. Nishizawa A. Acute herpes zoster without pain. UCLA Department of Medicine. [internet]. Los Angeles (CA): UCLA Department of Medicine; 1993 April [cited 7/10/2008]. Available from: <http://www.med.ucla.edu/modules/wfsection/article.php?articleid=55>.
5. CDC. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006; RR-15.
6. Brazil E & MacNamara AF. "Not So Immediate" Hypersensitivity—the danger of biphasic anaphylactic reactions. *J Accid Emerg Med* 1998; 4:252-253.
7. ZOSTAVAX® [package insert]. Whitehouse Station, NJ. Merck; 2007.

- Byetta: Fit or Not Fit?, p1
Table 1, p3
- Students Write; Don't Foster Zoster!, p4
- References, p5
- P&T Committee Brief Summary, July 2008, back cover

UNIVERSITY OF
WASHINGTON

DRUG INFORMATION CENTER
BOX 354735 SEATTLE, WA 98195-4735

P&T COMMITTEE BRIEF SUMMARY July 15, 2008

FORMULARY ADDITIONS	DOSAGE FORM(S), STRENGTH(S)	THERAPEUTIC CLASSIFICATION	USE	USUAL ADULT STARTING DOSE
Recombinant human thrombin (Recothrom®)	5000 IU, 20000 IU single-use vial; 20000 IU spray applicator kit	Hemostatic agent	Promotes hemostasis and acts locally when applied topically to a site of bleeding.	Variable depending on size and number of bleeding sites to be treated

FORMULARY DELETIONS	
Bovine Thrombin (Thrombin-JMI®/Thrombogen®)	Replaced with Recothrom®

OTHER ACTION	
ITEM	ACTION
Ceftriaxone and IV calcium	USE of ceftriaxone and IV calcium-containing products should not be administered within 48 hours in the neonatal population. No change in ceftriaxone or calcium usage is warranted at this time in the adult population. Because of the known IV incompatibility, adults requiring IV calcium replacement (or other calcium-containing solutions such as Lactated Ringers (LR), D5LR, or total parenteral nutrition (TPN), etc.) while on ceftriaxone should not be administered these two agents simultaneously in the same line.
Teriparatide (Forteo®)	EXPAND the restricted prescribing of teriparatide to include Drs. Lipkin and DeSantis.
VTE Toolkit	APPROVE for hospital-wide use; this is a web-based tool to standardize and improve patient care in the diagnosis, treatment, and prophylaxis of VTE and can be found at http://uwmcacc.org .