



# NAVIGATING the EVOLVING THERAPEUTIC LANDSCAPE for DIABETES MANAGEMENT:

## Addressing Implications for Clinical Practice

### Frequently Asked Questions

**Q. Since DPP-4 hydrolyzes GLP-1, would a DPP-4 inhibitor amplify the effects of exenatide, a GLP-1 analogue?**

**A.** A DPP-4 inhibitor will protect GLP-1 and other molecules that are degraded by DPP-4. Exenatide has only 53% homology to human GLP-1 and is not degraded by DPP-4; thus, a DPP-4 inhibitor should have no effect on exenatide structure or function. There may be a small additive effect due to protection of endogenous GLP-1, depending on the level of this hormone in a particular patient. Activity of human-derived incretins such as liraglutide may be prolonged by addition of a DPP-4 inhibitor, though this has not been shown. A combination of an incretin and a DPP-4 inhibitor has not been clinically evaluated.

**Q. Both sulfonylurea (SFU) drugs and exenatide act by enhancing insulin secretion. I have read about beta cell exhaustion, which should be expected with insulin secretagogues. Does this mean that SFUs and exenatide have similar durations before they fail to maintain glucose control?**

**A.** The SFU effect is short lived, with most patients losing control at about 1 year of therapy. Exenatide has not been on the market for as long as the SFUs, but its effect appears to be more durable. Glucose control frequently persists for 3 years or more. Other advantages of exenatide are fewer hypoglycemic events and weight loss in 50% or more of the patients. Exenatide is more costly than SFUs, and is administered by injection.

- Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med.* 2006;355(23):2427-2443.
- Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin.* 2008;24(1):275-286.

**Q. Many of my patients with type 2 diabetes are renally impaired. How should this affect the dosing of new medications such as exenatide and sitagliptin?**

**A.** Like metformin, exenatide is renally cleared. Both of these agents can be used in patients with mild/moderate renal impairment (GFR down to 30 ml/min) but are not recommended in patients with ESRD. Sulfonylurea drugs are also cleared by the kidney. Renal impairment slows clearance and increases the risk of hypoglycemia. Pioglitazone and rosiglitazone are metabolized in the liver and can be used even in the presence of ESRD. Sitagliptin, though renally cleared, can be used in patients with mild/moderate renal impairment, but the dose should be adjusted to 50 mg daily. If the GFR is below 30 ml/min, the dose should be reduced by another half (to 25 mg).

- Exenatide PI. Available at: <http://pi.lilly.com/us/byetta-pi.pdf>. Accessed March 2009.
- Sitagliptin PI. Available at: [http://www.merck.com/product/usa/pi\\_circulars/s/j/januvia/januvia\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/s/j/januvia/januvia_pi.pdf). Accessed March 2009.

**Q. Some of my patients experience nausea from exenatide. How should I advise them, and should I transfer them to another medication?**

**A.** If the nausea is extreme, you might consider another medication. However, mild nausea is experienced by many patients receiving exenatide, and usually subsides in 1-2 weeks. In clinical trials summarized in the package insert, 44% of the patients receiving exenatide and 18% of the patients receiving placebo experienced nausea. Patients should be aware of the following considerations:

1. Nausea is a normal response to rapid or excessive eating. Exenatide slows gastric emptying, and can exaggerate this feeling. It is OK to feel full, and eating less at a slower pace is good both for digestion and for weight management.
2. Nausea may be diminished by administering exenatide closer to meal time, about 15 minutes before eating. This tends to decrease nausea and increase satiety. After an initial period, this interval can be lengthened, up to 60 minutes (exenatide PI).
3. Some patients find that nausea is diminished by injecting in alternative sites.

- Exenatide PI. Available at: <http://pi.lilly.com/us/byetta-pi.pdf>. Accessed March 2009.

**Q. Exenatide is reportedly associated with pancreatitis. Is this association real, and what are the implications for treating patients with diabetes?**

**A.** It is not known whether the reported incidents of pancreatitis with exenatide are drug-related. Patients with diabetes or diabetes/obesity have an increased rate of pancreatitis, which has also been reported with other anti-hyperglycemic drugs. GLP-1 receptor level is very low in the exocrine pancreas, and toxicology studies in animals showed no exocrine pancreas damage. So while pancreatitis is a serious complication, an association with exenatide has not been firmly established. Balancing the benefits and risks for individual patients should guide the use of this drug.

- Wajsborg E, Tavarra A. Exenatide: clinical aspects of the first incretin-mimetic for the treatment of type 2 diabetes mellitus. *Expert Opin Pharmacother.* 2009;10(1):135-142.



# NAVIGATING the EVOLVING THERAPEUTIC LANDSCAPE for DIABETES MANAGEMENT:

## Addressing Implications for Clinical Practice

### Q. The new diabetes drugs are very expensive. How can I justify prescribing them when treatments such as metformin, SFUs, and insulin are cheap and effective?

A. Each patient is different, and the drugs you mentioned can be used if cost is an issue. Metformin is recommended by the ADA as the initial drug treatment. The danger of hypoglycemia with SFUs and especially insulin necessitates frequent glucose measurement. Since hypoglycemia is far less frequent with exenatide and sitagliptin, the diagnostic costs are reduced. Long- and short-acting insulins can also be expensive. Neither metformin nor SFUs preserve beta cell function. After an initial drop in HbA<sub>1c</sub>, there is a progressive rise in HbA<sub>1c</sub> due to progressive loss of beta cell function. Durability of glycemic control and preservation of beta cell function have been demonstrated for up to 3-5 years with TZDs and exenatide. The costs and benefits must always be evaluated, but the consistency, effectiveness, and durability of the newer drugs make them attractive alternatives.

### Q. What proportion of newly diagnosed type 2 diabetics eventually requires insulin?

A. Patients receiving metformin or sulfonylureas frequently experience a progressive rise in HbA<sub>1c</sub> after the first year of treatment and require multiple medications. Patients with HbA<sub>1c</sub> < 7% can usually be managed with metformin and pioglitazone, while a cocktail of metformin, pioglitazone, and exenatide has been useful for patients with HbA<sub>1c</sub> > 7%. This triple medication cocktail has given very satisfactory results; most patients do not require insulin, even after 4 years of therapy.

### Q. What are the factors to consider when weighing exenatide vs sitagliptin?

A. These new drugs have some mechanisms of action in common, but have several features that might be preferable for particular patients. Exenatide is an injectable peptide, while sitagliptin is orally administered. The pill formulation may be superior for elderly or visually impaired patients. Exenatide has been associated with weight loss, an advantage for the great majority of patients with type 2 diabetes, while sitagliptin has no significant effect on appetite and does not promote weight loss. There is some evidence that incretins preserve beta cell mass in animals, but this has not been documented in humans. Exenatide causes slightly greater reductions in HbA<sub>1c</sub> (Amori 2007) and much greater declines in post-prandial glucose and glucagon levels; it also causes a much greater increase in insulin secretion. Exenatide, but not sitagliptin, also causes a significant inhibition of gastric emptying, which contributes to the reduction in post-prandial glucose. New incretins and DPP-4 inhibitors should be reaching the market in the near future and provide useful options for treating type 2 diabetes.

– Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA*. 2007;298(2):194-206.

### Q. What is the risk of fracture with TZDs?

A. The risk of fracture for male and premenopausal female patients with type 2 diabetes receiving pioglitazone or rosiglitazone does not appear to be significantly elevated. However, postmenopausal women have a slightly elevated risk of fracture. Interestingly, these fractures are more often found in small bones such as wrists and ankles, rather than hips or spine. In the ADOPT trial women (77% postmenopausal) treated with rosiglitazone had a 1.81-fold higher risk of fracture compared to women treated with metformin, and a 2.13-fold higher risk compared to glyburide. The relative risk rates were highest for foot, hand, and proximal humerus (3.3, 2.6, and > 8, respectively).

– Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355(23):2427-2443.

– Schwartz AV. TZDs and Bone: A Review of the Recent Clinical Evidence. *PPAR Res*. 2008;2008:297893.

### Q. If TZDs are associated with peripheral edema and weight gain in some patients, isn't there a higher risk of CHF?

A. Both rosiglitazone and pioglitazone prescribing information have boxed warnings for CHF and both TZDs are contraindicated for patients with NYHA Class III or IV heart failure. The association with CHF is due to the TZD effect of increasing salt and water reabsorption in the distal/collecting tubules of the kidney. Fluid retention is best treated with distally acting diuretics. The PROactive study found a higher rate of CHF with pioglitazone than with placebo (5.7% vs. 4.1%). However, there was no increase in the incidence of death subsequent to a report of serious heart failure (1.5% vs. 1.4%, respectively).

– Erdmann E, Charbonnel B, Wilcox RG, et al. Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). *Diabetes Care*. 2007;30(11):2773-2778.

– Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355(23):2427-2443.