

# Commentary: Exenatide QW: A New Treatment Option for Type 2 Diabetes Offering Ease of Use, Improved Efficacy, and Reduced Side Effects

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**Editor's note:** *Once-weekly exenatide, which has recently been approved for patients with type 2 diabetes, has great potential as a new diabetes therapy in the primary care setting. This commentary and the feature article that follows it (p. 95) offer an overview of this new therapeutic tool and important insights about its clinical utility. In the interest of transparency, however, we want to point out that the authors of both articles are affiliated with Amylin Pharmaceuticals, which manufactures exenatide QW and markets it under the trade name Bydureon.*

Exenatide once weekly (QW) has recently been introduced for weekly subcutaneous injection as an adjunct to diet and lifestyle change for the treatment of type 2 diabetes. It is the first weekly diabetes therapy to come to market and offers a number of interesting possibilities for clinicians and patients.

Although this treatment is, at its core, the exenatide molecule that has been known for more than a decade and has been in widespread clinical use for at least 7 years,<sup>1</sup> exenatide QW has a unique microsphere encapsulation.<sup>2</sup> This feature delays absorption, thus producing continuous steady-state levels of exenatide in the bloodstream, which leads to lower A1C levels and greater weight loss than exenatide's twice-daily formulation<sup>3</sup> and a lower incidence of side effects than other glucagon-like peptide-1 (GLP-1) receptor agonists

(also called incretin mimetics) currently in use.<sup>3,4</sup>

Validation of the acceptance in clinical practice of GLP-1 receptor agonists can be found in the recently released American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement on the management of type 2 diabetes, which placed these drugs alongside older, well-accepted agents such as sulfonylureas (SUs) and thiazolidinediones (TZDs) as a second-line therapy after metformin.<sup>5</sup>

GLP-1 receptor agonists are described as having high efficacy and a low risk of hypoglycemia and as being on a cost tier (high) equal to other add-on agents except for SUs (low) and insulin (variable).<sup>5</sup> GLP-1 receptor agonists are the only class mentioned with which weight loss is expected.<sup>5</sup> Although gastrointestinal (GI) issues were cited as side effects with this class, exenatide QW has a lower incidence of these side effects than other available GLP-1 receptor agonists.<sup>3,4</sup>

## Clinical Properties

For clinicians providing diabetes care, and especially for primary care providers, these facts have significant implications. First, there is now clear, widely accepted validation for using GLP-1 receptor agonists as an add-on therapy to metformin and lifestyle modification if A1C levels are not controlled to goal. Second, treatment

with GLP-1 receptor agonists is the only form of anti-diabetes therapy offering proven weight loss. Finally, GLP-1 receptor agonist therapy is one of the recommended treatment strategies offering a low incidence of hypoglycemia, an important aspect of diabetes therapy learned from the Action to Control Cardiovascular Risk in Diabetes trial.<sup>6</sup>

As clinicians consider what to do when metformin and lifestyle change do not adequately control a patient's A1C, they frequently ask, "incretin or insulin next?" Fortunately, there is abundant evidence to inform this decision. Heine et al.<sup>7</sup> have shown exenatide twice daily to be non-inferior to insulin glargine for A1C reduction in a study population with an average A1C of 8.2%. Exenatide QW has been shown to produce lower A1C values than insulin glargine over the course of an 84-week study, with accompanying significant and durable weight loss in the exenatide QW group.<sup>8</sup> Therefore, clinicians can confidently select add-on therapy to metformin and lifestyle change, where necessary, based on patient-centered issues such as the need for lower hypoglycemia risk, weight reduction, and convenience of administration without being concerned about sacrificing efficacy. The new ADA/EASD guidelines clearly favor such patient-centric approaches to diabetes management.<sup>5</sup>

As of this writing, exenatide QW has been available for about 6 weeks. It has already found widespread use in my practice and has been met with almost uniform patient acceptance. Patients seem reassured that the drug being used (the exenatide molecule) has been in testing and clinical use for about a decade. All of the precautions and safety issues pertaining to exenatide also apply to exenatide QW.<sup>9</sup>

Exenatide QW and liraglutide, long-acting GLP-1 receptor agonists, carry box warnings concerning medullary thyroid carcinoma in rodents.<sup>9,10</sup> The implications of these findings in humans are not known, although it is somewhat reassuring that there has been no adverse signaling for thyroid cancer risk so far with the clinical use of liraglutide. However, this issue should be discussed with patients before they start using a long-acting GLP-1 receptor agonist.

Also, there have been reports of small subcutaneous bumps after exenatide QW injection, presumably a form of foreign-body reaction to the microsphere.<sup>2</sup> This is a normal and temporary response, resolving in ~4–6 weeks after any injection. So far, this has been very uncommon in my exenatide QW patients.

Patients should be reminded that the full effect of treatment is not likely to occur until exenatide QW has been used for 2 months and a steady-state level of exenatide has been achieved. In the world of instant gratification, neither clinicians nor patients should forget to appreciate this gradual onset of action. Proactive discussion of all the aspects of exenatide QW use will help patients and clinicians employ this therapy successfully. Remember: **SATISFACTION = RESULTS – EXPECTATIONS** (T.W. Olsen, unpublished observations).

### Use in Primary Care

My experience suggests that exenatide QW use in a busy primary care practice is likely to fall into one of five categories. First are patients whose diabetes is not well controlled with metformin and lifestyle therapy who either need to achieve A1C reductions beyond that expected by adding oral agents or need continuing weight loss or both. Second are those who have not tolerated the GI side effects of previous GLP-1 receptor agonists but who are more likely to tolerate exenatide QW with its less intense side effect profile. A third group includes patients who have not done well (poor A1C reduction, little weight loss) with either exenatide twice daily or liraglutide once daily therapy, possibly because of unreported compliance issues, who may be candidates for more convenient weekly therapy. Fourth are patients with literacy, numeracy, or psychosocial issues who have limited compliance to other therapies but may be good candidates for weekly therapy administered in the clinician's office. And finally, a fifth group includes the few patients who wish to abandon their currently effective GLP-1 receptor agonist therapy in favor of the more convenient weekly dosing of exenatide QW.

Surprisingly, few successful exenatide twice daily or liraglutide once daily patients in my practice have been motivated to switch to exenatide QW. It seems these patients are comfortable with their regimen and find little benefit in changing. I have realized that those who would like a change to simplify dosing or relieve side effects likely have already done so by quietly opting for poor compliance.

After initiating lifestyle modification and metformin therapy, a number of patients continue to have A1C levels > 8% and issues with excess weight. These patients are likely to benefit from the robust A1C

and weight reduction afforded by exenatide QW. Many patients seem relieved that the new therapy is not insulin. I appreciate that exenatide QW is easier and faster to implement in the office than other GLP-1 receptor agonists or insulin. A single dose strength, no ramp-up titration, and no need for self-monitored glucose determinations make exenatide QW simple to implement in the setting of a routine office visit.

Since the advent of exenatide QW, a number of previously professed "faithful" GLP-1 receptor agonist patients have admitted how often they missed their medication either because they forgot or because of travel, dining out, or other circumstances. These patients have done exceedingly well with once weekly dosing at a time convenient for them.

Some who have quit exenatide twice daily or liraglutide once daily because of GI side effects have been willing to consider trying again with exenatide QW, with its lesser levels of such side effects. To date, most have successfully tolerated exenatide QW, and none have stopped the drug because of side effects. So far in my practice, this group constitutes ~30% of the exenatide QW users.

Perhaps the most rewarding group of patients benefitting from exenatide QW in our practice has been individuals with literacy, numeracy, or psychosocial issues that have precluded compliant use of oral or other injectable agents. These patients, after learning that there is a weekly injection that can be given in the office, have been more forthcoming about the issues impairing their use of diabetes treatments and have been delighted to come to our office weekly for their injection of exenatide QW, a schedule that they and our office staff can easily accomplish. Many of these individuals previously had no effective control of their diabetes and no accountability

partners to help them. Our Thursday morning exenatide QW injection clinic has turned into something of an anticipated weekly social event for these patients. They have coalesced into an informal support group and enjoy encouraging each other.

### Conclusion

In my opinion, the value of any new medication in the primary care setting depends on the ease with which that medication can be understood, the ease with which it can be deployed in routine office use, and its efficacy in filling a previously unmet need. Exenatide QW is easy to understand; it is the same exenatide molecule we have been using for about a decade. It is also easy to initiate in a busy primary care office. Most patients can learn to use exenatide QW in a few minutes with a minimal time investment from clinicians and office staff. Finally, with a convenient dosing strategy that may enhance compliance, exenatide QW should prove to be useful in primary care because it is effective for weight loss and durable A1C reduction, even beyond that achieved by basal analog insulin, and without an undue risk of hypoglycemia.

The recent ADA/EASD position statement suggests that well-developed treatment strategies for type 2 diabetes draw on a

combination of clinicians' expertise and patients' inclinations.<sup>5</sup> Exenatide QW should meet both clinicians' demands for safe and effective therapy and patients' desire for few side effects, ease and convenience of use, and favorable weight outcomes. This new delivery of the exenatide molecule is likely to find a comfortable place in the primary care treatment toolbox.

### REFERENCES

- <sup>1</sup>Amylin Pharmaceuticals, Inc.: The discovery and development of Byetta (exenatide) injection and Bydureon (exenatide extended-release for injectable suspension) [article online]. Available from <http://www.multivu.com/assets/53897/documents/53897-Exenatide-History-FINAL-original.pdf>. Accessed 24 April 2012
- <sup>2</sup>DeYoung MB, MacConell L, Sarin V, Trautmann M, Herbert P: Encapsulation of exenatide in poly-(D,L-lactide-co-glycolide) microspheres produced an investigational long-acting once-weekly formulation for type 2 diabetes. *Diabetes Technol Ther* 13:1145–1154, 2011
- <sup>3</sup>Blevins T, Pullman J, Malloy J, Yan P, Taylor K, Schulteis C, Trautmann M, Porter L: DURATION 5: exenatide once weekly resulted in greater improvements in glycemic control compared to exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab* 96:1301–1310, 2011
- <sup>4</sup>Buse JB, Nauck M, Forst T, Sheu WH-H, Hoogwerf BJ, Shenouda SK, Heilman CR, Boardman M, Fineman M, Porter L, Scherthaner G: Efficacy and safety of exenatide once weekly versus liraglutide in subjects with type 2 diabetes (DURATION-6): a randomized open label study [Abstract]. *Diabetologia* 54:S38, 2011
- <sup>5</sup>Inzucchi SE, Bergenstahl RM, Buse JB, Diamant M, Ferrannini E, Nuack M, Peters AL, Tsapas A, Wender R, Matthews

DR: Management of hyperglycemia in type 2 diabetes: a patient-centered approach. *Diabetes Care*. Published electronically ahead of print on 19 April 2012 (DOI: 10.2337/dc12-0413)

<sup>6</sup>ACCORD Study Group: Effects of intense glucose lowering in type 2 diabetes. *N Engl J Med* 358:2545–2559, 2008

<sup>7</sup>Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodowa RG, for the GWAA Study Group: Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 143:559–569, 2005

<sup>8</sup>Diamant M, Van Gaal L, Stranks S, Guerci B, MacConnell L, Haber H, Scism-Bacon J, Trautmann M: Safety and efficacy of once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes. *Diabetes Care* 35:683–689, 2012

<sup>9</sup>Amylin Pharmaceuticals: Exenatide QW prescribing information. Available from [http://documents.bydureon.com/Bydureon\\_PI.pdf](http://documents.bydureon.com/Bydureon_PI.pdf). Accessed 24 April 2012

<sup>10</sup>Novo Nordisk: Liraglutide prescribing information. Available from <http://www.novo-pi.com/victoza.pdf>. Accessed 24 April 2012

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