

**Regence BlueCross BlueShield of Oregon • Regence BlueShield  
Regence BlueCross BlueShield of Utah • Regence BlueShield of Idaho  
Independent licensees of the Blue Cross and Blue Shield Association**

**Medication Policy Manual**

**Policy No:** dru120

**Topic:** Byetta<sup>®</sup>, exenatide

**Date of Origin:** September 14, 2005

**Revised/Effective Date:** May 8, 2009

**Next Review Date:** May 2010

**IMPORTANT REMINDER**

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Exenatide (Byetta<sup>®</sup>) is a synthetic injectable medication that resembles the human incretin hormone, glucagon-like-peptide-1 (GLP-1). Exenatide is administered subcutaneously as adjunctive therapy in patients with type II diabetes who have not achieved adequate glycemic control while taking metformin and/or a sulfonylurea.

## **Policy/Criteria**

- I.** Most contracts require prior authorization approval of exenatide prior to coverage. Exenatide may be considered medically necessary in patients with type 2 diabetes when both criteria A and B below are met.

- A.** There is documentation that the patient's A1C value is over 7%.

### **AND**

- B.** A 90-day treatment course with each of the following (criteria 1 and 2 below) did not adequately reduce A1C to goal of 7% or less, was not tolerated, or is contraindicated.

- 1.** Metformin

### **AND**

- 2.** One other preferred or generic medication for the treatment of type 2 diabetes (examples include insulin, glyburide, glipizide, rosiglitazone [Avandia<sup>®</sup>] and pioglitazone [Actos<sup>®</sup>]).

## **II.** Administration, Quantity Limitations, and Authorization Period

- A.** Regence considers exenatide to be a self-administered medication.

- B.** When prior authorization is approved, exenatide may be authorized in quantities of one penfill injection per month.

- C.** Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

## **III.** Exenatide is considered investigational when used for all other conditions, including, but not limited to:

- A.** Weight reduction in patients without diabetes. (Note: under some plan benefits, medications used for weight loss are contract exclusions).

- B.** In combination with pramlintide (Symlin<sup>®</sup>).

- C.** Islet-cell transplantation

**D** Polycystic-Ovary Syndrome

**E.** For medical conditions other than for type 2 diabetes.

## **Position Statement**

### ***Background***

- The American Diabetes Association has established a treatment algorithm for type 2 diabetes. <sup>[8, 12]</sup>
  - \* The recommended therapy for newly diagnosed type 2 diabetes includes using metformin in addition to lifestyle interventions.
  - \* Metformin can lower A1c by about 1.8% compared to placebo and is associated with reducing complications of diabetes.
  - \* If a goal A1C of  $\leq 7\%$  is not achieved, then the addition of either basal insulin, a sulfonylurea, or a thiazolidinedione is recommended, depending on individual patient considerations.
  - \* If the goal A1C is then not reached, the addition of a medication from one of the other classes is recommended.
  - \* Ultimately, the use of intensive insulin + metformin  $\pm$  a thiazolidinedione is recommended, if needed, to achieve the goal A1C level.

### ***Goal of Treatment***

- The American Diabetes Association has set an A1C treatment goal for patients with diabetes to not exceed 7%. <sup>[8]</sup>
  - Lowering A1C to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes.
  - \* Recent large-scale, randomized controlled trials have failed to find a significant long-term benefit of intensive glycemic control (A1C goals less than 6.5%) for lowering cardiovascular (macrovascular) risk. <sup>[8, 13-15]</sup>
  - \* Intensive glycemic control (A1C goals less than 6.5%) may increase mortality in some patients. <sup>[13]</sup>

- The American Association of Clinical Endocrinologists (AACE) treatment guidelines suggest an A1C treatment target for patients with diabetes of 6.5%. However, this recommendation was last updated in 2007 prior to the availability of the most recent diabetes treatment outcomes trials that raise concerns about aggressive A1C lowering.<sup>[10]</sup>

### *Exenatide Overview*

- Exenatide can lower A1C by up to 1% alone and when combined with other therapies.<sup>[1]</sup>
- Of the available alternatives, metformin, sulfonylureas and insulin, combined with lifestyle modifications, represent the best value in lowering A1C.<sup>[8, 12]</sup>
- There is no evidence that exenatide provides better A1C lowering or improvement in long-term outcomes than insulin therapy, thiazolidinediones, or other oral antihyperglycemic agents.<sup>[8-12]</sup>
- Exenatide is not a substitute for insulin and is not for use in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.<sup>[1]</sup>
- Like other antihyperglycemic medication used in diabetes, exenatide carries risk of hypoglycemia when used together with a sulfonylurea or other secretagogues. For example, up to 35.7% (when used in combination with a sulfonylurea).<sup>[1]</sup>
- Nausea (44%), vomiting (13%) and diarrhea (13%) are the other most frequently reported adverse events with exenatide.<sup>[1-4]</sup>
- There is no evidence to establish the safety and efficacy of exenatide for weight reduction or that the observed weight reductions in clinical trials with exenatide are clinically relevant and result in improved health outcomes.

### *Clinical Efficacy*

- Exenatide, when used alone or when added to a sulfonylurea, metformin and or a thiazolidinedione, provides a modest decrease in A1C of up to 1% compared to placebo.<sup>[1-4, 6, 16, 17]</sup>

- There is no evidence that exenatide with a sulfonylurea and/or metformin provides better A1C lowering or improvement in long-term outcomes than insulin therapy or oral hypoglycemic agents (other than a sulfonylurea or metformin).
- Both exenatide and insulin glargine may provide similar improvements in overall glycemic control in patients with type 2 diabetes that are suboptimally controlled with oral combination therapy. <sup>[5]</sup>
  - \* Weight reduction is generally observed with exenatide more often than with insulin.
  - \* Gastrointestinal adverse effects are reported more frequently than with insulin glargine.

### *Weight loss*

- The long-term clinical efficacy of exenatide for the reduction of body weight in patients with or without diabetes has not been established.
- In clinical trials, the observed mean weight loss at 30 weeks with exenatide was dose-dependent and ranged up to 6 ½ lb (3 kg) compared to placebo. <sup>[1-4, 16]</sup>
- In an open-label extension trial, the observed mean weight loss at 82 weeks in the subset of patients remaining in the trial (30% of those originally randomized) was about 9 lb (4 kg). <sup>[7]</sup>
- There are currently no well-designed studies to establish the long-term maintenance or a progressive weight reduction with exenatide.

### *Other Uses*

- Small-scale trials have evaluated exenatide in the post-transplant management of patients who have received islet-cell transplantation for treatment of type 1 diabetes. This work is still preliminary, and remains investigational at this time. <sup>[23]</sup>
- A small, randomized, controlled trial evaluated the combination of exenatide with metformin in the management of women with polycystic ovary syndrome (PCOS). Though results suggested that the combination might have advantages over either agent alone, larger trials of longer duration are needed to assess long-term efficacy and safety. <sup>[24]</sup>

*Safety*

- Primary adverse effects and reasons for discontinuation with exenatide are nausea and hypoglycemia. <sup>[1-5]</sup>
- Hypoglycemia occurred more often when exenatide was added to sulfonylureas with or without metformin (14.4% - 35.7%, or approximately 1/6 to 1/3 of patients). <sup>[1, 2, 4]</sup>
- When added to metformin, the incidence of hypoglycemia with exenatide is 4.5 – 5.3% (or approximately 1 out of 20 patients). <sup>[1,3]</sup>

<b>Appendix 1: Comparison Of Product Information Reported Reductions In A1C (Monotherapy Only)</b> <sup>[1, 18-22]</sup>				
<b>Drug</b>	<b>Baseline A1C (%)</b>	<b>Duration of Trial</b>	<b>Mean change from baseline (%)</b>	<b>Placebo Corrected change in A1C (%)</b>
<b>metformin (Glucophage<sup>®</sup>) up to 2550 mg per day</b>	8.4	29 weeks	-1.4	-1.8
<b>pioglitazone (Actos<sup>®</sup>) 30 mg to 45 mg daily</b>	10.2 to 10.3	26 weeks	-0.3 to -0.9	-1.0 to -1.6
<b>rosiglitazone (Avandia<sup>®</sup>) 2 mg bid to 4 mg bid</b>	8.9 to 9.0	26 weeks	-0.1 to -0.7	-0.9 to -1.5
<b>repaglinide (Prandin<sup>®</sup>) up to 4 mg daily (titration trial)</b>	8.5	12 weeks	-0.6	-1.7
<b>exenatide (Byetta<sup>®</sup>) 5 to 10 mcg BID (with metformin)</b>	8.2 to 8.3	30 weeks	-0.4 to -0.8	-0.5 to -0.9
<b>glimepiride 8 mg once daily (Amaryl<sup>®</sup>, generic)</b>	unknown	14 weeks	unknown	-2.0
<b>sitagliptin (Januvia<sup>®</sup>) 100 mg once daily</b>	8.0	18 to 24 weeks	-0.5 to -0.6	-0.6 to -0.8

\*Note: Data are pooled from separate studies or product literature and not necessarily comparable

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Cross References
Symlin <sup>®</sup> , pramlintide, dru121
Pioglitazone-containing medications, dru131
Rosiglitazone-containing medications, dru132
Januvia <sup>®</sup> , sitagliptin-containing medications (Januvia, Janumet <sup>®</sup> ) dru140
Transplant Section - Islet Transplantation, Transplant 13, September 1, 2008.

Codes	Number	Description
HCPCS	J3490	Unclassified drugs