

GLP-1 Receptor Agonists (Byetta[®]/Victoza[®]) Step Therapy Criteria

Brand	Generic	Dosage Form
Byetta [®]	exenatide	subcutaneous injection
Victoza [®]	liraglutide	subcutaneous injection

PROGRAM OBJECTIVES

The intent of the GLP-1 (glucagon-like peptide-1) Receptor Agonists (Byetta/ exenatide and Victoza/ liraglutide) Step Therapy program is to ensure appropriate selection of patients based on product labeling and/or clinical guidelines and/or clinical studies. Byetta and Victoza are currently approved by the Food and Drug Administration (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.^{1,2,6} In clinical trials exenatide and liraglutide have been studied as monotherapy as well as in combination with metformin, a sulfonylurea, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione (TZD). Exenatide has also been studied in combination with a TZD. The concurrent use of exenatide or liraglutide and insulin has not been studied and is not recommended in the current prescribing information. In guidelines GLP-1 receptor agonists are generally considered second, third, or fourth line agents.^{4,5} Appropriate patients for exenatide or liraglutide therapy are those with a diagnosis of type 2 diabetes who are concurrently receiving or have tried and failed metformin, a sulfonylurea, a thiazolidinedione, or a combination of these agents. The electronic step edit identifies patients with one of these prerequisite agents in claims history within the previous 90 days. The step edit allows continuation of therapy when patients have been receiving and are stabilized on exenatide or liraglutide. The step edit does not allow exenatide or liraglutide claims to go through when concomitant insulin therapy is seen. Patients without prerequisite agents in claims history or those who are unable to take a prerequisite agent due to allergy, contraindication, or intolerance will be reviewed through the manual prior authorization process when the patient's prescriber has submitted documentation to support use of exenatide or liraglutide in the patient.

PROGRAM FUNCTIONALITY

Electronic Edits

The overall process for step therapy requires that another drug or drugs be tried in a specific previous time period before the claim drug. If the patient has met any of the requirements outlined below, the requested step therapy medication will be paid under the patient's current prescription benefit. The 90-day look-back time period was chosen as an indicator of recent or current adjunct therapy; the 60-day look-back time period was chosen as an indicator of concomitant therapy. If the patient has not met the requirements, the system will reject with the message indicating that prior authorization is necessary. The Prior Authorization (PA) Criteria for Approval would then be applied to requests submitted by the patient's practitioner for evaluation.

A Division of Health Care Service Corporation, a Mutual Legal Reserve Company, an Independent Licensee of the Blue Cross and Blue Shield Association

Table 1: Summary of GLP-1 Receptor Agonists Step Therapy

Targeted Agent(s)	Byetta, Victoza
Is auto-grandfathering implemented? (with look-back time frame)	Yes (90 days ^a)
Prerequisite Agent(s)	metformin, sulfonylurea, TZD, metformin/TZD, or metformin/sulfonylurea
Number of prerequisites required	1
Prerequisite look-back time frame	90 days ^a
Age-related edit?	NA
Additional comments	Byetta and Victoza claims will NOT pay if a claim for an insulin product is found in the previous 60 days ^b even if one of the prerequisites or Byetta or Victoza is seen within the look-back time frame.

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

b - The system searches for a claim with a days supply that begins or ends in the past 60 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 90 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 150 days.

Table 2: Details of GLP-1 Receptor Agonists Step Therapy

Targeted Agents	GPIs	Prior Agents	GPIs	Look-back Time frames
Byetta, Victoza	27170020***** 27170050***** multisource code M, N, or O	Contraindicated Therapy – must NOT have: Insulin	2710***** multisource code M, N, O, or Y	Contraindicated Therapy look-back time frame: 60 days ^b
		For Prerequisites, ANY ONE of: Metformin Sulfonylurea TZD Metformin/sulfonylurea Metformin/TZD	27250050***** 272000***** 276070***** 279970***** 279980***** multisource code M, N, O, or Y	Prerequisite look-back time frame: 90 days ^a
		For Auto-grandfathering, ANY ONE of: Byetta, Victoza	27170020***** 27170050***** multisource code M, N, or O	Auto-grandfathering look-back time frame: 90 days ^a

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

b - The system searches for a claim with a days supply that begins or ends in the past 60 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 90 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 150 days.

If the patient does not meet the step therapy criteria, then the system will reject with the message indicating that prior authorization is necessary. The *Prior Authorization (PA) Criteria for Approval* would then be applied to requests submitted by the patient’s practitioner for evaluation.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

The intent of the *PA Criteria for Approval* is to ensure that patients who have used a required prerequisite drug not identifiable in electronic claims history may be approved for payment of exenatide or liraglutide through the manual process. If the patient has a prescription history of exenatide or liraglutide use or metformin, sulfonylurea, TZD, combination metformin/sulfonylurea or combination metformin/TZD use, exenatide or liraglutide may be approved for a period of 12 months. Exenatide or liraglutide may also be approved if the patient has allergies, contraindications, or intolerance to the prerequisite agents. New prescriptions for exenatide or liraglutide will not be approved for patients who are currently receiving an insulin product.

Step Therapy PA Criteria for Approval Byetta (exenatide), Victoza (liraglutide)

Initial and Renewal Evaluation

1. Does the patient's medication history indicate previous Byetta (exenatide) or Victoza (liraglutide) therapy?
If yes, approve for 12 months. If no, continue to 2.
2. Is the patient currently receiving an insulin product?
If yes, deny. If no, continue to 3.
3. Does the patient's current medication therapy include one or more of the following oral antidiabetic agents; metformin, a sulfonylurea, a thiazolidinedione, metformin/sulfonylurea combination, metformin/thiazolidinedione combination?
If yes, approve for 12 months. If no, continue to 4.
4. Does the patient have allergies, contraindications, or intolerance to all of the following classes of prerequisite oral agents; metformin, sulfonylureas, thiazolidinediones?
If yes, approve for 12 months. If no, deny.

CLINICAL RATIONALE

The intent of the prior authorization (PA) criteria for exenatide and liraglutide is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines. Appropriate patients are defined by product labeling as type 2 diabetics who are prescribed exenatide or liraglutide as adjunctive therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.^{1,6} The step edit electronically identifies one of the prerequisite agents (metformin, sulfonylurea, thiazolidinedione [TZD] or combinations of these agents) or exenatide or liraglutide in patient claims history as indicators of appropriate patients for exenatide or liraglutide use. Exenatide and liraglutide are not indicated for use in type 1 diabetes mellitus.

Exenatide has been shown to be effective, as adjunctive therapy in patients taking metformin, a sulfonylurea, a TZD, or a combination of metformin with a sulfonylurea or a TZD, in further reducing hemoglobin A1c (A1C) levels (see Formulary Chapter 4.6 J GLP-1 Analogues (Incretin Mimetics)).²

A systematic review³ of 29 published studies that included exenatide compared with placebo injection found that GLP-1 analogues such as exenatide showed a statistically significant difference in A1C decline from baseline favoring the incretin therapy (weighted mean difference -0.97%; 95% CI, -1.13 to -0.81). There was no difference in A1C lowering between exenatide and insulin glargine or biphasic aspart. In trials that reported data on changes in weight, there was a statistically significant weight loss observed with GLP-1 analogues vs comparator groups (weighted mean difference, -2.37 kg; 95% CI, -3.95 to -0.78). Weight loss was more pronounced when compared to insulin. Severe hypoglycemia was rare with GLP-1 analogues, reported in 5 of 2781 patients treated with exenatide and only in patients who also received sulfonylureas.³

A total of 3978 patients with type 2 diabetes participated in 5 double-blind (one of these trials had an open-label active control insulin glargine arm), randomized, controlled clinical trials with liraglutide, one of 52 weeks duration and four of 26 weeks duration. These multinational trials were conducted to evaluate the

glycemic efficacy and safety of liraglutide in type 2 diabetes as monotherapy and in combination with one or two oral anti-diabetic medications. The 4 add-on combination therapy trials enrolled patients who were previously treated with anti-diabetic therapy, and approximately two-thirds of patients in the monotherapy trial also were previously treated with anti-diabetic therapy. In these 5 clinical trials, patients ranged in age from 19-80 years old and 54% were men. In each of these trials, treatment with Victoza produced clinically and statistically significant improvements in hemoglobin A1C and fasting plasma glucose (FPG) compared to placebo.⁶

Concomitant insulin and exenatide or liraglutide therapy has not been evaluated. The step therapy criteria for exenatide and liraglutide do not include subcutaneous insulin as a prerequisite agent and will not provide for coverage of exenatide or liraglutide in new users on concurrent insulin therapy.

Exenatide has been added to the consensus algorithm for the management of hyperglycemia in type 2 diabetes mellitus from the American Diabetes Association and the European Association for the Study of Diabetes.⁴ The authors of the algorithm include exenatide as a second tier option for a step-2 addition (first tier step-2 options include basal insulin or a sulfonylurea) to pharmacologic therapy of metformin for patients in whom hypoglycemia is particularly undesirable, or if promotion of weight loss is a major consideration and A1C level is close to target (defined as <8.0%).⁴ Currently the American Association of Clinical Endocrinologists guidelines⁵ list exenatide as an option only for patients with type 2 diabetes mellitus who have already been treated pharmacologically. It can be combined with oral therapy (metformin, sulfonylurea, thiazolidinedione, or combination) in patients who have not achieved glycemic goals.⁵ Liraglutide is not mentioned specifically in these guidelines.^{4,5}

FDA APPROVED INDICATIONS^{1,6}

The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the section "Prior Authorization Criteria for Approval."

Byetta (exenatide) and Victoza (liraglutide) injection are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.^{1,6}

Important Limitations of Use

Byetta/Victoza is not a substitute for insulin. Byetta/Victoza should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.^{1,6}

The concurrent use of Byetta/Victoza with insulin has not been studied and cannot be recommended.^{1,6}

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.¹

In clinical trials of Victoza, there were more cases of pancreatitis with Victoza than with comparators. Victoza has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza. Use with caution in patients with a history of pancreatitis.⁶

Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.⁶

REFERENCES

1. Byetta prescribing information. Amylin Pharmaceuticals, Inc. October 2009.
2. Prime Therapeutics Formulary Chapter 4.6 J GLP-1 Analogues July 2008.

3. 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.
4. 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. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009;32(1):193-203.
5. Rodbard HW, Chairperson, for AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. American Association of Clinical Endocrinologists Medical Guideline for Clinical Practice for the Management of Diabetes Mellitus. *Endocrine Practice*. 2007;13(suppl 1):3-68.
6. Victoza prescribing information. Novo Nordisk Inc. January 2010

Document History

Original Prime Standard approved by External UMC 05/2007

Original Review of Prime Standard criteria approved by HCSC Corporate Clinical Committee 08/2007

Annual Review criteria maintained approved by External UM Committee 02/2008

Annual review of criteria, without changes; approved by P&T UM Committee: 02/2009

Annual Review, Client Specific criteria approved by HCSC Corporate Clinical Committee 06/2009

Administrative Action (addition of Victoza/liraglutide as a target) 02/2010