EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Glucagon-Like Peptide-1 (GLP-1) Agonists
- Adlyxin™ (lixisenatide injection – SanofiAventis)
- Byetta® (exenatide injection – Amylin)
- Bydureon™ (exenatide extended-release for injection – Amylin)
- Tanzeum™ (albiglutide for subcutaneous injection – GlaxoSmithKline)
- Trulicity™ (dulaglutide injection – Eli Lilly)
- Victoza® (liraglutide injection – NovoNordisk)

TAC APPROVAL DATE: 12/21/2016
LAY CRITERIA EFFECTIVE DATE: 12/30/2016

OVERVIEW

Adlyxin, Byetta, Bydureon, Tanzeum, Trulicity, and Victoza are glucagon-like peptide-1 (GLP-1) agonists, indicated in adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1-4,39] The GLP-1 agonists are administered by subcutaneous (SC) injection; Byetta is administered twice daily (BID), Bydureon, Tanzeum, and Trulicity are administered once weekly (QW) and Adlyxin and Victoza are administered once daily (QD).[1-4,35,39] GLP-1 agonists are incretin mimetic agents that bind and activate the human GLP-1 receptor.[1-4,35] Activation of this receptor increases glucose-dependent insulin secretion by pancreatic beta-cells, suppresses glucagon secretion, and slows gastric emptying. The GLP-1 agonists have been studied in a variety of settings and combinations.[2,5-26] In addition to glycemic efficacy, one advantage of the GLP-1 agonists is their propensity for weight reduction.[6] For more detailed information on the class see the ***Diabetes - GLP-1 agonists Therapy Class Summary*.**

Efficacy

As monotherapy, the glucose-lowering effectiveness of noninsulin pharmacological agents is considered to be high for metformin, sulfonylureas (SUs), thiazolidinediones (TZDs), and the GLP-1 agonists with an expected glycosylated hemoglobin (HbA_{1C}) reduction of 1.0% to 1.5%, dependent on baseline values. On average the addition of any second agent is generally expected to result in a further reduction in HbA_{1C} of approximately 1%. As monotherapy, based on pivotal trial data the GLP-1 agonists result in weight reductions of approximately 2 to 3 kg, depending on baseline weight.[1-2,4,20,27]

Guidelines/Consensus or Position Statements

Each year the ADA publishes Standards of Care in Diabetes.[11] These guidelines provide comprehensive recommendations for diabetes; however, pharmacologic management is only briefly mentioned in the guidelines. The American Association of Clinical Endocrinologists (AACE) provides an algorithm approach for the management of type 2 diabetes and discussion of the GLP-1 therapy class (2016) which serves as a supplement to the AACE/American College of Endocrinology (ACE) comprehensive care plan in diabetes (2015).[36-37] In addition, the ADA/European Association for the Study of Diabetes (EASD) provides a position statement for the management of type 2 diabetes with more discussion around specific medical therapies (2012 with a 2015 update).[6,38] In most cases, metformin is regarded as first-line therapy in patients with type 2 diabetes. When glycemic control is not achieved with metformin other agents may be added. The sequencing of add-on therapies varies between the algorithms and is

based on individual patient characteristics including glycemic control and comorbid medical conditions. The GLP-1 agonists are generally regarded as add-on therapy when glycemic control is not achieved with metformin. If metformin is not a first-line option, GLP-1 agonists may be considered.

The AACE/ACE Guidelines (2015) note that all currently available glucose-lowering agents are more or less similar in their glucose-lowering potency, tolerability and side-effect profile as well as extraglycemic effects.[37] Further, as monotherapy, most oral agents reduce HbA_{1C} by 0.5% to 2.0%. With respect to GLP-1 agonists, all five currently approved GLP-1 agonists are addressed and no preference for one over the other is expressed. This class is most useful as add-on therapy for patients with inadequately controlled diabetes during oral therapy. Several clinical trials have compared the effects of adding a GLP-1 agonist (Byetta or Victoza) to basal insulin in patients with inadequately controlled type 2 diabetes on oral therapy. The studies show equivalent or slightly better HbA_{1C} lowering by GLP-1 agonists with the advantages of weight loss with little to no additional hypoglycemia. The guidelines note that approximately 5% to 10% of patients cannot tolerate the GLP-1 agonists due to GI effects.

The AACE guidelines Consensus Statement (2016) discusses the GLP-1 class.[36] GLP-1 agonists have robust HbA_{1C} lowering properties, are usually associated with weight loss and blood pressure reductions, and are available in several formulations. The risk of hypoglycemia with GLP-1 agonists is low. They are not recommended for use in patients with a personal or family history of MTC or those with multiple endocrine neoplasia syndrome type 2 (MEN). The GLP-1 agonists are recognized as add-on therapy when metformin is not effective in attaining glycemic control or when metformin cannot be used as initial therapy. No recommendation for a specific GLP-1 agonist is made. A consensus statement from the ADA/EASD (2012) provides an algorithm for glycemic control in adults with type 2 diabetes and recommends metformin as initial drug therapy in most patients and the positioning of GLP-1 agonists as add-on therapy.[6] The ADA/EASD cites modest weight loss as the main advantage of the GLP-1 agonists.[6] The limiting AE is noted to be nausea and vomiting, particularly early in treatment. The glucose lowering efficacy of the non-insulin pharmacologic agents is considered to be high for the GLP-1 agonists, metformin, SUs, and TZDs with noted reductions ranging from 1.0% to 1.5%. The statement notes that any differential effect on glucose control is minimal, and therefore agent and patient specific properties such as dosing frequency, AE profile and other benefits often guide selection of the pharmacologic therapy. The placement of the GLP-1 agonists is generally after metformin therapy (as add-on); however, the statement noted that in cases where metformin cannot be used at initial therapy, that a GLP-1 agonist may be an option, especially when weight loss is seen as an essential aspect of therapy. When monotherapy alone does not maintain the HbA_{1C} target over about 3 months, the next step would be to add a second oral agent, a GLP-1 agonist, or basal insulin. On average any second agent is typically associated with an approximate further reduction in HbA_{1C} of about 1%. The statement also recognizes the accumulating data for the use of GLP-1 agonists in combination with basal insulin. In the 2015 update, all five GLP-1 agonists are recognized, and no preference for one over the other is expressed.[37]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of the GLP-1 agonists. The goal of this Express Scripts program (prior authorization) is to appropriately limit the coverage of Byetta, Bydureon, Tanzeum, Trulicity, and Victoza to use in type 2 diabetes mellitus and to prevent the use of these drugs for unapproved conditions (e.g., weight loss). All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: If criteria for previous use of an oral medication for diabetes (this includes all oral medications for diabetes) are not met at the point of service, coverage will be determined by prior authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA
Food and Drug Administration (FDA)-Approved Indications

1. **Type 2 Diabetes Mellitus.** Approve the requested GLP-1 agonist (Adlyxin, Byetta, Bydureon, Tanzuem, Trulicity, or Victoza).

   The GLP-1 agonists are indicated in adults with type 2 diabetes mellitus in adjunct to diet and exercise.[1-3]

CONDITIONS NOT RECOMMENDED FOR APPROVAL
The GLP-1 agonists have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Type 1 Diabetes Mellitus**. Exception is not recommended. Limited data are available.[32-34] Prospective, randomized studies are needed. None of the GLP-1 agonists are indicated for patients with type 1 diabetes.[1-4]

2. **Weight Loss Treatment**. Exception is not recommended. Saxenda contains the same chemical entity as Victoza at a higher dosage and is indicated in the treatment of weight loss. Additional studies with longer duration with Victoza are needed to demonstrate sustainability of weight loss.

   Victoza was studied in non-diabetic adults with body-mass index (BMI) 30 to 40 kg/m^2 (n = 564) in a randomized, double-blind, placebo-controlled, and open label Xenical (120 mg three times daily [TID]) comparator trial.[30] In addition to treatment with Victoza, patients were adherent to a low-fat diet, and exercise. Four doses of Victoza were studied, including two non-FDA-approved doses (2.4 mg QD and 3.0 mg QD). Estimated mean weight loss in the intent-to-treat (ITT) population at Week 20 was statistically greater for all Victoza doses (1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg) ranging from 4.8 kg to 7.2 kg compared to placebo (mean reduction 2.8 kg [95% confidence interval {CI}: -3.7, -1.8]). Only the 2.4 mg and 3.0 mg Victoza doses produced a statistically greater weight loss than Xenical. Patients who received Xenical (120 mg TID) had a mean weight loss of 4.1 kg (95% CI: 5, -3.2). Non-diabetic obese adults (BMI $\geq$ 30 kg/m^2) with or without impaired fasting glucose were randomized to Byetta (titrated to 10 mcg BID) or placebo for 24 weeks in addition to a structured diet and exercise program (n = 163).[31] Mean baseline body weight was 109.5 ± 2.7 kg and 107.6 ± 2.6 kg for Byetta and placebo groups respectively. Byetta-treated patients lost 5.1 ± 0.5 kg from baseline vs. 1.6 ± 0.5 kg with placebo (P < 0.001 for the difference). Withdrawal rates were similar for Byetta and placebo-treated patients (34% vs. 32%, respectively). Caloric intake was significantly reduced in both Byetta and placebo groups.

   A 35-week, double-blind, placebo controlled, crossover study with two 16-week treatment periods separated by a 3-week washout randomized 41 adult women with BMIs between 28 and 40 kg/m^2 and without type 1 or type 2 diabetes (24% of patients had prediabetes at baseline) to treatment with

Byetta 5µg or identically matched placebo administered BID (at breakfast and dinner); no lifestyle intervention was employed.[32] After 2 weeks, patients increased the dose of Byetta or matching placebo to 10µg BID. Enrolled patients were not allowed to have used any anti-obesity medications within 1 year of study entry, have a history of bariatric surgery, or to have prior treatment with Byetta. The primary outcome was assessment of body weight (kg) and BMI. After 16 weeks of Byetta treatment, patients lost (mean ± standard deviation [SD]) 2.49 ± 0.66 kg compared with an increase of 0.43 ± 0.63 kg during placebo treatment ($P < 0.01$). This corresponded to a 2.7% decrease in body weight during treatment with Byetta and a 0.2% increase in body weight during placebo treatment. The significant reduction in bodyweight was observed at Week 2 and persisted for the treatment period. A small, but statistically significant reduction in BMI was reported for Byetta treatment (-0.93 kg/m^2) compared with placebo (+0.18 kg/m^2) [$P = 0.01$]. A retrospective analysis revealed that weight loss with Byetta treatment was variable; three levels of response were identified. In total 30% of patients (n = 11) lost > 5% of their body weight (range 5% to 12.5%); 39% of patients (n = 14) lost < 5% of their body weight (range 0.4% to 4.8%; and 31% of patients (n = 12) were nonresponders who did not lose weight or experienced weight gain (range 0.19% to 5.8% increase in body weight). There were no significant changes in secondary parameters such as blood pressure, lipid profiles, insulin and adiponectin levels, or homeostasis model assessment (HOMA) scores between treatment and placebo.

The efficacy of Victoza treatment was compared to placebo in older (mean age 58 ± 8 years) overweight/obese adults (mean BMI 31.9 kg/m^2) with pre-diabetes (based on elevated fasting glucose or elevated 2-hour glucose) in a 14-week, double-bind, placebo-controlled, single-center study.[33] Patients were randomized to Victoza (titrated to 1.8 mg) or placebo daily (n = 68). Patients were advised to eat a moderate carbohydrate diet and to decrease total caloric intake by 500 kcal/day and to maintain their baseline physical activity. There were 24 and 27 Victoza and placebo patients, respectively, included in the efficacy analyses (31% of Victoza- and 18% of placebo-treated patients discontinued). All but three patients tolerated the 1.8 mg Victoza dose. Patients treated with Victoza lost 6.8 kg while patients receiving placebo lost 3.3 kg ($P < 0.001$). The majority of Victoza-treated patients (88%) lost 5% of baseline weight compared with 22% of patients assigned to placebo. Improvements in insulin resistance for Victoza-treated patients were also noted. Steady-state plasma glucose was decreased by 29% in the Victoza group compared with no change in the placebo group ($P < 0.001$ for the difference between groups). Victoza-treated patients also had significant reductions in systolic blood pressure, fasting glucose, and triglycerides concentrations as compared with placebo. In addition 75% of Victoza-treated patients attained normal fasting glucose as compared with 19% of placebo patients ($P < 0.001$). As a result, patients treated with Victoza but not placebo, had a significant decrease in the number of components of the metabolic syndrome (-1.1 vs. -0.2; $P = 0.001$). The majority of patients treated with Victoza experienced at least one GI AE (79%) compared with 46% of placebo patients.

A Phase III trial assessed the efficacy of Victoza in maintaining weight loss (at least 5%) achieved with a low calorie diet (n = 422) in non-diabetic patients.[34] Overweight/obese individuals who lost at least 5% of initial weight during a low-calorie diet run-in were randomly assigned to Victoza 3 mg/day or placebo for 56 weeks. Diet and exercise counseling were provided throughout the trial. Patients lost a mean 6.0% (SD 0.9) of screening weight during run-in. From randomization to Week 56, weight decreased an additional mean 6.2% (SD 7.3) with Victoza and 0.2% (SD 7.0) with placebo (estimated difference -6.1%; 95% CI: -7.5, -4.6; $P < 0.0001$). More patients receiving Victoza (81.4%) than placebo (48.9%) maintained the ≥ 5% run-in weight loss (estimated odds ratio [OR], 4.8; 95% CI: 3.0, 7.7; $P < 0.001$).

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria.

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