Glucagon-Like Peptide-1 (GLP-1) Agonists/and Insulin Combination

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Origination: 06/2014  Next Review: 07/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for GLP-1 agonist products when it is determined to be medically necessary because the following criteria are met.

When Policy Topic is covered
Food and Drug Administration (FDA)-Approved Indications

Patient with Type 2 Diabetes Mellitus. Members must try metformin, unless contraindicated, before GLP-1 Agonist

Step 1: metformin
Step 2: Members must try TWO preferred alternatives Byetta, Bydureon, Trulicity, or Xultophy before a Step 3, or non-preferred product
Step 3: Victoza, Tanzeum; Adlyxin

When Policy Topic is not covered
Coverage of GLP-1 Agonists is recommended in circumstances that are listed in the Recommended Authorization Criteria (FDA-Approved Indications and Other Uses with Supportive Evidence). The following provides rationale for specific Exclusions. This is not an exhaustive list of Exclusions.

Weight Loss Treatment. Exception is not recommended. Additional studies with longer duration are needed to demonstrate sustainability of weight loss. (Saxenda is indicated for weight loss and not Type 2 Diabetes Mellitus)

Victoza was studied in non-diabetic adults with body-mass index (BMI) 30 to 40 kg/m² (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 ≥ 30 kg/m²) 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/m² 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. 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/m²) compared with placebo (+0.18 kg/m²) [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/m²) with pre-diabetes (based on elevated fasting glucose or elevated 2-hour glucose) in a 14-week, double-blind, placebo-controlled, single-center study. 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. 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).

**Type 1 Diabetes Mellitus.** Exception is not recommended.

Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria.
Considerations
GLP-1 agonists require prior authorization through the pharmacy services department.

This Blue Cross and Blue Shield of Kansas City policy statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

Description of Procedure or Service
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. 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 Victoza is administered once daily (QD). GLP-1 agonists are incretin mimetic agents that bind and activate the human GLP-1 receptor. 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. In addition to glycemic efficacy, one advantage of the GLP-1 agonists is their propensity for weight reduction.

GLP-1 Agonists are pharmacy benefit

Rationale
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 (HbA1c) 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 HbA1c 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.

Guidelines/Consensus or Position Statements
The American Diabetes Association (ADA) Standards of Medical Care for type 2 diabetes (2015) recommend to initiate metformin along with lifestyle interventions, unless metformin is contraindicated, at diagnosis. In newly diagnosed patients with type 2 diabetes who have markedly symptomatic and/or elevated blood glucose levels or HbA1c, insulin therapy should be considered, with or without additional agents, from the outset. When noninsulin monotherapy at maximal tolerated doses do not achieve or maintain the HbA1c target over 3 to 6 months, a second oral agent, a GLP-1 receptor agonist, or insulin should be added. Because there is a lack of long-term comparative-effectiveness information available, the ADA does not offer a uniform recommendation for the best agent to be combined with metformin, rather the statement considers the importance of individualized treatment based on the advantages and disadvantages of the various drug classes.

The AACE and the American College of Endocrinology (ACE) comprehensive diabetes management algorithm (2013) recommends agents for glycemic control in patients with type 2 diabetes listed in a hierarchy with choices broken down by baseline HbA1c. In patients with a baseline HbA1c of < 7.5%, the hierarchy of treatment (monotherapy) is metformin, GLP-1 agonist, dipeptidyl peptidase-4 (DPP-4) inhibitor, alpha glucosidase inhibitor, sodium glucose co-transporter 2 inhibitor (SGLT-2), TZD, and SU or meglitinide. In patients with a baseline HbA1c of ≥ 7.5% dual therapy is warranted and would include one of the following agents in combination with metformin: GLP-1 agonist, DPP-4 inhibitor, TZD, SGLT-2, basal insulin, colesvelam, Cycloset® (bromocriptine tablets), alpha-glucosidase inhibitor, SU/meglititide. When patients do not reach their goal HbA1c in 3 months on dual therapy, triple therapy
is warranted and may include the addition of any of the following agents as the third drug (listed in hierarchical order): GLP-1, TZD, SGLT-2, basal insulin, DPP-4 inhibitor, coleselam, Cycloset, alpha glucosidase inhibitor, SU/meglitinide. In patients with a baseline HbA1c > 9.0% who are asymptomatic, dual or triple therapy at initiation is recommended. The GLP-1 agonists are also recommended for intensifying insulin therapy when patients are not at goal with basal insulin alone. Recognized benefits of the GLP-1 agonist class are weight reduction and neutral effects on hypoglycemia.

A position statement from the ADA and European Association for the Study of Diabetes (EASD) for the management of type 2 diabetes (2012) recommends initial therapy with metformin unless it is contraindicated. Metformin therapy is recommended to be initiated at, or soon after, diagnosis, especially for patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, glycemic goals (i.e., HbA1c). If metformin cannot be used, another oral agent could be chosen (e.g., sulfonylurea/meglitinide, pioglitazone, or a DPP-4 inhibitor); in cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 agonist may be useful. When monotherapy alone does not achieve or maintain an HbA1c over a course of about 3 months, the addition of a second oral agent, a GLP-1 agonist, or basal insulin is recommended to escalate therapy. The higher the HbA1c the more likely insulin will be required. The addition of a second agent generally results in an additional 1% reduction in HbA1c. In patients with a high baseline HbA1c (e.g., ≥ 9.0%) it may be justified to initiate therapy with two non-insulin agents or to start with insulin.

References


**Other References Utilized**

**Billing Coding/Physician Documentation Information**
Pharmacy benefit

**Additional Policy Key Words**
5.01.565

**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Update Details</th>
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<tbody>
<tr>
<td>06/2014</td>
<td>New Policy titled Glucagon-Like Peptide-1 (GLP-1) Agonists</td>
</tr>
<tr>
<td>07/2015</td>
<td>Policy reviewed—no changes</td>
</tr>
<tr>
<td>09/2015</td>
<td>Updated policy to include step therapy requirement; updated references</td>
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<tr>
<td>03/2016</td>
<td>Added the dual step</td>
</tr>
<tr>
<td>03/2017</td>
<td>Added the step therapy of two preferred products before non-preferred</td>
</tr>
<tr>
<td>07/2017</td>
<td>Policy reviewed—no changes</td>
</tr>
<tr>
<td>08/2017</td>
<td>Changed title to include GLP1 with Insulin combinations; added the following products as non-preferred: Adlyxin, Soliqua</td>
</tr>
<tr>
<td>09/2017</td>
<td>Removed Soliqua from non-preferred.</td>
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