Medication Policy Manual

Policy No: dru345

Topic: Non-Preferred Branded DPP4-Inhibitor-Containing Medications:
-alogliptin (Nesina®, Kazano®, Oseni®)
-linagliptin (Tradjenta®, Jentadueto®)

Date of Origin: May 9, 2014

Committee Approval Date: July 14, 2017

Next Review Date: July 2018

Effective Date: August 1, 2017

IMPORTANT REMINDER

This Medication 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 Medication Policy is to provide a guide to coverage. Medication 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

Alogliptin (Nesina®), linagliptin (Tradjenta®), and saxagliptin (Onglyza®) are oral medications used for the treatment of type 2 diabetes. They block the dipeptidyl peptidase-4 (DPP-4) enzyme. By blocking this enzyme, insulin production increases, glucose production in the liver goes down, and blood sugar levels decrease. Combination products containing these medications include: alogliptin/ metformin (Kazano®), alogliptin/ pioglitazone (Oseni®), and linagliptin/ metformin (Jentadueto®).

Policy/Criteria

I. Most contracts require prior authorization approval of alogliptin- and linagliptin-containing medications prior to coverage. These medications may be considered medically necessary for the treatment of type 2 diabetes when criteria A, B, and C below are met.

A. Treatment with metformin is contraindicated, not tolerated, or has been ineffective after 90 days of therapy.

AND

B. Treatment with a sitagliptin-containing medication (e.g. Januvia, Janumet, Janumet XR) is contraindicated, not tolerated, or has been ineffective after 90 days of therapy.

AND

C. Treatment with a saxagliptin-containing medication (e.g. Onglyza, Kombiglyze) is contraindicated, not tolerated, or has been ineffective after 90 days of therapy.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers alogliptin- and linagliptin-containing medications to be a self-administered medication.

B. When prior authorization is approved, non-preferred DPP-4 inhibitor-containing medications may be authorized in quantities as follows:

1. Alogliptin (Nesina): 30 tablets per month
2. Alogliptin/ metformin (Kazano): 60 tablets per month
3. Alogliptin/ pioglitazone (Oseni): 30 tablets per month
4. Linagliptin (Tradjenta): 30 tablets per month
5. Linagliptin/ metformin (Jentadueto): 60 tablets 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. Alogliptin- and linagliptin-containing medications are considered investigational when used for any condition other than type 2 diabetes, including, but not limited to:

A. Pre-diabetes/ prevention of diabetes

B. Weight loss

C. Metabolic syndrome

D. Polycystic Ovary Syndrome

E. Type 1 diabetes or diabetic ketoacidosis

Position Statement

Summary

- Metformin (along with lifestyle changes) is the best value for the initial treatment of type 2 diabetes, with proven efficacy and safety track record.
- DPP4-inhibitors are treatment options when metformin results in inadequate glucose lowering or is not tolerated.
- Among the DPP4-inhibitors, sitagliptin and saxagliptin are the best value for members.
- The safety and effectiveness of DPP4-inhibitors in conditions other than type 2 diabetes have not been established.

Background

- The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have published a joint position statement on the management of type 2 diabetes. [1, 2]
    - Glycemic targets and glucose-lowering therapies must be individualized; however diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.
    - 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 preliminary data suggest there are some potential cardiovascular benefits.
    - If a goal A1C of ≤ 7% is not achieved, then the addition of one or more oral or injectable agents from other classes is reasonable, depending on individual patient considerations. Of note, SGLT2-inhibitors are not included in the ADA guidelines as a treatment option.
    - Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.
    - Comprehensive cardiovascular risk reduction (e.g. controlling blood pressure, cholesterol, and smoking cessation) must be a major focus of therapy.

Goal of Treatment

- The American Diabetes Association has set an A1C treatment goal for patients with diabetes to not exceed 7%. [1]
    - Lowering A1C to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes.
    - 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. [1, 3-5]
    - Intensive glycemic control (A1C goals less than 6.5%) may increase mortality in some patients. [3]

- The American Association of Clinical Endocrinologists (AACE) treatment guidelines suggest an A1C treatment target for patients with diabetes of 6.5%. However, this goal must be customized for the individual patient in consideration of factors such as comorbid conditions, duration of diabetes, history of hypoglycemia, hypoglycemia unawareness, patient education, motivation, adherence, age, limited life expectancy, and use of other medications.[6, 7]

Clinical Efficacy

- DPP4-inhibitors lower A1C compared to placebo by 0.3% to 0.8%, but they have not been proven to reduce complications of diabetes. [9-12]
- Metformin can lower A1C by about 1.8% compared to placebo and is associated with reducing complications of diabetes. [8]
- There are no clinical studies establishing conclusive evidence of macrovascular risk reduction with DPP4-inhibitors. [9-12]
- There are no clinical trials that have demonstrated a superior benefit of DPP4-inhibitors over first line therapies such as metformin (see Appendix 1).
- There is no evidence that one DPP4-inhibitor is more effective than another.
- A high-quality systematic review of DPP4-inhibitors concluded that, in patients with type 2 diabetes who do not achieve the glycemic targets with metformin alone, DPP4-inhibitors can lower A1C in a similar way to sulfonylureas or pioglitazone, with neutral effects on body weight. Increased costs of the DPP4-inhibitors and unknown long-term safety continue to be concerns regarding their use. [24]

Safety

- The most common adverse reactions (reported in ≥ 5% of patients treated with DPP4-inhibitors and more commonly than in patients treated with placebo) are: upper respiratory tract infection, headache, and nasopharyngitis. [9-12]
- The prescribing information for DPP4-inhibitors includes a warning regarding severe and disabling arthralgia and the risk of acute pancreatitis. Risk of acute pancreatitis is small and likely a class effect, which has been appreciated with more extensive post-marketing clinical experience. The FDA is currently reviewing all incretin mimetics (DPP-4 inhibitors and GLP-1 agonists) for risk of pancreatitis and pancreatic cancer. Saxagliptin- and alogliptin-containing medications also have a warning for the risk of heart failure in patients who have known risk factors for heart failure. [9-12, 25,26]

Dosing

- The recommended dose of alogliptin (in patients with an estimated creatinine clearance ≥ 60 mL/min) is 25 mg once daily, either as monotherapy or combination. [9]
    - In moderate renal insufficiency (CrCl ≥ 30 mL/min to <60 mL/min), the dose of alogliptin should be 12.5 mg once daily. [9]
    - In severe renal insufficiency (CrCl < 30 mL/min), or with ESRD requiring hemodialysis or peritoneal dialysis, the dose of alogliptin should be 6.25 mg once daily. [9]

- The recommended dose of linagliptin is 5 mg once daily, either as monotherapy or combination. No dosage adjustment is needed for renal or hepatic impairment. [10]
- The safety and effectiveness of higher doses have not been established.

Investigational Conditions

- Prediabetes / Prevention of Diabetes / Metabolic Syndrome
    - There are no clinical trials that have demonstrated that DPP4-inhibitors can prevent or delay the development of type 2 diabetes.
    - DPP4-inhibitors have not been proven to improve health outcomes in the treatment of "metabolic syndrome".
- Weight Loss
    - Some medications used for the management of diabetes, such as DPP4-inhibitors and GLP1-agonists, have been associated with weight loss in clinical studies. It is unknown, however, if the observed weight reductions are clinically relevant and result in improved health outcomes.
- Polycystic Ovary Syndrome
    - There are no reliable clinical trials that have shown DPP4-inhibitors to be beneficial in the management of polycystic ovary disease.
- Type 1 Diabetes / Diabetic Ketoacidosis
    - There are no well-designed, randomized controlled trials that demonstrate a benefit to using DPP4-inhibitors in type 1 diabetes.
    - The FDA approved prescribing information for DPP4-inhibitors states that they 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. [9-12]

Appendix 1: Comparison of Product Information Reported Reductions In A1C (Monotherapy Only) [8-23]				
Drug	**Baseline A1C (%)**	**Duration of Trial**	**Mean change from baseline (%)**	**Placebo Corrected change in A1C (%)**
Biguanide				
metformin (Glucophage®, generic) up to 2550 mg per day	8.4	29 weeks	-1.4	-1.8
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors				
alogliptin (Nesina®) 12.5 mg to 25 mg once daily	7.9	26 weeks	-0.6	-0.6
linagliptin (Tradjenta®) 5 mg once daily	7.7 to 8.6	18 to 104 weeks	-0.4 to -0.7	-0.6 to -0.7
saxagliptin (Onglyza®) 2.5 mg to 5 mg once daily	7.9 to 8.0	24 weeks	-0.4 to -0.5	-0.6
sitagliptin (Januvia®) 100 mg once daily	8.0	18 to 24 weeks	-0.5 to -0.6	-0.6 to -0.8
Glucagon-like Peptide-1 (GLP-1) Agonists				
albiglutide (Tanzeum®) up to 50 mg weekly (with metformin)	8.1	104 weeks	-0.6	-0.9
dulaglutide (Trulicity™) up to 1.5 mg weekly (with metformin)	7.6	26 weeks	-0.9 to -1.1	-0.8 to -1.0
exenatide (Byetta®) up to 10 mcg twice daily (with metformin)	8.2 to 8.3	30 weeks	-0.4 to -0.8	-0.5 to -0.9
exenatide ER (Bydureon®) 2 mg once weekly (with metformin)	8.6	26 weeks	-1.5	N/A†
liraglutide (Victoza®) up to 1.8 mg once daily (with metformin)	8.3 to 8.4	26 weeks	-1.0	-1.1
Meglitinide				
repaglinide (Prandin®) up to 4 mg daily	8.5	12 weeks	-0.6	-1.7
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors				
canagliflozin (Invokana®) up to 300 mg once daily	8.01	26 weeks	-1.03	-1.16
dapagliflozin (Farxiga™) up to 10 mg once daily	8	24 weeks	-0.9	-0.7
empagliflozin (Jardiance®) up to 25 mg once daily	7.9	24 weeks	-0.7	-0.7
Sulfonylurea				
glimepiride (Amaryl®, generic) 8 mg once daily	unknown	14 weeks	unknown	-2.0
Thiazolidinedione (TZD)				
pioglitazone (Actos®, generic) 30 mg to 45 mg daily	10.2 to 10.3	26 weeks	-0.3 to -0.9	-1.0 to -1.6

*Note: Data are pooled from separate studies or product literature and not necessarily comparable
† No placebo-controlled trials available

Cross References
Non-Preferred Branded GLP1-Agonist-Containing Medications, dru347
SGLT2-Inhibitor-Containing Medications, dru506

Codes	Number	Description
N/A		

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Revision History

Revision Date	Revision Summary
07/14/2017	Removed Onglyza and Kombiglyze XR from policy (now a preferred brand).
05/13/2016	No changes to coverage criteria with this annual update