Pharmacy Policy Bulletin

Title: Oral Antidiabetic Agents
Policy #: Rx.01.68

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

**Intent:**
The intent of this policy is to communicate the medical necessity criteria for alogliptin (Nesina®), alogliptin/pioglitazone (Oseni®), alogliptin/metformin (Kazano®), linagliptan (Tradjenta®), linagliptan/metformin (Jentadueto®), dapagliflozin (Farxiga™), dapagliflozin/metformin (Xigduo™), and metformin ER (Glumetza) as provided under the member’s pharmacy benefit.

**Description:**
Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and usually relative (rather than absolute) insulin deficiency. Patients with T2DM may have insulin levels that appear normal or elevated. However, the higher blood glucose levels in these patients would be expected to result in even higher insulin values with normally functioning beta cells. Hence, insulin secretion is defective and insufficient to compensate for insulin resistance.

Metformin, a biguanide, is the recommended first line agent for T2DM, barring any contraindications or intolerance. Other agents may be considered if metformin is not tolerated. Combination therapy may be considered when monotherapy with metformin is ineffective at lowering A1C to goal or A1C at diagnosis is 7.5% or greater.

**Dipeptidyl peptidase (DPP)- 4 inhibitors** (alogliptin, linagliptin)

DPP-4 is an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinoirotropic polypeptide (GIP). By inhibiting DPP-4, these agents increase the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal
level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta-cells in the presence of normal and elevated blood glucose levels. Additionally, GLP-1 reduces glucagon secretion from pancreatic alpha-cells, resulting in a reduction in hepatic glucose output.

**Metformin**

Metformin is a biguanide that improves glucose tolerance in patients with T2DM, lowering basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in patients with T2DM or in healthy subjects except in special circumstances and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged, while fasting insulin levels and day-long plasma insulin response may actually decrease.

**Sodium-glucose cotransporter (SGLT) 2 inhibitors (dapagliflozin)**

SGLT2 is expressed in the proximal renal tubules and is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. SGLT2 inhibitors reduce reabsorption of filtered glucose and lower the renal threshold for glucose, thereby increasing urinary glucose excretion.

**Thiazolidinediones (TZDs) (pioglitazone)**

TZDs are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, thus improving insulin sensitivity in muscle and adipose tissue while inhibiting hepatic gluconeogenesis. TZDs are not insulin secretagogues, but require the presence of insulin to exert their effects. TZDs are agonists for peroxisome proliferator-activated receptor (PPAR)-gamma. PPAR-gamma receptors are found in tissues important for insulin action such as adipose, skeletal muscle, and liver. Activation of PPAR-gamma nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

Alogliptin (Nesina®), alogliptin/pioglitazone (Oseni®), and alogliptin/metformin hydrochloride (Kazano®), canagliflozin (Invokana®), linagliptin (Tradjenta®), linagliptin/metformin (Jentadueto®) and dapagliflozin (Farxiga), dapagliflozin/metformin (Xigduo™), and metformin ER (Glumetza) are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

**Policy:**

Alogliptin (Nesina), alogliptin/pioglitazone (Oseni), alogliptin/metformin hydrochloride (Kazano), linagliptin (Tradjenta), linagliptin/metformin (Jentadueto) are approved when there is an inadequate response or inability to tolerate ALL of the following:

1. Metformin; and
2. Januvia or Janumet; and
3. Onglyza or Kombiglyze XR

Dapagliflozin (Farxiga) and dapagliflozin/metformin (Xigduo XR) are approved when there is an inadequate response or inability to tolerate ONE of the following:

1. Canagliflozin (Invokana, Invokamet) or
2. Empagliflozin (Jardiance, Synjardy)

Metformin ER (Glumetza and generic for Glumetza only) is approved when there is inadequate response or inability to tolerate BOTH of the following:

1. Two generic forms of extended release metformin and
2. Glucophage XR

**Black Box Warning:**

Metformin containing products (Kazano, Jentadueto, Xigduo)

Lactic acidosis is a rare, but serious, complication that can occur because of metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure.

The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, discontinue metformin containing agent and immediately hospitalize the patient.

**TZD containing products (Oseni):**

Congestive heart failure:

TZDs cause or exacerbate congestive heart failure (CHF) in some patients. After initiation and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain; dyspnea, edema). If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the thiazolidinedione must be considered.

TZDs are not recommended in patients with symptomatic heart failure. Initiation in patients with established New York Heart Association (NYHA) class III or IV heart failure is contraindicated.

**Guidelines:**

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

**BENEFIT APPLICATION**

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the pharmacy benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

**References:**


Garber AJ, et al. Consensus statement by the American Association of Clinical Endocrinologists and the American College of Endocrinology on the comprehensive type 2 diabetes management
Applicable Drugs:

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
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<tbody>
<tr>
<td>Nesina</td>
<td>alogliptin</td>
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<tr>
<td>Oseni</td>
<td>alogliptin/pioglitazone</td>
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<tr>
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<td>linagliptan</td>
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<td>Xigduo XR</td>
<td>dapagliflozin/metformin</td>
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Synjardy: empagliflozin/metformin
Glumetza: metformin ER

Cross References: