



Pharmacy Benefit Coverage Criteria

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Coverage Policy Number P0098

Antihyperglycemic Therapy (Non-Insulin)

Table of Contents

- Overview 1
- Medical Necessity Criteria 2
- Authorization Duration 5
- Conditions Not Covered..... 5
- FDA Approved Indications 5
- Recommended Dosing 7
- Background 8
- References 9

Related Coverage Resources

- [Quantity Limitations](#)
- [Step Therapy - Standard/Performance Prescription Drug Lists \(Employer group plans\) - \(1801\)](#)
- [Step Therapy - Value/Advantage Prescription Drug Lists \(Employer Group Plans\) - \(1802\)](#)
- [Step Therapy - Legacy Prescription Drug Lists \(Employer Group Plans\) - \(1803\)](#)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy addresses coverage criteria for the following antihyperglycemic therapy classes:

Single agent

- **Dipeptidyl Peptidase-4 (DPP-4) Inhibitors** [refer to [Appendix 1](#) for products]
- **Metformin Products**

Combination

- **DPP-4 Fixed-dose Combinations** [refer to [Appendix 5](#) for products]

The below **metformin requirement criteria** apply to new starts AND only for the specified antihyperglycemic therapies.

Coverage for **antihyperglycemic therapy** varies across plans and requires the use of preferred products in addition to the criteria listed below. Refer to the customer's benefit plan document for coverage details.

Receipt of sample product does not satisfy any criteria requirements for coverage.



Medical Coverage Policy

Medical Necessity Criteria

Single-agent DPP-4 inhibitors, SGLT2 inhibitors, GIP/GLP-1 RAs, GLP-1 RAs, and fixed-dose combinations of DPP-4 inhibitors/Metformin, SGLT2 inhibitors/Metformin, DPP-4/SGLT2 inhibitors, SGLT2/DPP-4 inhibitors/Metformin are medically necessary when **ALL** of the following criteria are met:

1. Prescriber attestation of **ONE** of the following:
 - Unable to achieve goal HbA1C despite metformin or metformin-containing regimen (meglitides, sulfonyleureas, or thiazolidinediones) at greater than or equal to 1,500 mg per day
 - Intolerance to metformin 1,500 mg per day despite appropriate dose titration duration (for example, period of 8-12 weeks)
 - Contraindication to metformin per FDA label (for example, acute/chronic metabolic acidosis, severe renal dysfunction)
 - Not a candidate for metformin (for example, hepatic impairment, moderate renal dysfunction, unstable heart failure, individual is using an agent for a non-diabetic FDA-approved indication)
 - Initial metformin combination therapy is clinically appropriate for elevated HbA1C (for example; HbA1C greater than 1.5% above goal)
 - Initial metformin combination therapy is clinically appropriate in an individual with co-morbid conditions (such as ASCVD, heart failure, or CKD)

2. Individual will continue maximally tolerated metformin therapy, if not contraindicated per FDA label, intolerant, or otherwise not a candidate

3. Where coverage requires the use of preferred products, there is documentation of **ONE** of the following:
 - The individual has a contraindication according to FDA label OR significant intolerance to ALL of covered alternatives* according to the table below
 - OR**
 - The individual is not a candidate for ALL covered alternatives* according to the table below due to being subject to a warning per the prescribing information (labeling), having a disease characteristic, individual clinical factor[s], or other attributes/conditions or is unable to administer and requires this dosage formulation

The below preferred product requirements apply to **BOTH** new starts AND existing product users.

Employer Group Non-Covered Products and Preferred Covered Alternatives by Drug List:

	Standard / Performance	Value / Advantage	Cigna Total Savings	Legacy
DPP-4 Inhibitors				
Alogliptin	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[‡] • sitagliptin (Januvia, Janumet / Janumet XR) 	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[‡] • sitagliptin (Januvia, Janumet / Janumet XR) 	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[‡] • linagliptin (Tradjenta, Jentaduetto / Jentaduetto XR) 	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[‡] • sitagliptin (Januvia, Janumet / Janumet XR)
Januvia® (sitagliptin)	Covered as Preferred Brand (step therapy may apply)	Covered as Preferred Brand (step therapy may apply)	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[‡] 	Covered as Preferred Brand (step therapy may apply)

	Standard / Performance	Value / Advantage	Cigna Total Savings	Legacy
			<ul style="list-style-type: none"> linagliptin (Tradjenta, Jentaduetto / Jentaduetto XR) 	
Nesina (alogliptin)	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] sitagliptin (Januvia, Janumet / Janumet XR) 	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] sitagliptin (Januvia, Janumet / Janumet XR) 	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] linagliptin (Tradjenta, Jentaduetto / Jentaduetto XR) 	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] sitagliptin (Januvia, Janumet / Janumet XR)
Onglyza [®] (saxagliptin)	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] sitagliptin (Januvia, Janumet / Janumet XR) 	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] sitagliptin (Januvia, Janumet / Janumet XR) 	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] linagliptin (Tradjenta, Jentaduetto / Jentaduetto XR) 	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] sitagliptin (Januvia, Janumet / Janumet XR)
Tradjenta [®] (linagliptin) Effective until 12/31/2024	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] sitagliptin (Januvia, Janumet/ Janumet XR) 	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] sitagliptin (Januvia, Janumet / Janumet XR) 	Covered as Preferred Brand	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] sitagliptin (Januvia, Janumet / Janumet XR)
DPP-4 Fixed-dose Combinations				
Alogliptin-metformin	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] Janumet / Janumet XR (sitagliptin-metformin) 	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] Janumet / Janumet XR (sitagliptin-metformin) 	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] Jentaduetto / Jentaduetto XR (linagliptin-metformin) 	BOTH of the following: <ul style="list-style-type: none"> Metformin requirement criteria[‡] Janumet / Janumet XR (sitagliptin-metformin)
Alogliptin-pioglitazone	<ul style="list-style-type: none"> Januvia[®] (sitagliptin) with pioglitazone 	<ul style="list-style-type: none"> Januvia[®] (sitagliptin) with pioglitazone 	<ul style="list-style-type: none"> Tradjenta[®] (linagliptin) with pioglitazone 	<ul style="list-style-type: none"> Januvia[®] (sitagliptin) with pioglitazone
Janumet [®] Janumet XR [®] (sitagliptin-metformin)	Covered as Preferred Brand (step therapy may apply)	Covered as Preferred Brand (step therapy may apply)	BOTH of the following:	Covered as Preferred Brand (step therapy may apply)

	Standard / Performance	Value / Advantage	Cigna Total Savings	Legacy
			<ul style="list-style-type: none"> • Metformin requirement criteria[†] • Jentaduetto / Jentaduetto XR (linagliptin-metformin) 	
Jentaduetto[®] Jentaduetto XR[®] (linagliptin-metformin) Effective until 12/31/2024	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[†] • Janumet[®] / Janumet XR[®] (sitagliptin-metformin) 	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[†] • Janumet[®] / Janumet XR[®] (sitagliptin-metformin) 	Covered as Preferred Brand (step therapy may apply)	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[†] • Janumet[®] / Janumet XR[®] (sitagliptin-metformin)
Kazano (alogliptin-metformin)	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[†] • Janumet[®] / Janumet XR[®] (sitagliptin-metformin) 	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[†] • Janumet[®] / Janumet XR[®] (sitagliptin-metformin) 	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[†] • Jentaduetto / Jentaduetto XR (linagliptin-metformin) 	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[†] • Janumet[®] / Janumet XR[®] (sitagliptin-metformin)
Kombiglyze XR[®] (saxagliptin-metformin)	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[†] • Janumet XR[®] (sitagliptin-metformin) 	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[†] • Janumet XR[®] (sitagliptin-metformin) 	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[†] • Jentaduetto XR[®] (linagliptin-metformin) 	BOTH of the following: <ul style="list-style-type: none"> • Metformin requirement criteria[†] • Janumet XR[®] (sitagliptin-metformin)
Oseni (alogliptin-pioglitazone)	<ul style="list-style-type: none"> • Januvia[®] (sitagliptin) with pioglitazone 	<ul style="list-style-type: none"> • Januvia[®] (sitagliptin) with pioglitazone 	<ul style="list-style-type: none"> • Tradjenta[®] (linagliptin) with pioglitazone 	<ul style="list-style-type: none"> • Januvia[®] (sitagliptin) with pioglitazone
Metformin Products				
Fortamet[®] (metformin extended-release tablets)	BOTH of the following: <ul style="list-style-type: none"> • metformin ER (Glucophage[®] XR) • metformin immediate-release tablet 			
Glumetza[®] (metformin extended-release tablets)	BOTH of the following: <ul style="list-style-type: none"> • metformin ER (Glucophage[®] XR) • metformin immediate-release tablet 			
Metformin IR 625 mg	Individual meets BOTH of the following (A and B): A. Documented inadequate response to ONE of the following (i or ii):			

	Standard / Performance	Value / Advantage	Cigna Total Savings	Legacy
(metformin immediate release tablets)	i. Metformin immediate-release 500 mg oral tablet ii. Metformin extended release 500 mg oral tablet B. Documented intolerance to BOTH of the following (i <u>and</u> ii): i. Metformin immediate-release 850 mg oral tablet ii. Metformin extended release 750 mg oral tablet			
Metformin ER osmotic tablets (Fortamet®)	BOTH of the following: <ul style="list-style-type: none"> metformin ER (Glucophage® XR) metformin immediate-release tablet 			
Metformin ER tablets (Glumetza®)	BOTH of the following: <ul style="list-style-type: none"> metformin ER (Glucophage® XR) metformin immediate-release tablet 			

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

*If you're a Cigna provider, please [log in to the Cigna for Health Care Professionals](#) website and search for specific patients to view their covered medications.

Authorization Duration

Initial and reauthorization is up to 12 months unless otherwise stated.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven.

FDA Approved Indications

FDA Approved Indication

Brand Name	Approved Indication
DPP-4 Inhibitors	
Januvia (sitagliptin)	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. <u>Limitations of Use</u> Januvia 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. Januvia 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 the development of pancreatitis while using Januvia.
Nesina (alogliptin)	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. <u>Limitations of Use</u>

Brand Name	Approved Indication
	Nesina is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.
Onglyza (saxagliptin)	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. <u>Limitation of Use</u> Onglyza is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.
Tradjenta (linagliptin)	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. <u>Limitations of Use</u> Tradjenta 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. Tradjenta has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using Tradjenta.
DPP-4 Fixed-dose Combinations	
Janumet / Janumet XR (sitagliptin-metformin)	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin/metformin ER is appropriate. <u>Limitations of Use</u> Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. 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 the development of pancreatitis.
Jentadueto / Jentadueto XR (linagliptin-metformin)	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate. <u>Limitation of Uses</u> 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. Has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis.
Kazano (alogliptin-metformin)	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both alogliptin and metformin is appropriate. <u>Limitation of Use</u> Kazano is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.
Kombiglyze XR (saxagliptin-metformin)	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate. <u>Limitation of Use</u> Kombiglyze XR is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
Oseni (alogliptin-pioglitazone)	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both alogliptin and pioglitazone is appropriate.

Brand Name	Approved Indication
	<u>Limitation of Use</u> Oseni is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

Recommended Dosing

FDA Recommended Dosing

Brand Name	Recommended Dosing
DPP-4 Inhibitors	
Januvia (sitagliptin)	The recommended dose of Januvia is 100 mg once daily. Januvia can be taken with or without food.
Nesina (alogliptin)	The recommended dose of Nesina is 25 mg once daily. Nesina may be taken with or without food.
Onglyza (saxagliptin)	The recommended starting dose of Onglyza is 2.5 mg or 5 mg once daily taken regardless of meals. Onglyza tablets must not be split or cut.
Tradjenta (linagliptin)	The recommended dose of Tradjenta is 5 mg once daily. Tradjenta tablets can be taken with or without food.
DPP-4 Fixed-dose Combinations	
Janumet / Janumet XR (sitagliptin-metformin)	<p>The maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin.</p> <p><u>Janumet</u></p> <ul style="list-style-type: none"> The starting dose of JANUMET should be based on the patient's current regimen. JANUMET should be given twice daily with meals The recommended starting dose in patients not currently treated with metformin is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin The starting dose in patients already treated with metformin should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken. For patients taking metformin 850 mg twice daily, the recommended starting dose of JANUMET is 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily <p><u>Janumet XR</u></p> <ul style="list-style-type: none"> In patients not currently treated with metformin, the recommended total daily starting dose of Janumet XR is 100 mg sitagliptin and 1000 mg metformin hydrochloride (HCl) extended release. Patients with inadequate glycemic control on this dose of metformin can be titrated gradually, to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily dose In patients already treated with metformin, the recommended total daily starting dose of Janumet XR is 100 mg sitagliptin and the previously prescribed dose of metformin. For patients taking metformin immediate-release 850 mg twice daily or 1000 mg twice daily, the recommended starting dose of Janumet XR is two 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablets taken together once daily Maintain the same total daily dose of sitagliptin and metformin when changing between Janumet (sitagliptin and metformin HCl immediate release) and Janumet XR. Patients with inadequate glycemic control on this dose of metformin can be titrated gradually, to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily dose
Jentadueto / Jentadueto XR	<p><u>Jentadueto</u></p> <ul style="list-style-type: none"> In patients currently not treated with metformin, initiate treatment with 2.5 mg linagliptin/500 mg metformin hydrochloride twice daily

Brand Name	Recommended Dosing
(linagliptin-metformin)	<ul style="list-style-type: none"> In patients already treated with metformin, start with 2.5 mg linagliptin and the current dose of metformin taken at each of the two daily meals (e.g., a patient on metformin 1000 mg twice daily would be started on 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily with meals) Patients already treated with linagliptin and metformin individual components may be switched to Jentadueto containing the same doses of each component <p><u>Jentadueto XR</u></p> <ul style="list-style-type: none"> In patients currently not treated with metformin, initiate Jentadueto XR treatment with 5 mg linagliptin/1000 mg metformin hydrochloride extended release once daily with a meal In patients already treated with metformin, start Jentadueto XR with 5 mg of linagliptin total daily dose and a similar total daily dose of metformin once daily with a meal In patients already treated with linagliptin and metformin or Jentadueto, switch to Jentadueto XR containing 5 mg of linagliptin total daily dose and a similar total daily dose of metformin once daily with a meal Jentadueto XR should be swallowed whole. The tablets must not be split, crushed, dissolved, or chewed before swallowing.
Kazano (alogliptin-metformin)	<p>Healthcare providers should individualize the starting dose of Kazano based on the patient's current regimen.</p> <p>Kazano should be taken twice daily with food with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin. Kazano tablets must not be split before swallowing. The maximum total daily dose is 25 mg alogliptin/2000 mg metformin.</p>
Kombiglyze XR (saxagliptin-metformin)	<p>Kombiglyze XR should generally be administered once daily with the evening meal, with gradual dose titration to reduce the gastrointestinal side effects associated with metformin.</p> <p>The recommended starting dose of KOMBIGLYZE XR in patients who need 5 mg of saxagliptin and who are not currently treated with metformin is 5 mg saxagliptin/500 mg metformin extended release once daily with gradual dose escalation to reduce the gastrointestinal side effects due to metformin</p> <p>In patients treated with metformin, the dosage of KOMBIGLYZE XR should provide metformin at the dose already being taken, or the nearest therapeutically appropriate dose. Following a switch from metformin immediate-release to metformin extended-release, glycemic control should be closely monitored and dosage adjustments made accordingly</p> <p>Patients who need 2.5 mg saxagliptin in combination with metformin extended release may be treated with Kombiglyze XR 2.5 mg/1000 mg</p> <p>Patients who need 2.5 mg saxagliptin who are either metformin naive or who require a dose of metformin higher than 1000 mg should use the individual components.</p>
Oseni (alogliptin-pioglitazone)	<p>The maximum total daily dose is 25 mg / 45 mg. Oseni should be taken once daily and can be taken with or without food. The tablets must not be split before swallowing.</p> <p>The recommended starting dose can be 25 mg/15 mg or 25 mg/30 mg. Oseni can be titrated up to a maximum of 25 mg/45 mg once daily based on glycemic response as determined by hemoglobin A1c (A1C).</p>

Background

Professional Societies/Organizations

American Diabetes Association (ADA)

The 2019 ADA: Standards of Medical Care in Diabetes recommends, for the pharmacological management of type 2 diabetes mellitus (T2DM), metformin as the initial therapy, and that metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated. Among patients

with type 2 diabetes who have established atherosclerotic cardiovascular disease (ASCVD), sodium–glucose cotransporter 2 (SGLT2) inhibitors, or glucagon-like peptide 1 (GLP-1) receptor agonists with demonstrated cardiovascular disease benefit are recommended as part of the antihyperglycemic regimen. Among patients with ASCVD at high risk of heart failure (HF) or in whom heart failure coexists, SGLT2 inhibitors are preferred. For patients with T2DM and chronic kidney disease (CKD), consider use of a SGLT2 inhibitor or GLP-1 receptor agonist shown to reduce risk of CKD progression, cardiovascular events, or both. For patients without established ASCVD or CKD, the choice of a second agent to add to metformin is not yet guided by empiric evidence. Drug choice should be based on avoidance of side effects, particularly hypoglycemia and weight gain, cost, and patient preferences. ADA does not recommend one DPP-4 inhibitor over another. (ADA, 2019)

American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE)

The 2019 Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm states that if T2DM is recent onset or mild hyperglycemia (HbA1C < 7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended. In patients who do not reach their glycemic target on metformin monotherapy, metformin should be continued in combination with other agents, including insulin. Patients who present with an A1C >7.5% (whether newly diagnosed or not) and who are not already taking any antihyperglycemic agents should be started initially on metformin plus another agent in addition to lifestyle therapy. In those with cardiovascular disease (CVD) and/or CKD, GLP-1 receptor agonists and SGLT2 inhibitors with proven CVD and/or CKD benefits is preferred as add-on therapy to metformin. Additionally, if individual has coronary heart disease (CHD), a GLP-1 receptor agonist or SGLT2 inhibitor should be included in antihyperglycemic treatment regimen. (AACE/ACE, 2019)

Metformin

Current guidelines recommend, along with lifestyle interventions, that metformin should be the initial pharmacologic therapy for T2DM in the absence of specific contraindications. Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death. Metformin has a low risk of hypoglycemia, can promote modest weight loss, and has good antihyperglycemic efficacy at doses of 1,000 to 2,000 mg/day. (AACE/ACE, 2019; ADA, 2019)

In most DPP-4, GLP-1, and SGLT2 metformin add-on studies, the target metformin dose was 1,500 mg/day or greater. (Adlyxin PI, 2016; Bydureon/Byetta PI, 2018; Farxiga PI, 2019; Invokana, 2018; Januvia, 2019; Jardiance, 2018; Nesina, 2019; Onglyza, 2019; Ozempic, 2019; Steglatro, 2018; Tradjenta, 2019; Trulicity, 2019; Victoza, 2019). In the cardiovascular outcome trials for respective GLP-1 (liraglutide) and SGLT2 (canagliflozin, empagliflozin) agents that carry such risk reduction indication, the vast majority of individuals had metformin as part of their pre-trial antihyperglycemic regimen in those for whom metformin was not contraindicated or was tolerated (percent of patients on metformin therapy: 73% to 77%). (Marso, 2016; Neal, 2017; Zinman, 2015)

Single agents

Appendix 1

DPP-4 Inhibitors
alogliptin (Nesina)
linagliptin (Tradjenta)
saxagliptin (Onglyza)
sitagliptin (Januvia)

Appendix 5

DPP-4 Inhibitor Fixed-dose Combinations
alogliptin-metformin (Kazano)
alogliptin-pioglitazone (Oseni)
linagliptin-metformin (Jentadueto / Jentadueto XR)
saxagliptin-metformin (Kombiglyze XR)
sitagliptin-metformin (Janumet / Janumet XR)

References

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2. ADA Standards of Medical Care in Diabetes, *Diabetes Care* January 2019;42(Suppl. 1):S90–S102. Available at: http://care.diabetesjournals.org/content/42/Supplement_1/S90
3. Ahmann AJ, Capehorn M, Charpentier G et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): A 56-week, open-label, randomized clinical trial. *Diabetes Care.* 2018;41(2):258-266.
4. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomized, open-label study. *Lancet.* 2013;381(9861):117-124.
5. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day vs exenatide twice a day for type 2 diabetes: a 26-week randomized, parallel-group, multinational, open-label trial (LEAD-6). *Lancet.* 2009;374:39-47.
6. Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide in metformin-treated patients with Type 2 diabetes (AWARD-6): a randomized, open-label, phase 3, non-inferiority trial. *Lancet.* 2014;384(9951):1349-1357.
7. Januvia (sitagliptin) [package insert]. Whitehouse Station, NJ. Merck & Co., Inc. July 2019.
8. Janumet/Janumet XR (sitagliptin and metformin/metformin ER) [package insert]. Whitehouse Station, NJ. Merck & Co., Inc. July 2019.
9. Jentadueto/Jentadueto XR (linagliptin and metformin/metformin ER) [package insert]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. July 2019.
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