

Pharmacologic Agents for Type 2 Diabetes

Drug/Class & How Supplied	MOA & A1c Drop	Doses & Adjustments	Adverse Reactions	Comments
Alpha glucosidase inhibitors Acarbose (Precose) <ul style="list-style-type: none"> 25, 50, 100mg tablets Miglitol (Glyset) <ul style="list-style-type: none"> 25, 50, 100mg tablets 	MOA: Slows carbohydrate absorption and digestion in the intestine. A1c: 0.7%	Acarbose Initial dose: 25mg 3 times daily with the first bite of each main meal. Increase dose at 4-8-week intervals until maintenance dose of 50-100mg 3 times daily is reached. <u>Renal</u> : SCr >2 mg/dL or CrCl <25 ml/min: use is not recommended (6x AUC increase) Miglitol Initial dose: 25mg 3 times daily with the first bite of each main meal. Increase dose at 4-8-week intervals to 50mg 3 times daily. May increase to 100mg 3 times daily after 3 months if A1c not satisfactory. <u>Renal</u> : SCr >2 mg/dL or CrCl <25 ml/min: use is not recommended.	<ul style="list-style-type: none"> Flatulence Diarrhea 	<ul style="list-style-type: none"> Weight neutral Requires frequent dosing Acarbose can be used in treatment of prediabetes
Amylin analog Pramlintide (Symlin) <ul style="list-style-type: none"> 1500 mcg/1.5mL solution 2700 mcg/1.5mL solution 	MOA: Slows gastric motility, increases satiety, and reduces postprandial glucagon secretion. A1c: ~0.36% when added to insulin	Initial: 60 mcg immediately before major meals. Titrate to 120 mcg after 3 days if no significant nausea occurs. When initiating, reduce mealtime insulin dose by 50% to avoid hypoglycemia.	<ul style="list-style-type: none"> Nausea Vomiting 	<ul style="list-style-type: none"> Weight neutral/loss Increases satiety Injectable formulation Requires frequent dosing

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<p>Biguanide Metformin (Glucophage, Glucophage XR)</p> <p>Immediate release: 500, 850, 1000mg tablets</p> <p>Extended release: 500, 750, 1000mg tablets</p>	<p>MOA: Inhibits production of glucose, intestinal absorption of glucose, and increases insulin sensitivity in peripheral sites.</p> <p>A1c: 1%</p>	<p>Immediate release Initial: 500 mg once or twice daily or 850 mg once daily. Titrate gradually to minimize GI adverse effects, usually in 500mg or 850mg increments every 7 days. Usual maintenance dose of 1g twice daily or 850mg twice daily.</p> <p>Extended release Initial: 500 mg to 1 g once daily. Titrate gradually to minimize GI adverse effects, usually in 500mg or 850mg increments every 7 days. Max dose of 2g/day</p> <p><u>Renal:</u> eGFR 30-44 mL/min: reduce dose by 50% eGFR <30 mL/min: use is contraindicated <u>Hepatic:</u> Manufacturer recommends avoiding therapy – use cautiously in patients at risk for lactic acidosis.</p>	<ul style="list-style-type: none"> ▪ GI (nausea, diarrhea) ▪ B12 deficiency ▪ Rare lactic acidosis in patients with cardiovascular, renal, or hepatic dysfunction 	<ul style="list-style-type: none"> ▪ Weight neutral (can improve insulin-associated weight gain) ▪ May have cardiovascular benefit. ▪ Monitor renal function at least annually. More frequent monitoring (every 3-6 months) is recommended for patients with eGFR >45 to <60 mL/min.
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<p>Dipeptidyl peptidase 4 (DPP-4) inhibitors (-gliptins)</p> <p>Alogliptin (Nesina, with metformin [Kazano], with pioglitazone [Oseni])</p> <ul style="list-style-type: none"> 6.25, 12.5, 25mg tablets <p>Linagliptin (Tradjenta, with metformin [Jentadueto, Jentadueto XR], with empagliflozin [Glyxambi])</p> <ul style="list-style-type: none"> 5mg tablets <p>Saxagliptin (Onglyza, with metformin [Kombiglyze XR], with dapagliflozin [Qtern], with metformin and dapagliflozin [Qternmet XR])</p> <ul style="list-style-type: none"> 2.5, 5mg tablets <p>Sitagliptin (Januvia, with metformin [Janumet, Janumet XR])</p> <ul style="list-style-type: none"> 25, 50, 100mg tablets 	<p>MOA: Increases insulin synthesis, decreases glucagon secretion, and slows gastric emptying.</p> <p>A1c: 0.5-1%</p>	<p>Alogliptin 25mg once daily</p> <p><u>Renal:</u> CrCl 50-30mL/min: 12.5mg once daily CrCl <30mL/min: 6.25mg once daily <u>Hepatic:</u> Not studied in severe impairment</p> <p>Linagliptin 5mg once daily</p> <p>No dose adjustments needed</p> <p>Saxagliptin 2.5-5mg once daily</p> <p><u>Renal:</u> eGFR <45mL/min: 2.5mg once daily</p> <p>Sitagliptin 100mg once daily</p> <p><u>Renal:</u> eGFR 30-44mL/min: 50mg once daily eGFR <30mL/min: 25mg once daily</p>	<ul style="list-style-type: none"> Common cold symptoms (sore throat, runny nose, headache) Upper respiratory tract infection New or worsening heart failure (saxagliptin and alogliptin) Severe joint pain (rare) 	<ul style="list-style-type: none"> Weight neutral Generally very well tolerated Reduces postprandial glucose CYP3A4 interactions with saxagliptin and linagliptin Should NOT be used in combination with a GLP-1 receptor agonist due to lack of glycemic benefit. Per ADA 2019 guidelines, sitagliptin may be used as an alternative for monotherapy in patients who fail initial therapy with lifestyle intervention and metformin.
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<p>Glucagon-like peptide-1 (GLP-1) agonists</p> <p>Dulaglutide (Trulicity)</p> <ul style="list-style-type: none"> 0.75mg/0.5mL solution 1.5mg/0.5mL solution <p>Exenatide (Byetta) and exenatide ER (Bydureon, Bydureon BCise)</p> <ul style="list-style-type: none"> Byetta <ul style="list-style-type: none"> 10mcg/0.04mL solution 5mcg/0.02mL solution Bydureon <ul style="list-style-type: none"> 2mg pen Bydureon BCise <ul style="list-style-type: none"> 2mg/0.85mL solution <p>Liraglutide (Victoza, with insulin degludec [Xultophy])</p> <ul style="list-style-type: none"> 18mg/3mL solution <p>Lixisenatide (Adlyxin, with insulin glargine [Soliqua])</p> <ul style="list-style-type: none"> 10mcg/0.2mL solution 20mcg/0.2mL solution <p>Semaglutide (Ozempic, Rybelsus*)</p> <ul style="list-style-type: none"> 2mg/1.5mL solution (Ozempic) 7, 14mg tablets (Rybelsus) <p>*(As of 09/20/2019, Rybelsus tablets are FDA approved and will be available in the U.S. beginning in Q4 2019)</p>	<p>MOA: Increases glucose-dependent insulin secretion, decreases inappropriate glucagon secretion, and slows gastric emptying.</p> <p>A1c: 1-1.5%</p>	<p>Dulaglutide</p> <p>Initial: 0.75mg once weekly. May increase to a max dose of 1.5mg once weekly.</p> <p>No dose adjustments provided; monitor GI side effects in renal impairment.</p> <p>Exenatide</p> <p>Initial: 5mcg twice daily within 60 minutes prior to meals. After 1 month, can increase to max of 10mcg twice daily.</p> <p><u>Renal:</u> CrCl <30mL/min: use is not recommended</p> <p>Exenatide ER</p> <p>2mg once weekly</p> <p><u>Renal:</u> eGFR <45mL/min: use is not recommended</p> <p>Liraglutide</p> <p>Initial: 0.6mg once daily for 1 week, then increase to 1.2mg once daily. May increase to max of 1.8mg once daily if needed to achieve glycemic control.</p> <p>No dose adjustments provided</p> <p>Lixisenatide</p> <p>Initial: 10mcg once daily for 14 days; on day 15 increase to 20 mcg once daily.</p> <p><u>Renal:</u> eGFR 89-15mL/min: monitor closely for GI side effects eGFR <15mL/min: use is not recommended</p> <p>Semaglutide</p> <p>Initial: 0.25mg once weekly for 4 weeks</p>	<ul style="list-style-type: none"> GI (diarrhea, nausea) Injection site reaction Pancreatitis (rare). Gallbladder disease (liraglutide, exenatide) May lead to retinopathy complications (semaglutide). 	<ul style="list-style-type: none"> Weight loss is expected (~1.4-4kg) Dose titration is necessary with some formulations to decrease nausea Low risk of hypoglycemia when used as monotherapy. Injectables that must be refrigerated before use Linked to thyroid cancer in rats CV benefit shown with liraglutide and semaglutide (injection) Injection needles are included with dulaglutide, exenatide ER, and semaglutide. Per ADA 2019 guidelines, liraglutide may be used as an alternative for monotherapy in patients who fail
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<p>Meglitinides</p> <p>Nateglinide (Starlix, generics)</p> <ul style="list-style-type: none"> 60, 120mg tablets <p>Repaglinide (Prandin, others, with metformin [PrandiMet])</p> <ul style="list-style-type: none"> 0.5, 1, 2mg tablets 	<p>MOA: Glucose-dependent stimulation of insulin secretion.</p> <p>A1c: 0.7-1.1%</p>	<p>Nateglinide</p> <p>120mg three times daily before meals</p> <p>May start at 60mg TID if close to HbA1c goal.</p> <p><u>Renal:</u> eGFR <30 mL/min, start at 60mg TID. eGFR <15 mL/min, use with caution due to metabolite accumulation.</p> <p>Repaglinide</p> <p>HbA1c <8%: Initial: 0.5 mg before each meal. May titrate to a max of 4 mg/dose or 16 mg/day.</p> <p>HbA1c is ≥8%: Initial: 1 or 2 mg before each meal. May titrate to a max of 4 mg/dose or 16 mg/day.</p> <p><u>Renal:</u> CrCl 20 to 40 mL/min, start 0.5mg with meals; titrate carefully. Not studied when CrCl <20 mL/min.</p>	<ul style="list-style-type: none"> Hypoglycemia Weight gain Headache 	<ul style="list-style-type: none"> Requires frequent dosing, but can be flexible (can hold dose if skipping meal) Reduces postprandial glucose Consider over sulfonylureas due to less hypoglycemia and better postprandial glucose control.
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<p>Sodium-glucose cotransporter 2 (SGLT2) inhibitors (-flozins) Canagliflozin (Invokana, with metformin [Invokamet, Invokamet XR])</p> <ul style="list-style-type: none"> 100, 300mg tablets <p>Dapagliflozin (Farxiga, with metformin [Xigduo XR], with saxagliptin [Qtern], with saxagliptin and metformin [Qternmet XR])</p> <ul style="list-style-type: none"> 5, 10mg tablets <p>Empagliflozin (Jardiance, with linagliptin [Glyxambi], with metformin [Synjardy, Synjardy XR])</p> <ul style="list-style-type: none"> 10, 25mg tablets <p>Ertugliflozin (Steglatro, with Metformin [Segluromet], with Sitagliptin [Steglujan])</p> <ul style="list-style-type: none"> 5, 15mg tablets 	<p>MOA: reduces reabsorption of filtered glucose in the kidney and increases urinary excretion of glucose.</p> <p>A1c: 0.4-0.7%</p>	<p>Canagliflozin Initial: 100mg once daily prior to first meal of the day. May increase to 300mg once daily.</p> <p><u>Renal:</u> eGFR 45-60mL/min: Max 100mg once daily eGFR 30-44mL/min: Initiation not recommended. CREDENCE trial suggests use is associated with decreases in neuropathy and CV events. eGFR <30mL/min: Use is contraindicated</p> <p><u>Hepatic:</u> Severe impairment; use is not recommended</p> <p>Dapagliflozin Initial: 5mg once daily; may increase to 10mg once daily</p> <p><u>Renal:</u> eGFR 30-44mL/min: manufacturer does not recommend use eGFR <30mL/min: Use is contraindicated</p> <p>Empagliflozin Initial: 10mg once daily; may increase to 25mg once daily if needed to achieve glycemic goal</p> <p><u>Renal:</u> eGFR 30-44mL/min: Initiation not recommended. EMPA-REG OUTCOME trial suggests use is associated with decreases in neuropathy and CV events. eGFR <30mL/min: Use is contraindicated</p> <p>Ertugliflozin Initial: 5 mg once daily; if initial dose is tolerated and further glycemic control is</p>	<ul style="list-style-type: none"> UTI Dizziness Hypotension Fractures, decreased BMD (canagliflozin) Genital fungal infections Hyperkalemia, especially in renal failure Amputations occur in ~6 /1,000 over 1 year, compared to about 3/1,000 patients on other diabetes agents (canagliflozin). 	<ul style="list-style-type: none"> Weight loss CV benefit (canagliflozin, empagliflozin) Renal benefit (canagliflozin)
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<p>Sulfonylureas (2nd generation) Glyburide (Glynase, Micronase, generics, with metformin [Glucovance])</p> <ul style="list-style-type: none"> 1.25, 1.5, 2.5, 3, 5, 6 mg tablets <p>Glipizide (Glucotrol, Glucotrol XL, generics, with metformin [Metaglip])</p> <ul style="list-style-type: none"> 2.5, 5, 10 mg tablets <p>Glimepiride (Amaryl, generics, with pioglitazone [Duetact], with rosiglitazone [Avandaryl])</p> <ul style="list-style-type: none"> 1, 2, 4 mg tablets 	<p>MOA: Stimulates insulin secretion, increases insulin sensitivity at peripheral sites, and reduces glucose release from liver.</p> <p>A1c: 0.7-1.3%</p>	<p>Glimepiride Initial: 1-2mg once daily with first main meal of the day. May titrate by 1-2 mg every 1-2 weeks up to 8 mg once daily.</p> <p><u>Renal</u>: eGFR <15 mL/min: consider alternate therapy.</p> <p>Glipizide IR Initial: 2.5mg once daily 30 minutes before a meal. May titrate by 2.5-5mg every few days.</p> <p>Doses >15 mg/day should be administered in 2 divided doses. Doses >20mg/day have not been shown to improve glycemic control.</p> <p><u>Renal</u>: eGFR <50 mL/min: initial 2.5mg/day, use caution</p> <p>Glipizide XL Initial: 2.5-5mg once daily with first meal of the day. May titrate by 5-10mg to max dose of 20mg/day.</p> <p><u>Renal</u>: initial 2.5mg/day, use caution.</p> <p>Glyburide Initial: 2.5-5mg once daily with first main meal of the day. May titrate by 2.5mg weekly to a max dose of 20mg/day.</p> <p><u>Renal</u>: Not recommended in CKD.</p>	<ul style="list-style-type: none"> Hypoglycemia (especially with renal dysfunction and less so with glimepiride) Weight gain (less with glimepiride and glipizide compared to glyburide) 	<ul style="list-style-type: none"> Geriatrics: In general, if a sulfonylurea is chosen, a shorter-duration sulfonylurea (eg. glipizide) is preferred (ADA 2019). Glyburide is associated with severe hypoglycemia. Glipizide is a preferred sulfonylurea in patients with CKD Cross-reactivity between antibiotic sulfonamides and nonantibiotic sulfonamides may not occur or at the very least this potential is extremely low Discontinue when complex insulin regimens are started.
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<p>Thiazolidinediones (TZD) Pioglitazone (Actos, generics, with metformin [ACTOplus Met or ACTOplus Met XR], with glimepiride [Duetact], with alogliptin [Oseni]) <ul style="list-style-type: none"> 15, 30, 45mg tablets Rosiglitazone (Avandia, with metformin [Avandamet]) <ul style="list-style-type: none"> 2, 4, 8mg tablets </p>	<p>MOA: Increases insulin sensitivity without increasing insulin secretion</p> <p>A1c: 0.8-0.9%</p>	<p>Pioglitazone Initial: 15-30mg daily. Titrate based on A1c to a max of 45mg daily</p> <p>Dosage adjustment for hypoglycemia with combination therapy:</p> <ul style="list-style-type: none"> With an insulin secretagogue (eg, sulfonylurea): Decrease the insulin secretagogue dose. With insulin: Decrease insulin dose by 10% to 25% <p>Rosiglitazone Initial: 4mg daily in single or divided doses. May titrate to max of 8mg/day.</p> <p>Do not initiate when ALT >2.5x U</p>	<ul style="list-style-type: none"> Weight gain Edema Heart failure Increased fracture risk Increased LDL (rosiglitazone) 	<ul style="list-style-type: none"> CV benefit and may improve lipid profile (pioglitazone) Avoid use in patients with symptomatic heart failure Max 15mg/day with CYP2C8 inhibitors (eg. gemfibrozil)
<p>Miscellaneous - bile acid sequestrant Colesevelam (Welchol) <ul style="list-style-type: none"> 625mg tablet 3.75g packet </p>	<p>MOA: May reduce hepatic glucose production, increase incretin levels, and decrease glucose absorption.</p> <p>A1c: 0.5%</p>	<p>3.75 g daily in 1 or 2 divided doses</p> <p>No dose adjustments needed (not absorbed from GI tract)</p>	<ul style="list-style-type: none"> Nausea Constipation Bloating Hypertriglyceridemia 	<ul style="list-style-type: none"> Lowers LDL cholesterol, may increase triglycerides May decrease absorption of other medications
<p>Miscellaneous - dopamine agonist Bromocriptine (Cycloset) <ul style="list-style-type: none"> 0.8mg tablet </p>	<p>MOA: May reverse insulin resistance and decrease glucose production.</p> <p>A1c: 0.5% when added to metformin and a sulfonylurea</p>	<p>Initial: 0.8 mg daily; may increase by 0.8mg weekly as tolerated; usual dose: 1.6 to 4.8 mg once daily (maximum: 4.8 mg/day)</p>	<ul style="list-style-type: none"> Dizziness Fatigue, weakness Headache Constipation, nausea 	<ul style="list-style-type: none"> Weight neutral ~\$750 CYP3A4 interactions