Drugs for Type 2 Diabetes (United States)

The table below summarizes the agents available in the US for the treatment of type 2 diabetes, including expected A1c reduction when added to metformin, cost, adverse effects, and other pertinent information (e.g., frequency of dosing, cardiovascular benefits). For additional details on cardiovascular benefits associated with drugs for type 2 diabetes, see our chart, *Diabetes Medications and Cardiovascular Impact*.

Expected A1c Drop[b] **MOA**	**Maximum Daily Dose**[2] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Alpha-glucosidase inhibitors: acarbose and miglitol			
0.7% to 0.8% (acarbose, when added to metformin)[1] ~0.3% to 0.8% (miglitol, as monotherapy)[3] MOA: slows intestinal carbohydrate digestion/absorption.[2]	**Acarbose** 300 mg, divided TID (~$50) **Miglitol** 300 mg, divided TID (~$240)	• GI (e.g., abdominal pain, flatulence, diarrhea).[1,2] • Relatively low risk of hypoglycemia.[1]	• Weight neutral.[1] • Taken at the start of each main meal.[2] • Reduces postprandial glucose.[6] • Requires frequent dosing (e.g., TID).[1] • Beneficial in the treatment of prediabetes (acarbose).[5,7]
Amylin analog: pramlintide (*Symlin*)			
0.3% to 0.4% (when added to insulin with or without metformin and/or a sulfonylurea)[4] MOA: slows gastric emptying, causes satiety, and reduces postprandial glucagon secretion.[2]	**Pramlintide** 120 mcg/dose (usually 360 mcg/day; divided, prior to major meals) (~$2,320)	• GI (e.g., nausea, vomiting).[2,7] • Hypoglycemia can occur if used with insulin. Reduce mealtime insulin dose to reduce risk.[2]	• Weight loss (~1 kg).[4] • Injectable.[4] • Taken immediately before each main meal.[2] • Reduces postprandial glucose.[8] • Requires frequent dosing (e.g., TID).[2]

Expected A1c Drop[b] **MOA**	**Maximum Daily Dose**[2] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Biguanide: metformin (*Fortamet*, *Glumetza*, *Riomet*, generics). Available in combination with alogliptin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, glipizide, glyburide, linagliptin, pioglitazone, saxagliptin, and sitagliptin. See specific agents.			

1% (as monotherapy)[1]
 	
MOA: inhibits glucose production and absorption; increases insulin sensitivity in muscle and fat.[2]
	Metformin
	2,000 to 2,550 mg, divided BID to TID
	(<$10)
	
	Metformin XR
	2,000 to 2,500 mg, once daily or divided BID
	(<$20)
		• B12 deficiency (periodic testing suggested).[4]
		• GI (e.g., abdominal discomfort, diarrhea, nausea).[4]
		• Lactic acidosis (very rare) in patients with unstable heart failure, severe kidney impairment or liver impairment.[4,9,11]
		• Low risk of hypoglycemia when used as monotherapy.[4]
			• Weight neutral to slight weight loss.[1,7]
			• Ameliorates insulin-associated weight gain.[10]
			• First-line with diet and exercise for most patients, including those with prediabetes.[4,7]
			• May reduce CV events and mortality.[4]
			• Safe in patients with stable heart failure and moderate kidney impairment:[4,9]
			  o Can be initiated in patients with an eGFR >45 mL/min/1.73m^2.[12]
			  o Discontinue if eGFR falls below 30 mL/min/1.73m^2.[12]

Dipeptidyl peptidase-4 (DPP-4) inhibitor ("gliptins") or incretin enhancer: • alogliptin (*Nesina*; with metformin [*Kazano*]; with pioglitazone [*Oseni*]; authorized generics) • linagliptin (*Tradjenta*; with metformin [*Jentadueto*, *Jentadueto XR*]; with empagliflozin [*Glyxambi*]; with metformin and empagliflozin [*Trijardy XR*]) • saxagliptin (*Onglyza*; with metformin [*Kombiglyze XR*]; with dapagliflozin [*Qtern*]; with dapagliflozin and metformin [*Qternmet XR*]) • sitagliptin (*Januvia*; with metformin [*Janumet*, *Janumet XR*]; with ertugliflozin [*Steglujan*])			
0.5% to 0.7%[1] MOA: increases insulin secretion in response to elevated blood glucose, decreases glucagon secretion, and slows gastric emptying.[1]	**Alogliptin** 25 mg (~$195) **Linagliptin** 5 mg (~$505) **Saxagliptin** 5 mg (~$470) **Sitagliptin** 100 mg (~$520)	• Rare cases of pancreatitis.[1] • New or worsening heart failure (saxagliptin and alogliptin).[7] • Rare cases of severe joint pain.[1] • Low risk of hypoglycemia when used as monotherapy.[4]	• Weight neutral.[7] • Dosage modification with kidney impairment needed (alogliptin, saxagliptin, sitagliptin).[2] • CYP3A4 interactions (linagliptin, saxagliptin).[2] • Reduces postprandial glucose.[13] • Generally, well tolerated.[14]

Expected A1c Drop[b] **MOA**	**Maximum Daily Dose**[2] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Glucagon-like, peptide-1 (GLP-1) agonist or incretin mimetic: • dulaglutide (*Trulicity*) • exenatide (*Byetta*) and exenatide extended release (*Bydureon BCise*) • liraglutide (*Victoza;* with insulin degludec [*Xultophy*]) • lixisenatide (*Adlyxin*; with insulin glargine [*Soliqua*]) • semaglutide (*Ozempic*, *Rybelsus*)			
Dulaglutide 1.8%[32] Exenatide 0.9%[33] Exenatide extended release 1.5%[34] Liraglutide 1.5%[35] Lixisenatide 0.73%[36] Semaglutide 2.3%[38] Semaglutide, oral 1.3%[37] MOA: increases insulin secretion in response to elevated blood glucose, decreases glucagon secretion, slows gastric emptying.[1]	**Dulaglutide** 4.5 mg once weekly (~$885) **Exenatide** 10 mcg twice daily (~$800) **Exenatide extended release** 2 mg once weekly (~$780) **Liraglutide** 1.8 mg once daily (~$1,065) **Lixisenatide** 20 mcg once daily (~$680) **Semaglutide** 2 mg once weekly (~$890) **Semaglutide, oral** 14 mg once daily (~$890)	• GI (e.g., diarrhea, nausea, vomiting).[10] • Unclear association with acute pancreatitis.[15] • Low risk of gallbladder disease.[16] • Low risk of hypoglycemia when used as monotherapy.[4] • May lead to retinopathy complications.[1] • Linked to pancreatic and medullary thyroid cancer in rats.[10]	• Weight loss (up to 14 pounds [6.4 kg] with semaglutide injection).[38] • All are injectable, but an oral formulation of semaglutide is available.[4] • Avoid if eGFR <45 mL/min/1.73m^2 (extended-release exenatide), <30 mL/min/1.73m^2 (immediate-release exenatide), or <15 mL/min/1.73m^2 (lixisenatide).[2] • Reduces postprandial glucose.[13] • CV benefit (except lixisenatide and immediate-release exenatide).[1] • Kidney benefit (liraglutide, semaglutide).[1] • In patients who need "higher glycemic efficacy," generally start with a GLP-1 agonist, then add basal insulin.[4]

Expected A1c Drop[b] **MOA**	**Maximum Daily Dose**[2] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Glucagon-like, peptide-1 (GLP-1) agonist and glucose-dependent insulinotropic polypeptide (GIP) agonist (a "twincretin"): • Tirzepatide (*Mounjaro*)			
2.3%[31] MOA: increases insulin secretion in response to elevated glucose, decreases glucagon secretion, slows gastric emptying.[31]	**Tirzepatide** 15 mg once weekly (~$975)	• GI (e.g., diarrhea, nausea, vomiting).[31] • Pancreatitis rarely reported in clinical trials (23 events per 10,000 years of exposure [~twice the placebo rate]).[31] • Low risk of gallbladder disease in clinical trials (0.6% vs 0% placebo).[31] • Low risk of hypoglycemia when used as monotherapy.[31] • Linked to medullary thyroid cancer in rats.[31]	• More weight loss than GLP-1 agonists (up to 25 pounds [11.2 kg] with maximum dose in patients with type 2 diabetes).[31] • More A1c reduction than most GLP-1 agonists. • No CV or kidney outcomes data yet. • Monitor for retinopathy progression.[31] • May delay oral contraceptive absorption.[31] Advise switching to a non-oral contraceptive or adding a barrier contraceptive for four weeks after initiation or a dosage increase.[31]
Insulin: various			
0.9% to 1.2% or more[1] MOA: promotes uptake of glucose into muscle and fat tissues; inhibits glucose production.[2]	No maximum dose.[1] See our chart, *Comparison of Insulins*, for cost info.	• Hypoglycemia.[4] Educate patient to prevent, recognize, and manage.[1] • Highest risk of weight gain (1 to 3.5 kg or more).[1]	• Consider initial therapy with insulin plus metformin if blood glucose is ≥300 mg/dL and/or A1c is >10%.[4]
Meglitinide: nateglinide and repaglinide			
0.7% to 1.1%[1] MOA: stimulates pancreatic insulin secretion.[2]	**Nateglinide** 360 mg, divided TID (~$60) **Repaglinide** 16 mg, divided TID (~$270)	• Hypoglycemia.[7] Educate patient to prevent, recognize, and manage.[1] • Weight gain: 1.4 to 3.3 kg.[1,7]	• Requires frequent dosing (e.g., TID).[10] • Reduces postprandial glucose more than sulfonylureas.[10] • Safer than sulfonylureas in kidney impairment.[1] • Can hold dose if skipping meal.[13] • Less hypoglycemia than sulfonylurea.[7]

Expected A1c Drop[b] **MOA**	**Maximum Daily Dose**[2] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Sodium-glucose co-transporter 2 (SGLT2) inhibitors: • canagliflozin (*Invokana*; with metformin [*Invokamet*, *Invokamet XR*]) • dapagliflozin (*Farxiga*; with metformin [*Xigduo XR*]; with saxagliptin [*Qtern*]; with metformin and saxagliptin [*Qternmet XR*]) • empagliflozin (*Jardiance*; with linagliptin [*Glyxambi*]; with metformin [*Synjardy, Synjardy XR*], with linagliptin and metformin [*Trijardy XR*]) • ertugliflozin (*Steglatro*; with metformin [*Segluromet*]; with sitagliptin [*Steglujan*])			

0.5% to 0.7%[1]
 	
MOA: blocks glucose reabsorption in the kidney, increases urinary excretion of glucose.[2]
	Canagliflozin 300 mg (~$570)
	
	Dapagliflozin 10 mg (~$550)
	
	Empagliflozin 25 mg (~$570)
	
	Ertugliflozin 15 mg (~$325)
		• Genital fungal (yeast) infections (male/female).[17]
		• UTI (may be severe), ketoacidosis (rare).[18]
		• Increased urination may lead to volume depletion, hypotension, syncope, falls, and acute kidney injury (some cases requiring dialysis).[2,7]
		• Slight increase in LDL.[7]
		• Hyperkalemia (canagliflozin), especially with kidney impairment, high baseline potassium, and use of medications that reduce potassium excretion.[2]
		• Fractures (rare, in susceptible patients) and decrease in BMD (canagliflozin).[4,20]
		• Rare reports of acute pancreatitis.[21]
		• Fournier's gangrene (rare; in men and women). Onset: days to years into therapy.[17]
		• May be associated with rare amputations (canagliflozin).[19]
		• Low risk of hypoglycemia when used as monotherapy.[4]
			• Weight loss (2 to 3 kg).[1,7]
			• Limited efficacy for **glycemic control** if eGFR <45 mL/min/1.73m^2 (canagliflozin and empagliflozin [<30 mL/min/1.73m^2]), but can continue for **heart failure** (empagliflozin), **albuminuria** (canagliflozin), or **CV and kidney** (dapagliflozin) indications.[2]
			  ○ Reduce **canagliflozin** to 100 mg/day in patients with eGFR <60 mL/min/1.73m^2.[2]
			  ○ **Empagliflozin** is not recommended when eGFR <20 mL/min/1.73m^2.
			• CV benefit (canagliflozin, dapagliflozin [heart failure], empagliflozin, ertugliflozin heart failure])[4]
			• Kidney benefit (canagliflozin, dapagliflozin, empagliflozin).[4]
			• Consider amputation risk factors (ulcer or amputation history; reduced sensation). Emphasize foot care and monitor for foot/leg pain, tenderness, or sores.[1,19]

Expected A1c Drop[b] **MOA**	**Maximum Daily Dose**[2] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Sulfonylurea-second generation • glimepiride (*Amaryl*, generics; with pioglitazone [*Duetact*, generics]) • glipizide (*Glucotro*l [brand discontinued], generics; *Glucotrol XL*, generics; with metformin [generics]) • glyburide (*DiaBeta*, generics; *Glynase*, generics; with metformin [generics])			
0.6% to 1.2%[1] MOA: stimulates pancreatic insulin secretion.[1]	**Glimepiride** 8 mg (~$15) **Glipizide IR** 40 mg (daily doses >30 mg should be divided BID) (<$10) **Glipizide XL** 20 mg (~$25) **Glyburide** (standard) 20 mg (daily doses >10 mg can be divided BID) (~$25) **Glyburide** (micronized) 12 mg (once daily or in divided doses) (~$15)	• Hypoglycemia, especially with glyburide and/or in kidney impairment.[1] Educate patient to prevent, recognize, and manage.[1] ○ Less with glimepiride versus glyburide.[13] Avoid both in the elderly.[22] • Weight gain: 1.2 to 3.2 kg.[1] ○ Less with glipizide and glimepiride versus glyburide.[23]	• Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started.[4] • Relatively short-lived efficacy.[1] • For those with liver or kidney impairment, start with low doses and titrate up.[4,24] • In the elderly, start low and titrate. Periodically consider need for dose reduction as the patient ages and circumstances change (e.g., reduced oral intake, kidney impairment).[25]

Expected A1c Drop[b] **MOA**	**Maximum Daily Dose**[2] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Thiazolidinedione (TZD): pioglitazone (*Actos*, generics; with metformin [*ACTOplus Met*, generics]; with glimepiride [*Duetact*, generics], with alogliptin [*Oseni*, authorized generics])			
0.7% to 0.9%[1] MOA: increases insulin sensitivity in liver, muscle, and fat.[2]	**Pioglitazone** 45 mg (<$15)	• Edema.[1] • Weight gain: 2 to 2.5 kg or more.[1] • Heart failure.[1] • Increased fracture risk.[1] • Possible increased risk of bladder cancer.[4] Do not use in active bladder cancer, and use caution in patients with a history of bladder cancer.[27] Counsel patients to report hematuria.[27] • Low risk of hypoglycemia when used as monotherapy.[4]	• Glycemic control better sustained over diabetes course than metformin or sulfonylureas.[13] • Pioglitazone may improve lipid profile (e.g., lowers triglycerides).[26] • Avoid in patients with symptomatic heart failure.[2,27] • CV benefit.[26]
Others – bile acid sequestrant: colesevelam (*Welchol*, generics)			
0.5%[28] MOA: may reduce liver glucose production, increase incretin levels, and decrease glucose absorption.[28,29]	**Colesevelam** 3.75 gm, given once daily or divided BID (~$400 [powder for suspension]; ~$150 [tablets])	• GI (e.g., constipation, nausea, dyspepsia).[28] • May increase triglycerides.[28] (Can be partially offset by adding a statin.[7]) • Low incidence of mild to moderate hypoglycemia.[28]	• Weight neutral.[7] • Lowers LDL cholesterol.[28] • May decrease absorption of other meds.[2]
Others – dopamine agonist: bromocriptine (*Cycloset*)			
0.5% (when added to metformin and a sulfonylurea)[30] MOA: increases insulin sensitivity.[30]	**Bromocriptine** 4.8 mg (~$930)	• Orthostasis.[7] • Nausea.[7] • Infrequent hypoglycemia.[2]	• Weight neutral.[7] • CYP3A4 interactions.[2] • Do not use with antipsychotics.[7]

a. Pricing (for generic when available) based on wholesale acquisition cost (WAC). Medication pricing by Elsevier, accessed June 2022.
b. As a metformin add-on, unless otherwise noted.

Abbreviations: BID = two times daily; BMD = bone mineral density; CV = cardiovascular; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; LDL = low-density lipoprotein; MOA = mechanism of action; TID = three times daily; UTI = urinary tract infection.

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