# Treatment Guidelines
from The Medical Letter®

Published by The Medical Letter • 145 Huguenot Street, New Rochelle, NY 10801 • A Nonprofit Publication


**IN THIS ISSUE** (starts on next page)

Treatment Guidelines
from The Medical Letter®

Published by The Medical Letter • 145 Huguenot Street, New Rochelle, NY 10801 • A Nonprofit Publication

Volume 12 (Issue 139) March 2014
www.medicalletter.org
Take CME exams



# Drugs for Type 2 Diabetes

**RECOMMENDATIONS:** Used alone, oral antihyperglycemic drugs generally lower glycated hemoglobin (A1C) by 0.5-1.5%. In the absence of contraindications, metformin is the preferred first-line agent.[1] If metformin does not achieve the desired goal, a sulfonylurea, a GLP-1 receptor agonist, or possibly a DPP-4 inhibitor could be added. Most patients with type 2 diabetes eventually require multi-drug therapy or insulin to achieve glycemic control. If maximum doses of 2 drugs prove insufficient, a third one can be added. Some diabetes experts favor early use of insulin if A1C remains poorly controlled on maximal-dose single-drug therapy.

**GLYCEMIC THERAPY GOALS —** The goal of drug therapy for type 2 diabetes is to achieve and maintain a near-normal A1C concentration without inducing hypoglycemia; the target is generally an A1C of <7.0%. Treating to this target has been shown to prevent the microvascular complications of retinopathy and nephropathy, but whether it prevents macrovascular outcomes remains unclear. Three large trials found that intensive glucose control did not reduce the incidence of macrovascular events.[2-4] One of these trials (ACCORD) in >10,000 patients with type 2 diabetes, with or at high-risk for cardiovascular disease, found that treating patients intensively with antihyperglycemic drugs to an A1C target of 6.0% for a mean of 3.7 years did not significantly reduce the incidence of major cardiovascular events (the primary endpoint) and was associated with increased all-cause mortality compared to patients treated to an A1C target of 7.0-7.9%.[2] An A1C target of 7-8% may be prudent in older patients and in those with underlying cardiovascular disease, severe hypoglycemia, or multiple diabetes-related complications or co-morbidities.[5]

**LIFESTYLE MODIFICATIONS —** Diet, exercise, and weight loss are helpful in improving glucose control, but most patients with type 2 diabetes ultimately require drug therapy. A 10-year randomized controlled trial in 5145 overweight or obese patients with type 2 diabetes found that an intensive lifestyle modification program reduced weight, lowered A1C, and improved cardiovascular risk factors, but did not reduce the incidence of cardiovascular events.[6]

**METFORMIN —** The biguanide metformin (*Glucophage*, and others) is generally the first drug prescribed for treatment of type 2 diabetes. It decreases hepatic glucose production and intestinal absorption of glucose and, to a lesser extent, increases peripheral glucose uptake. Metformin produces about the same reduction in A1C as a sulfonylurea (1-1.5%), but metformin-induced reductions are more durable.[7]

**Compared to Dietary Restriction –** A 10-year post-study follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) found that patients treated with metformin had a 33% lower risk of myocardial infarction and a 27% reduction in the risk of death from any cause compared to patients treated with dietary restriction alone.[8]

**In Renal Impairment –** Metformin can cause lactic acidosis in patients with severe renal impairment. It should be discontinued before radiographic studies with IV iodinated contrast, which can cause a temporary impairment in renal function, and should not be restarted until 48 hours after the procedure. Metformin should not be used in patients with an eGFR <30 mL/min/1.73m$^2$, and a reduction in dosage may be advisable for an eGFR 30-45 mL/min/1.73m$^2$.[9]

**SULFONYLUREAS —** The sulfonylureas **glimepiride** (*Amaryl*, and generics), **glipizide** (*Glucotrol*, and generics), and **glyburide** (*DiaBeta*, and others) all reduce A1C by 1-1.5%. They interact with ATP-sensitive potassium channels in the beta-cell membrane to increase secretion of insulin independent of

meal intake. In one study, the incidence of monotherapy failure at 5 years in patients with type 2 diabetes was higher with glyburide (34%) than with metformin (21%) or the thiazolidinedione rosiglitazone (15%).[7] A 10-year follow-up of a randomized controlled trial (UKPDS) found a reduction in the risk of myocardial infarction, microvascular disease, and all-cause mortality among newly diagnosed patients with type 2 diabetes treated with a sulfonylurea or insulin compared to those treated with dietary restriction alone, although the reductions were less than those seen with metformin.[8]

**MEGLITINIDES — Repaglinide** (*Prandin*, and generics) and **nateglinide** (*Starlix*, and generics), although structurally different from the sulfonylureas, also bind to ATP-sensitive potassium channels on beta cells and increase insulin release. Repaglinide is more effective than nateglinide in lowering A1C (~1% vs. 0.5%). Both are rapidly absorbed and cleared; plasma levels of insulin peak 30-60 minutes after each dose and multiple daily doses are required.

**THIAZOLIDINEDIONES (TZDs) — Pioglitazone** (*Actos*, and generics) and **rosiglitazone** (*Avandia*, and generics) reduce A1C by 1-1.5% by increasing the insulin sensitivity of adipose tissue, skeletal muscle and the liver, and by reducing hepatic glucose production. Whether the benefits of these agents outweigh their risks is unclear. They are FDA-approved for use as monotherapy or in combination with metformin, a sulfonylurea, or insulin (only pioglitazone).

**Cardiovascular Risk –** Both pioglitazone and rosiglitazone have been associated with a risk of heart failure.[10] A meta-analysis found an increased risk of myocardial infarction with rosiglitazone,[11] but an independent reevaluation of data from a randomized controlled trial (RECORD) found no significant difference between rosiglitazone and metformin/sulfonylurea in the risk of cardiovascular death, MI, or stroke.[12] Restrictions that were placed on rosiglitazone in 2010 because of concerns about its cardiovascular safety have been lifted.[13]

**GLP-1 RECEPTOR AGONISTS —** Given by subcutaneous injection, GLP-1 receptor agonists potentiate glucose-dependent secretion of insulin, suppress glucagon secretion, slow gastric emptying, and promote satiety. They lower A1C by 1-1.5% and have been associated with weight loss of 1.5-2.8 kg.

**Exenatide** (*Byetta*, and others) is FDA-approved for twice-daily subcutaneous injection in patients with type 2 diabetes who have not achieved adequate glycemic control with lifestyle modification, metformin, or other oral drugs.[14] It is not recommended for use with regular or rapid-acting insulin. In an open-label trial in 977 patients not meeting A1C goals on metformin monotherapy, more patients achieved an A1C <7% with twice-daily exenatide than with the sulfonylurea glimepiride (44% vs. 31%).[15]

Exenatide is also available in a once-weekly, extended-release formulation *(Bydureon)*.[16] In an open-label 24-week trial (DURATION-5) in 252 patients, once-weekly exenatide was more effective than twice-daily exenatide in reducing A1C (additional 0.7% reduction) and was associated with less nausea and an additional weight loss of about 1 kg.[17] In an open-label 26-week trial in 216 patients inadequately controlled on metformin alone or with a sulfonylurea, once-weekly exenatide was more effective than titrated insulin detemir in lowering A1C (additional reduction of 0.4%) and in reducing weight (additional reduction of 1.9 kg), with equivalent hypoglycemia.[18]

**Liraglutide** *(Victoza)*, like exenatide, is not recommended for first-line therapy.[19] In clinical studies, liraglutide added to other drugs was either equal to or significantly better than oral comparators in reducing A1C. In an open-label, randomized trial (DURATION-6) in 911 patients taking oral medications for diabetes, liraglutide once daily was associated with a slightly greater (0.2%) reduction in A1C than once-weekly exenatide, but with more gastrointestinal side effects.[20]

**Pancreatitis –** Both GLP-1 receptor agonists and DPP-4 inhibitors have been linked to acute pancreatitis (see below).[21]

**DPP-4 INHIBITORS — Alogliptin** *(Nesina)*,[22] **linagliptin** *(Tradjenta)*,[23] **saxagliptin** *(Onglyza)*,[24] and **sitagliptin** *(Januvia)* potentiate glucose-dependent secretion of insulin and suppress glucagon secretion. They produce small reductions in A1C (0.5-1%) when used as monotherapy.

**Cardiovascular Risk –** The cardiovascular safety of DPP-4 inhibitors was assessed in two randomized controlled trials. Saxagliptin neither increased nor decreased the risk of ischemic events compared to placebo in 16,492 patients with type 2 diabetes who either had a history of cardiovascular disease or were at risk for cardiovascular events; rates of hospitalization for heart failure were higher in the saxagliptin group (3.5% vs. 2.8%).[25] In 5380 patients with type 2 diabetes who had had a recent acute coronary syndrome, alogliptin did not increase the composite endpoint of death from cardiovascular disease, nonfatal myocardial infarction, or nonfatal stroke, compared to placebo.[26]

**Pancreatitis –** Both GLP-1 receptor agonists and DPP-4 inhibitors have been linked to acute pancreatitis.[21] A

## Table 1. Advantages and Adverse Effects

| Drug Class (A1C Reduction)[1] | Some Advantages | Adverse Effects |
|---|---|---|
| **Biguanide (1-1.5%)** | | |
| Metformin | Durable A1C lowering; weight neutral or weight loss (2-3 kg); hypoglycemia is rare when used as monotherapy | Gastrointestinal effects (metallic taste, nausea, diarrhea, abdominal pain)[2]; vitamin B12 deficiency[3]; cognitive decline[4]; lactic acidosis[5] |
| **Sulfonylureas[6] (1-1.5%)** | | |
| Glimepiride, Glipizide, Glyburide | Inexpensive; demonstrated long-term reduction in microvascular risk | Hypoglycemia; weight gain; possible aggravation of myocardial ischemia; glyburide has a higher incidence of hypoglycemia and mortality than glimepiride or glipizide[7] |
| **Meglitinides (0.5-1%)** | | |
| Nateglinide, Repaglinide | Short-acting | Hypoglycemia; weight gain; must be taken before each meal; use with caution in patients with moderate to severe liver disease; increased risk of hypoglycemia in patients with severe renal impairment taking nateglinide |
| **Thiazolidinediones (1-1.5%)** | | |
| Pioglitazone, Rosiglitazone | Low risk of hypoglycemia; durable A1C lowering | Weight gain (2-3 kg over 6-12 months)[8]; peripheral edema; increased risk of heart failure[9,10]; macular edema; decrease in bone mineral density and increased incidence of fractures, especially in women[11]; hepatic failure; pioglitazone has been associated with an increased risk of bladder cancer with high doses and long-term use[12] |
| **GLP-1 Receptor Agonists (1-1.5%)** | | |
| Exenatide, Liraglutide | Weight loss[13]; no hypoglycemia when used as monotherapy; *Bydureon* is administered once weekly | Nausea[14]; vomiting; diarrhea; renal insufficiency and acute renal failure with nausea and vomiting[15]; acute pancreatitis; can decrease the rate and extent of absorption of other drugs; should not be used in patients with gastroparesis; thyroid C-cell carcinomas have been reported in animals and thyroid C-cell hyperplasia has been reported in humans (liraglutide and extended-release exenatide)[16]; must be injected subcutaneously |
| **DPP-4 Inhibitors (0.5-1%)** | | |
| Sitagliptin, Saxagliptin, Linagliptin, Alogliptin | Weight neutral; hypoglycemia is rare when used as monotherapy[17] | Hypersensitivity reactions (urticaria, angioedema, anaphylaxis, Stevens-Johnson syndrome, and vasculitis); acute pancreatitis; fatal hepatic failure; long-term safety unknown; higher rate of hospitalization for heart failure in one study with saxagliptin[18] |
| **Alpha-Glucosidase Inhibitors (0.5-1%)** | | |
| Acarbose, Miglitol | No hypoglycemia when used as monotherapy[19] | Abdominal pain, diarrhea, and flatulence[20]; contraindicated in patients with intestinal disease; acarbose can cause transaminase elevations |
| **SGLT2 Inhibitors (0.5-1%)** | | |
| Canagliflozin, Dapagliflozin | Weight loss; risk of hypoglycemia comparable to placebo[21] | Genital mycotic infections in men and women; recurrent urinary tract infections; volume depletion; increased urinary frequency and volume; increased serum creatinine and decreased eGFR; hyperkalemia; hypermagnesemia; hyperphosphatemia; fractures; increase in LDL-cholesterol; increased risk of cardiovascular events in the first 30 days of treatment; cardiovascular and long-term safety unknown; possible increased risk of bladder cancer with dapagliflozin |
| **Others (0.5%)** | | |
| Pramlintide | Weight loss | Nausea; vomiting; headache; anorexia; may delay or decrease absorption of other drugs; contraindicated in patients with gastroparesis or in those taking drugs that alter gastric motility; must be injected subcutaneously; severe hypoglycemia (when taken with insulin) |
| Colesevelam | No hypoglycemia | Constipation; nausea; dyspepsia; increases serum triglyceride concentrations; interferes with the absorption of other drugs |
| Bromocriptine | No hypoglycemia; may reduce risk of cardiovascular events | Nausea, vomiting, fatigue, headache, and dizziness (more common during titration and lasting for a median of 14 days); somnolence; orthostatic hypotension; syncope, especially in patients taking antihypertensives; lowers prolactin levels |

1. When used as monotherapy.
2. Gastrointestinal adverse effects can be minimized by starting with a low dose, titrating dose slowly, dividing doses, and taking the drug with food. Use of long-acting formulations may also reduce GI adverse effects.
3. L Reinstatler et al. Diabetes Care 2012; 35:327.
4. EM Moore et al. Diabetes Care 2013; 36:2981.
5. Impaired renal function, liver failure, major surgery, decompensated or acute heart failure, and alcoholism may increase the risk of lactic acidosis. Patients ≥80 years old whose renal function cannot be monitored may also be at increased risk.
6. First-generation sulfonylureas, such as tolbutamide or chlorpropamide, have been associated with an increased risk of cardiovascular mortality.
7. Because of its adverse effects, glyburide is no longer recommended (MC Riddle. J Clin Endocrinol Metab 2010; 95:4867).
8. Weight gain can be greater if used in combination with insulin.
9. Contraindicated in patients with NYHA class III or IV heart failure.
10. CB Maxwell and AT Jenkins. Am J Health Syst Pharm 2011; 68:1791.
11. YK Loke et al. CMAJ 2009; 180:32.
12. IN Colmers et al. CMAJ 2012; 184:E675; RM Turner et al. Br J Clin Pharmacol 2013 December 10 (epub).
13. Weight loss is greater with the extended-release formulation of exenatide.
14. Titrating the dose over one week for liraglutide and over one month for exenatide can help reduce nausea.
15. In patients with pre-existing kidney disease or taking other nephrotoxic drugs (TD Filippatos and MS Elisaf. World J Diabetes 2013; 4:190).
16. Liraglutide and extended-release exenatide should not be used in patients with, or who have a family history of, medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.
17. The risk of hypoglycemic events increases significantly when taken concurrently with a sulfonylurea (AR Chacra et al. Int J Clin Pract 2009; 63:1395) or insulin.
18. BM Scirica et al. N Engl J Med 2013; 369:1317.
19. Hypoglycemia should be treated with oral glucose because these drugs interfere with the breakdown of sucrose.
20. Slow titration can minimize these effects.
21. WT Cefalu et al. Lancet 2013; 382:941.

## Table 2. Formulations, Dosage, and Cost

| Drug | Some Available Formulations | Pregnancy Category[1] | Usual Daily Dosage | Cost[2] |
|---|---|---|---|---|
| **Biguanide** | | | | |
| Metformin[3] – generic | 500, 850, 1000 mg tabs | B | 1500-2550 mg PO divided[4] | $ 6.30 |
| *Glucophage* (BMS) | | | | 83.70 |
| liquid – *Riomet* (Ranbaxy) | 500 mg/5 mL (4, 16 oz) | | 1500-2550 mg PO divided[4] | 212.00[5] |
| extended-release – generic | 500, 750 mg ER tabs | | 1500-2000 mg PO once/d[6] | 16.50 |
| *Glucophage XR* (BMS) | | | | 85.60 |
| *Glumetza* (Salix) | 500, 1000 mg ER tabs | | 500-2000 mg PO once/d[6] | 149.10 |
| *Fortamet* (Shionogi) | 500, 1000 mg ER tabs | | 1500-2500 mg PO once/d[6] | 1633.80 |
| **Sulfonylureas** | | | | |
| Glimepiride – generic | 1, 2, 4 mg tabs | C | 1-4 mg PO once/d[7] | 2.80 |
| *Amaryl* (Sanofi) | | | | 24.80 |
| Glipizide – generic | 5, 10 mg tabs | C | 10-20 mg PO once/d or divided[8] | 2.60 |
| *Glucotrol* (Pfizer) | | | | 47.10 |
| extended-release – generic | 2.5, 5, 10 mg tabs | | 5-20 mg PO once/d[7] | 10.10 |
| *Glucotrol XL* | | | | 25.20 |
| Glyburide[9] – generic | 1.25, 2.5, 5 mg tabs | C | 5-20 mg PO once/d or divided[7] | 9.60 |
| *DiaBeta* (Sanofi) | | | | 49.70 |
| micronized tablets – generic | 1.5, 3, 4.5, 6 mg tabs | B | 0.75-12 mg PO once/d or divided[7] | 1.60 |
| *Glynase Prestab* (Pfizer) | 1.5, 3, 6 mg tabs | | | 13.70 |
| **Meglitinides** | | | | |
| Nateglinide – generic | 60, 120 mg tabs | C | 60-120 mg PO tid[10] | 118.60 |
| *Starlix* (Novartis) | | | | 213.20 |
| Repaglinide – generic | 0.5, 1, 2 mg tabs | C | 1-4 mg PO tid[10,11] | 199.90 |
| *Prandin* (Novo Nordisk) | | | | 385.20 |
| **Thiazolidinediones** | | | | |
| Pioglitazone – generic | 15, 30, 45 mg tabs | C | 15-45 mg PO once/d[12] | 16.70 |
| *Actos* (Takeda) | | | | 258.60 |
| Rosiglitazone – generic | 2, 4, 8 mg tabs | C | 4-8 mg PO once/d or divided bid[13] | N.A. |
| *Avandia* (GSK) | | | | 117.00 |
| **GLP-1 Receptor Agonists** | | | | |
| Exenatide – immediate-release | | | | |
| *Byetta* (BMS/AstraZeneca) | 250 mcg/mL (1.2, 2.4 mL prefilled pen) | C | 5 or 10 mcg SC bid[14,15] | 395.50[16] |
| extended-release | | | | |
| *Bydureon* (BMS/AstraZeneca)[17] | 2 mg powder for injectable suspension | C | 2 mg SC 1x/week[15] | 407.50 |
| Liraglutide – *Victoza* (Novo Nordisk)[17] | 6 mg/mL (3 mL prefilled pen) | C | 1.2 or 1.8 mg SC once/d[18] | 357.10[19] |
| **DPP-4 Inhibitors** | | | | |
| Alogliptin – *Nesina* (Takeda) | 6.25, 12.5, 25 mg tabs | B | 25 mg PO once/d[20] | 283.80 |
| Linagliptin – *Tradjenta* (Boehringer Ingelheim) | 5 mg tabs | B | 5 mg PO once/d | 283.80 |
| Saxagliptin – *Onglyza* (BMS) | 2.5, 5 mg tabs | B | 2.5-5 mg PO once/d[21] | 278.90 |
| Sitagliptin – *Januvia* (Merck) | 25, 50, 100 mg tabs | B | 100 mg PO once/d[22] | 283.80 |

N.A. = Cost not available

1. FDA pregnancy categories: B = no evidence of risk in humans; C = risk cannot be ruled out.
2. Approximate wholesale acquisition cost (WAC) of 30 days' treatment with the lowest usual daily dose. Source: Analy$ource® Monthly (Selected from FDB MedKnowledge™) February 5, 2014. Reprinted with permission by FDB, Inc. All rights reserved. ©2014. www.fdbhealth.com/policies/drug-pricing-policy. Actual retail prices may be higher.
3. Metformin is contraindicated, according to the labeling, in men with serum creatinine ≥1.5 mg/dL and in women with serum creatinine ≥1.4 mg/dL, but most experts now use a cut-off of eGFR 30 mL/min/1.73m$^2$.
4. Should be taken with meals.
5. Cost of one 16-ounce bottle.
6. Once-daily dose should be given with the evening meal.
7. Once-daily dose should be given with breakfast or first meal.
8. Doses >15 mg/day should be divided and given before meals of adequate caloric content.
9. Glyburide is no longer recommended (more hypoglycemia, higher mortality).
10. Doses should be taken 15-30 minutes before meals. Should not be taken if meal is missed.
11. A starting dose of 0.5 mg tid with meals is recommended for patients with severe renal impairment.
12. Should not be started in patients with ALT >3x upper limit of normal (ULN) with serum total bilirubin >2x ULN.
13. Should not be started in patients with active liver disease or ALT >2.5x ULN.
14. Starting dose is 5 mcg twice daily, up to an hour before the morning and evening meals. After one month, the dose can be increased to 10 mcg twice daily.
15. Not recommended for patients with a CrCl <30 mL/min.
16. Cost of one 1.2 mL prefilled pen.
17. Contraindicated in patients, with or who have a family history of, medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2.
18. Starting dose is 0.6 mg once daily for 7 days, followed by 1.2 mg thereafter.
19. Cost of two 18 mg/3mL pens.
20. A dose of 12.5 mg once daily is recommended for patients with a CrCl of 30 to 59 mL/min and 6.25 mg once daily is recommended for a CrCl <30 mL/min.

**Table 2. Formulations, Dosage, and Cost (continued)**

| Drug | Some Available Formulations | Pregnancy Category[1] | Usual Daily Dosage | Cost[2] |
|---|---|---|---|---|
| **Alpha-Glucosidase Inhibitors** | | | | |
| Acarbose – generic | 25, 50, 100 mg tabs | B | 50-100 mg PO tid[4,23] | $ 44.60 |
| *Precose* (Bayer) | | | | 88.20 |
| Miglitol – *Glyset* (Pfizer) | 25, 50, 100 mg tabs | B | 50-100 mg PO tid[4,23] | 138.60 |
| **SGLT2 Inhibitors** | | | | |
| Canagliflozin – *Invokana* (Janssen) | 100, 300 mg tabs | C | 100-300 mg PO once/d[7,24] | 289.10 |
| Dapagliflozin – *Farxiga* (BMS/AstraZeneca) | 5, 10 mg tabs | C | 5-10 mg PO once/d[25] | 289.20 |
| **Other** | | | | |
| Colesevelam – *Welchol* (Daiichi Sankyo) | 625 mg tabs; 3.75g/packet | B | 3.75 g PO once or divided bid[4] | 334.80 |
| Bromocriptine[26] – *Cycloset* (VeroScience) | 0.8 mg tabs | B | 1.6-4.8 mg PO once/d[27] | 137.40 |
| Pramlintide – *Symlin* (AstraZeneca) | 1000 mcg/mL (1.5, 2.7 mL prefilled pen) | C | 60-120 mcg SC tid[28] | 595.60 |
| **Combination Products** | | | | |
| Metformin/glipizide[3] – generic | 250/2.5, 500/2.5, 500/5 mg tabs | C | 500 mg/2.5 mg PO bid[4] | 45.80 |
| Metformin/glyburide[3] – generic | 250/1.25, 500/2.5, | B | 500 mg/5 mg PO bid[4] | 13.00 |
| *Glucovance* (BMS) | 500/5 mg tabs | | | 73.20 |
| Metformin/repaglinide[3] – *PrandiMet* (Novo Nordisk) | 500/1, 500/2 mg tabs | C | 500 mg/1-2 mg PO bid-tid[3,10] | 233.40 |
| Metformin/pioglitazone[3] – generic | 500/15, 850/15 mg tabs | C | 500 mg/15 mg PO bid[4,12] | 231.60 |
| *Actoplus Met* (Takeda) | | | | 393.00 |
| *Actoplus Met XR* | 1000/15, 1000/30 mg ER tabs | | 1000 mg/15 mg PO once[4,12] | 212.70 |
| Metformin/rosiglitazone[3] – *Avandamet* (GSK) | 500/2, 500/4, 1000/2, 1000/4 mg tabs | C | 500 mg/2 mg PO bid[4,13] | 137.80 |
| Metformin/alogliptin[3] – *Kazano* (Takeda) | 12.5/500, 12.5/1000 mg tabs | B | 12.5/500-12.5/1000 mg PO bid[4] | 283.90 |
| Metformin/linagliptin[3] – *Jentadueto* (Boehringer Ingelheim) | 500/2.5, 850/2.5, 1000/2.5 mg tabs | B | 1 tab PO bid[4] | 283.80 |
| Metformin/saxagliptin[3] – *Kombiglyze XR* (BMS) | 500/5, 1000/2.5, 1000/5 mg ER tabs | B | 1000-2000 mg/5 mg PO once/d[6] | 278.90 |
| Metformin/sitagliptin[3] – *Janumet* (Merck) | 500/50, 1000/50 mg tabs | B | 500 mg/50 mg PO bid[4] | 283.80 |
| *Janumet XR* | 500/50, 1000/50, 1000/100 mg ER tabs | B | 1000 mg/100 mg PO once/d[6] | 283.80 |
| Glimepiride/pioglitazone – *Duetact* (Takeda) | 2/30, 4/30 mg tabs | C | 4 mg/30 mg PO once/d[7,12] | 395.20 |
| Glimepiride/rosiglitazone – *Avandaryl* (GSK) | 1/4, 2/4, 4/4, 2/8, 4/8 mg tabs | C | 2 mg/4 mg PO bid[13] | 261.00 |
| Alogliptin/pioglitazone – *Oseni* (Takeda) | 12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, 25/45 mg tabs | C | 25/15-25/45 mg PO once/d[12,29] | 283.90 |

21. A dose of 2.5 mg once daily is recommended for patients with a CrCl ≤50 mL/min.
22. A dose of 50 mg once daily is recommended for patients with a CrCl of ≥30 to 50 mL/min and 25 mg once daily is recommended for a CrCl <30 mL/min.
23. Not recommended for patients with a serum creatinine >2 mg/dL.
24. Maximum dose is 100 mg in patients with moderate renal impairment (eGFR 45-59 mL/min/1.73m$^2$). It should not be given to patients with an eGFR <45 mL/min/1.73m$^2$.
25. Dapagliflozin should not be started in patients with an eGFR <60 mL/min/1.73m$^2$ or in those with active bladder cancer.
26. Contraindicated in women who are breastfeeding.
27. Should be taken within 2 hours of waking in the morning.
28. Dose for patients with type 2 diabetes. Immediately before meals. Insulin dose should be reduced by 50%.
29. Limit the initial dose of pioglitazone to 15 mg once daily in patients with NYHA class I or II heart failure. Reduce the alogliptin dose to 12.5 mg/d in patients with a CrCl of 30-59 mL/min.

case-control study of 2538 patients with type 2 diabetes found that use of either sitagliptin or exenatide was associated with an increased risk of hospitalization for acute pancreatitis.[27] The FDA recently published a drug safety communication about unpublished findings of precancerous changes in the pancreas in patients with type 2 diabetes treated with a GLP-1 receptor agonist or a DPP-4 inhibitor.[28] Until more data became available, their benefits appear to outweigh these unproven risks.[29]

**ALPHA-GLUCOSIDASE INHIBITORS — Acarbose** (*Precose*, and generics) and **miglitol** *(Glyset)* inhibit the alpha-glucosidase enzymes that line the brush border of the small intestine, interfering with hydrolysis of carbohydrates and delaying absorption of glucose and other monosaccharides. They are generally less effective than other drugs in lowering A1C (0.5-1%). To lower postprandial glucose concentrations, these drugs must be taken with each meal.

**SGLT2 INHIBITORS —** SGLT2 (sodium-glucose co-transporter 2), a membrane protein expressed in the kidney, transports filtered glucose from the

**Table 3. Some Insulin Products**

| | Some Available Formulations[1] | Onset | Peak | Duration | Pregnancy Category[2] | Cost[3] |
|---|---|---|---|---|---|---|
| **Rapid-Acting** | | 10-30 min | 30 min-3 hrs | 3-5 hrs | | |
| Insulin aspart – *Novolog* (Novo Nordisk) | 10 mL vial, 3 mL cartridge, 3 mL *FlexPen*[4] | | | | B | 168.20 |
| Insulin glulisine – *Apidra* (Sanofi) | 10 mL vial, 3 mL *Solostar* | | | | C | 156.80 |
| Insulin lispro – *Humalog* (Lilly) | 10 mL vial, 3 mL cartridge, 3 mL *KwikPen*[4] | | | | B | 167.70 |
| **Regular Insulin** | | 30-60 min | 2½-5 hrs | 4-12 hrs | | |
| *Humulin R* (Lilly) | 10 mL vial[5] | | | | B | 90.80 |
| *Novolin R* (Novo Nordisk) | 10 mL vial | | | | B | 90.70 |
| **Intermediate-Acting** | | 1-2 hrs | 4-8 hrs | 10-20 hrs | | |
| NPH – *Humulin N* (Lilly) | 10 mL vial, 3 mL *KwikPen*[4] | | | | B | 90.80 |
| *Novolin N* (Novo Nordisk) | 10 mL vial | | | | B | 90.70 |
| **Long-Acting** | | | | | | |
| Insulin detemir – *Levemir* (Novo Nordisk) | 10 mL vial, 3 mL *FlexPen*[4] | 1-4 hrs | relatively flat | 12-20 hrs | B | 191.30 |
| Insulin glargine – *Lantus* (Sanofi) | 10 mL vial, 3 mL *SoloStar* | 1-4 hrs | no peak | 22-24 hrs | C | 191.30 |
| **Pre-Mixed** | | | | | | |
| *Novolin* 70/30 (Novo Nordisk) (70% NPH, human insulin isophane susp and 30% regular human insulin injection) | 10 mL vial | 30-60 min | 2-12 hrs | 18-24 hrs | B | 90.70 |
| *Novolog Mix* 70/30 (Novo Nordisk) (70% insulin aspart protamine susp and 30% insulin aspart injection) | 10 mL vial, 3 mL *FlexPen*[4] | 10-20 min | 1-4 hrs | 18-24 hrs | B | 174.40 |
| *Humalog Mix* 75/25 (Lilly) (75% insulin lispro protamine susp and 25% insulin lispro injection) | 10 mL vial, 3 mL *Pen*, 3 mL *KwikPen*[4] | 10-30 min | 1-6½ hrs | 14-24 hrs | B | 173.80 |

1. Available in a concentration of 100 units/mL.
2. FDA pregnancy categories: B = no evidence of risk in humans; C = risk cannot be ruled out.
3. Approximate wholesale acquisition cost (WAC) of one 10-mL vial. Source: Analy$ource® Monthly (Selected from FDB MedKnowledge™) February 5, 2014. Reprinted with permission by FDB, Inc. All rights reserved. ©2014. www.fdbhealth.com/policies/drug-pricing-policy. Actual retail prices may be higher.
4. Prefilled, disposable syringe.
5. Also available in a concentration of 500 units/mL.

proximal renal tubule into tubular epithelial cells. The SGLT2 inhibitors **canagliflozin** *(Invokana)*[30] and **dapagliflozin** *(Farxiga)*[31] decrease renal glucose reabsorption and increase urinary glucose excretion, reducing fasting and prandial blood glucose levels and achieving a 0.5-1% reduction in A1C either as monotherapy or in addition to other medications. Other beneficial effects include a 3-6 mm Hg reduction in systolic blood pressure and weight loss of about 0.1-4 kg.[32] The two drugs appear to be similarly effective. Frequent mycotic genital infections in both women and men and a possible increased risk of bladder cancer with dapagliflozin may limit their use.

**PRAMLINTIDE —** An amylinomimetic agent that is injected subcutaneously before meals, pramlintide *(Symlin)* is approved for use in patients with type 1 or type 2 diabetes on prandial insulin.[33] The dose of the short-acting insulin, including pre-mixed insulins, should be reduced by 50% with initiation of pramlintide therapy and frequent (including postprandial) glucose monitoring is recommended. Pramlintide acts by slowing gastric emptying, increasing satiety, and suppressing postprandial plasma glucagon and hepatic glucose production. It reduces postprandial glucose excursions and promotes weight loss, but it reduces A1C by only 0.5%.

**COLESEVELAM —** A bile-acid sequestrant used to lower LDL cholesterol, colesevelam *(Welchol)* is also FDA-approved as an adjunct to diet and exercise for the treatment of type 2 diabetes.[34] A meta-analysis of six 8-26 week, randomized controlled trials including 1450 patients with type 2 diabetes found a mean reduction of 0.5% in A1C when colesevelam was added to other agents.[35] Its mechanism of action remains unclear. Colesevelam is not recommended for use as monotherapy.

**BROMOCRIPTINE —** An immediate-release formulation of the ergot-derived dopamine agonist bromocriptine mesylate *(Cycloset)* is modestly effective in decreasing blood glucose levels in patients with type 2 diabetes.[36] Despite minimal A1C reduction (0.5%),

this formulation may reduce the risk of cardiovascular events. In a randomized, placebo-controlled 52-week trial in 3070 patients with type 2 diabetes, *Cycloset* reduced the composite end point of myocardial infarction, stroke, and hospitalization for unstable angina, heart failure, or revascularization surgery.[37]

**REGULAR AND RAPID-ACTING INSULINS —** Rapid-acting insulin analogs have a faster onset and shorter duration of action than regular insulin and are generally administered at or just before a meal. In general, **insulin aspart** *(Novolog)*, **insulin glulisine** *(Apidra)*, and **insulin lispro** *(Humalog)* are slightly more effective than regular insulin in decreasing A1C, with less hypoglycemia.[38-40]

**LONGER-ACTING INSULINS — NPH**, an intermediate-acting insulin, can be used in combination with regular and rapid-acting insulins. Alternatively, patients can use pre-mixed combinations. While these formulations simplify administration of insulin, titration of dose is more difficult and hypoglycemia may be more frequent than with individual insulins.

**Insulin glargine** *(Lantus)*, a recombinant DNA analog of human insulin, forms microprecipitates in subcutaneous tissue, prolonging its duration of action to a mean of about 24 hours. It has no peak effect and causes less nocturnal hypoglycemia than NPH insulin. A 6-month open-label trial in 515 patients with type 2 diabetes inadequately controlled on metformin found improvement in A1C with insulin glargine compared to sitagliptin (additional 0.6% reduction in A1C), but with higher rates of symptomatic and nocturnal hypoglycemia.[41]

**Insulin detemir** *(Levemir)* has both delayed absorption from subcutaneous tissue and, due to reversible binding to albumin, delayed clearance from the circulation. Like insulin glargine, insulin detemir causes less nocturnal hypoglycemia than NPH.[42,43] Insulin detemir may be more effective when used twice daily; after 12 hours, its effectiveness appears to decrease. In a 26-week trial in 457 patients with type 2 diabetes inadequately controlled on metformin alone, insulin detemir was found to be slightly less effective than insulin glargine in reducing A1C (0.48% vs. 0.74%), but was associated with a mean weight loss of 0.5 kg compared to a weight gain of 1 kg with insulin glargine.[44]

**Adverse Effects –** All insulins, including long-acting formulations, can cause hypoglycemia and weight gain. Some observational studies have found an increased risk of cancer, in particular breast cancer, in patients using glargine, but a randomized controlled trial in >12,000 patients found no increase in cancer with insulin glargine compared to standard-of-care diabetes therapy.[45]

**ADDITION OF INSULIN —** When insulin is added to oral agents, it is usually given either as a single dose in the evening or at bedtime. In general, 10 units (or 0.2-0.5 units/kg) of a pre-mixed combination at dinnertime or NPH, insulin detemir, or insulin glargine at bedtime can be added initially. The dose can then be increased to achieve fasting plasma glucose concentrations between 70-130 mg/dL.

A pre-mixed insulin (30% rapid-acting insulin aspart and 70% intermediate-acting protaminated insulin aspart) given twice daily, prandial insulin aspart given before meals three times daily, and basal insulin detemir (bedtime or twice-daily) have been compared as initial insulin therapy in patients with type 2 diabetes and suboptimal glucose control (mean A1C 8.5%) on metformin and a sulfonylurea. All regimens achieved similar A1C levels (6.8-7.1%) with the most weight gain and hypoglycemia in the prandial group and the least in the basal group.[46]


1. American Diabetes Association. Standards of medical care in diabetes – 2014. Diabetes Care 2014; 37 (suppl 1):s14.
2. ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011; 364:818.
3. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358:2560.
4. W Duckworth et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360:129.
5. JS Skyler et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Circulation 2009; 119:351.
6. Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013; 369:145.
7. SE Kahn et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006; 355:2427.
8. RR Holman et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359:1577.
9. WR Lu et al. Unleash metformin: reconsideration of the contraindication in patients with renal impairment. Ann Pharmacother 2013; 47:1488.
10. AV Hernandez et al. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. Am J Cardiovasc Drugs 2011; 11:115.
11. SE Nissen and K Wolski. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356:2457.
12. KW Mahaffey et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J 2013; 166:240.
13. In brief: rosiglitazone (Avandia) unbound. Med Lett Drugs Ther 2014; 56:12.
14. Exenatide (Byetta) for type 2 diabetes. Med Lett Drugs Ther 2005; 47:45.
15. B Gallwitz et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. Lancet 2012; 379:2270.
16. Extended-release exenatide (Bydureon) for type 2 diabetes. Med Lett Drugs Ther 2012; 54:21.
17. T Blevins et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab 2011; 96:1301.

18. M Davies et al. Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. Diabetes Care 2013; 36:1368.
19. Liraglutide (Victoza) for type 2 diabetes. Med Lett Drugs Ther 2010; 52:25.
20. JB Buse et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet 2013; 381:117.
21. PC Butler et al. A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe? Diabetes Care 2013; 36:2118.
22. Alogliptin (Nesina) for type 2 diabetes. Med Lett Drugs Ther 2013; 55:41.
23. Linagliptin (Tradjenta) – a new DPP-4 inhibitor for type 2 diabetes. Med Lett Drugs Ther 2011; 53:49.
24. Saxagliptin (Onglyza) for type 2 diabetes. Med Lett Drugs Ther 2009; 51:85.
25. BM Scirica et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013; 369:1317.
26. WB White et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013; 369:1327.
27. S Singh et al. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. JAMA Intern Med 2013; 173:534.
28. FDA Drug Safety Communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes. Available at www.fda.gov/drugs/drugsafety/ucm343187.htm. Accessed February 18, 2014.
29. MA Nauck. A critical analysis of the clinical use of incretin-based therapies: the benefits by far outweigh the potential risks. Diabetes Care 2013; 36:2126.
30. Canagliflozin (Invokana) for type 2 diabetes. Med Lett Drugs Ther 2013; 55:37.
31. Dapagliflozin (Farxiga) for type 2 diabetes. Med Lett Drugs Ther 2014; 56:13.
32. D Vasilakou et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013; 159:262.
33. Pramlintide (Symlin) for diabetes. Med Lett Drugs Ther 2005; 47:43.
34. In brief: A new indication for colesevelam (Welchol). Med Lett Drugs Ther 2008; 50:33.
35. CP Ooi and SC Loke. Colesevelam for Type 2 diabetes mellitus: an abridged Cochrane review. Diabet Med 2014; 31:2.
36. Bromocriptine (Cycloset) for type 2 diabetes. Med Lett Drugs Ther 2010; 52:97.
37. JM Gaziano et al. Effect of bromocriptine-QR (a quick-release formulation of bromocriptine mesylate) on major adverse cardiovascular events in type 2 diabetes subjects. J Am Heart Assoc 2012; 1:e002279.
38. SR Singh et al. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. CMAJ 2009; 180:385.
39. Rapid-acting insulin analogs. Med Lett Drugs Ther 2009; 51:98.
40. Insulin glulisine (Apidra): a new rapid-acting insulin. Med Lett Drugs Ther 2006; 48:33.
41. P Aschner et al. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial. Lancet 2012; 379:2262.
42. Insulin detemir (Levemir), a new long-acting insulin. Med Lett Drugs Ther 2006; 48:54.
43. K Hermansen et al. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care 2006; 29:1269.
44. L Meneghini et al. Once-daily initiation of basal insulin as add-on to metformin: a 26-week, randomized, treat-to-target trial comparing insulin detemir with insulin glargine in patients with type 2 diabetes. Diabetes Obes Metab 2013; 15:729.
45. ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012; 367:319.
46. RR Holman et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med 2009; 361:1736.


**Coming Soon in *Treatment Guidelines*:**
Drugs for Peptic Ulcer Disease and GERD – April 2014
Drugs for Hypertension – May 2014

**Follow us on Twitter @MedicalLetter**


Treatment Guidelines
from The Medical Letter®





**Subscription Services**

**Mailing Address:**
The Medical Letter, Inc.
145 Huguenot St. Ste. 312
New Rochelle, NY 10801-7537

**Customer Service:**
Call: 800-211-2769 or 914-235-0500
Fax: 914-632-1733
Web Site: www.medicalletter.org
E-mail: custserv@medicalletter.org

**Permissions:**
To reproduce any portion of this issue, please e-mail your request to:
permissions@medicalletter.org

**Subscriptions (US):**
1 year - $98; 2 years - $189;
3 years - $279. $49.00 per year for students, interns, residents and fellows in the US and Canada.

**E-mail site license inquiries to:**
info@medicalletter.org or call 800-211-2769 x315.
Special fees for bulk subscriptions.
Special classroom rates are available.
Back issues are $12 each. Major credit cards accepted.

# *Treatment Guidelines*: Online Continuing Medical Education

## Up to 24 credits included with your subscription

medicalletter.org/cme

### Choose CME from *Treatment Guidelines from The Medical Letter* and earn up to 24 Category 1 Credits per year:

**Free Individual Exams -** Free to active subscribers of *Treatment Guidelines from The Medical Letter*. Answer 12 questions per issue and submit answers online. Earn up to 2 credits/exam.
**Paid Individual Exams -** Available to non-subscribers. Answer 12 questions per issue and submit answers online. Earn up to 2 credits/exam. $12/exam.

**ACCREDITATION INFORMATION:**
**ACCME:** The Medical Letter is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Medical Letter Inc. designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity. This CME activity was planned and produced in accordance with the ACCME Essentials and Policies.

**AAFP:** This enduring material activity, Treatment Guidelines from the Medical Letter Continuing Medical Education Program, has been reviewed and is acceptable for up to 7.50 Prescribed credit(s) by the American Academy of Family Physicians. AAFP certification begins January 1, 2014. Term of approval is for one year from this date. Each issue is approved for 1.25 Prescribed credits. Credit may be claimed for one year from the date of each issue. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

**ACPE:** The Medical Letter is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This exam is acceptable for 2.0 hour(s) of knowledge-based continuing education credit (0.2 CEU).

**AANP and AAPA:** The **American Academy of Nurse Practitioners (AANP)** and the **American Academy of Physician Assistants (AAPA)** accept *AMA Category 1 Credit* for the Physician's Recognition Award from organizations accredited by the ACCME.

**AOA:** This activity, being ACCME (AMA) approved, is acceptable for Category 2-B credit by the **American Osteopathic Association (AOA)**.

**Physician Assistants:** The **National Commission on Certification of Physician Assistants (NCCPA)** accepts *AMA PRA Category 1 Credit(s)™* from organizations accredited by ACCME. NCCPA also accepts AAFP Prescribed credits for recertification. *Treatment Guidelines* is accredited by both ACCME and AAFP.

**Physicians in Canada:** Members of **The College of Family Physicians of Canada** are eligible to receive Mainpro-M1 credits (equivalent to AAFP Prescribed credits), as per our reciprocal agreement with the American Academy of Family Physicians.

Physicians, nurse practitioners, pharmacists and physician assistants may earn 2 credits with this exam.

**MISSION:**
The mission of The Medical Letter's Continuing Medical Education Program is to support the professional development of healthcare professionals including physicians, nurse practitioners, pharmacists and physician assistants by providing independent, unbiased drug information and prescribing recommendations that are free of industry influence. The program content includes current information and unbiased reviews of FDA-approved and off-label uses of drugs, their mechanisms of action, clinical trials, dosage and administration, adverse effects and drug interactions. The Medical Letter delivers educational content in the form of self-study material.

The expected outcome of the CME Program is to increase the participant's ability to know, or apply knowledge into practice after assimilating, information presented in materials contained in *Treatment Guidelines.*

The Medical Letter will strive to continually improve the CME program through periodic assessment of the program and activities. The Medical Letter aims to be a leader in supporting the professional development of healthcare professionals through Core Competencies by providing continuing medical education that is unbiased and free of industry influence. The Medical Letter is supported solely by subscription fees and accepts no advertising, grants or donations.

**GOAL:**
Through this program, The Medical Letter expects to provide the healthcare community with unbiased, reliable and timely educational content that they will use to make independent and informed therapeutic choices in their practice.

**LEARNING OBJECTIVES:**
The objective of this activity is to meet the need of healthcare professionals for unbiased, reliable and timely information on treatment of major diseases. The Medical Letter expects to provide the healthcare community with educational content that they will use to make independent and informed therapeutic choices in their practice. Participants will be able to select and prescribe, or confirm the appropriateness of the prescribed usage of the drugs and other therapeutic modalities discussed in *Treatment Guidelines* with specific attention to clinical evidence of effectiveness, adverse effects and patient management.

Upon completion of this program, the participant will be able to:

1. Explain the current approach to the management of type 2 diabetes.
2. Discuss the pharmacologic options available for treatment of type 2 diabetes and compare them based on their efficacy, dosage and administration, and potential adverse effects.
3. Determine the most appropriate therapy given the clinical presentation of an individual patient.

**Privacy and Confidentiality:** The Medical Letter guarantees our firm commitment to your privacy. We do not sell any of your information. Secure server software (SSL) is used for commerce transactions through VeriSign, Inc. No credit card information is stored.

**IT Requirements:** Windows 98/NT/2000/XP/Vista/7/8, Pentium+ processor, Mac OS X+ w/ compatible processor; Microsoft IE 6.0+, Mozilla Firefox 2.0+ or any other compatible Web browser. Dial-up/high-speed connection.

**Have any questions?** Call us at 800-211-2769 or 914-235-0500 or e-mail us at: custserv@medicalletter.org

**Questions start on next page**

**DO NOT FAX OR MAIL THIS EXAM**
**To take CME exams and earn credit, go to:w**
**medicalletter.org/CMEstatus**

# Issue 139 Questions

1. Which of the following drugs is generally preferred for first-line treatment of type 2 diabetes?
   a. rosiglitazone
   b. nateglinide
   c. metformin
   d. glyburide

2. Most oral antihyperglycemic drugs lower glycated hemoglobin (A1C) by:
   a. 0.5-1.5%
   b. 1.5-2%
   c. 2-2.5%
   d. 2-3%

3. Which of the following sulfonylureas is most likely to cause hypoglycemia?
   a. glyburide
   b. glipizide
   c. glimepiride
   d. nateglinide

4. Meglitinides:
   a. bind to ATP-sensitive potassium channels on beta cells and increase insulin release
   b. are rapidly absorbed and cleared
   c. cause plasma levels of insulin to peak within 30-60 minutes
   d. all of the above

5. A 68-year-old man with active liver disease and type 2 diabetes poorly controlled on metformin alone asks his physician to prescribe rosiglitazone. Which of the following would you tell him?
   a. access to rosiglitazone-containing products is restricted because of concerns regarding its cardiovascular safety
   b. rosiglitazone should not be used in patients with active liver disease
   c. rosiglitazone must be injected
   d. rosiglitazone is only approved by the FDA for use as monotherapy

6. GLP-1 receptor agonists:
   a. potentiate glucose-dependent secretion of insulin
   b. suppress glucagon secretion
   c. slow gastric emptying
   d. all of the above

7. Which of the following drugs is also available in an extended-release formulation?
   a. pioglitazone
   b. liraglutide
   c. exenatide
   d. acarbose

8. Which of the following drugs has been associated with thyroid C-cell hyperplasia?
   a. acarbose
   b. liraglutide
   c. miglitol
   d. metformin

9. Adverse effects of SGLT2 inhibitors include:
   a. genital mycotic infections
   b. urinary tract infections
   c. hyperkalemia
   d. all of the above

10. Which of the following drugs can be taken without regard to meals?
    a. metformin
    b. pioglitazone
    c. glimepiride
    d. acarbose

11. A 54-year-old woman with type 2 diabetes is admitted to the hospital and is going to have a CT scan with intravenous iodinated contrast. She is currently taking metformin, alogliptin, and insulin. Which of the following would you recommend?
    a. administer an extra dose of insulin before the procedure
    b. withhold the metformin dose before the procedure
    c. discontinue metformin permanently and double the dose of alogliptin
    d. continue therapy as directed

12. Which of the following insulin products should be administered at dinnertime when added to oral antihyperglycemic therapy?
    a. NPH
    b. insulin detemir
    c. insulin glargine
    d. *Novolin 70/30*

**ACPE UPN: 0379-0000-14-139-H01-P; Release: February 2014, Expire: February 2015**