PHARMACIST'S LETTER

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PRESCRIBER'S LETTER

Drugs for Type 2 Diabetes

(Last modified September 2015)

Diabetes is a worldwide problem affecting millions of people. Glucose control is the mainstay of therapy in these patients. In recent years, a variety of new agents with novel mechanisms of action have been approved for the treatment of type 2 diabetes. While this provides more options for the treatment of these patients, the wide array of medications can lead to confusion as to which agents should be used. In general, both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) recommend that in addition to lifestyle modification, metformin is first-line for the treatment of type 2 diabetes in most patients.[1,2] In general, the target A1C concentrations are 7% (ADA) or 6.5% (AACE), but the goal may be individualized in patients with other illnesses and in those at risk for hypoglycemia.[1,2] Therapy can be started with more than one agent in patients with an A1C ≥9% (ADA) or ≥7.5% (AACE). However, for patients who fail metformin monotherapy, a broad variety of agents can be used in combination with metformin, or as monotherapy in those who cannot use metformin.[1,2] The choice of second-line and third-line agents varies based on patient characteristics, patient preferences, and properties of the medications such as the risk of hypoglycemia or weight gain. The table below summarizes the agents available for the treatment of type 2 diabetes, including expected A1C reduction, mechanism of action, dosing, and advantages and disadvantages of each class of medication.

Abbreviations: BID - twice daily; CVD - cardiovascular disease; MOA - mechanism of action; PO - by mouth; SC - subcutaneously; TID - three times daily.

Class/ Expected A1C Reduction[c]	**Specific Agents**	**Initial Dose[a] (Approximate cost for 30-day supply[b])**	**Advantages [a,1-3]**	**Disadvantages[a,1-3]**
Alpha-glucosidase inhibitor 0.5% to 1%[3] MOA: Slows intestinal carbohydrate digestion/ absorption.	Acarbose (*Precose*, others) Miglitol (*Glyset*)	**Acarbose** INITIAL: 25 mg PO TID ($45) **Miglitol** INITIAL: 25 mg PO TID ($145)	• Lack of hypoglycemia when used as monotherapy • Weight neutral • Reduces postprandial glucose values • Not absorbed • Likely reduces CVD events (acarbose) • Beneficial in the treatment of prediabetes (acarbose)[9]	• Modest effect on A1C • Flatulence • Diarrhea • Need for frequent dosing

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Class/ Expected A1C Reduction[c]	**Specific Agents**	**Initial Dose[a] (Approximate cost for 30-day supply[b])**	**Advantages [a,1-3]**	**Disadvantages[a,1-3]**
Amylin analog 0.5% to 1%[5] MOA: Slows gastric emptying, increases the feeling of fullness, reduces postprandial glucagon secretion.	Pramlintide (*Symlin*)	**Pramlintide** INITIAL: 60 mcg SC prior to major meals (≥250 kcal or containing ≥30 g carbohydrate) ($590)	• Lack of hypoglycemia when used as monotherapy • Weight loss • Reduces postprandial glucose values • Increases feeling of fullness after meal	• Modest effect on A1C • Nausea • Vomiting • Hypoglycemia if insulin dose is not reduced • Need for frequent dosing • Injectable
Biguanide 1% to 1.5%[3] MOA: Inhibits hepatic glycogenolysis and gluconeogenesis. Enhances insulin sensitivity in muscle and fat.	Metformin (*Glucophage*, *Glucophage XR*) Available in combination with alogliptin, glimepiride, glipizide, glyburide, linagliptin, pioglitazone, rosiglitazone, saxagliptin, sitagliptin, repaglinide, and canagliflozin. See specific agents.	**Metformin** INITIAL: 500 mg PO BID or 850 mg PO once daily (less than $20/month)	• Lack of hypoglycemia • Weight neutral • Likely reduces CVD events • Beneficial in the treatment of prediabetes[10]	• Diarrhea • Abdominal cramping • B12 deficiency • Lactic acidosis (rare) in patients with cardiovascular, renal, or hepatic dysfunction

Class/ Expected A1C Reduction[c]	**Specific Agents**	**Initial Dose[a] (Approximate cost for 30-day supply[b])**	**Advantages [a,1-3]**	**Disadvantages[a,1-3]**
Dipeptidyl peptidase-4 (DPP-4) inhibitor ("gliptins") or incretin enhancer 0.5% to 1%[3] (However, some experts feel that the actual range is lower [e.g., ≤0.7%].) MOA: Inhibits degradation of endogenous incretins resulting in increased insulin secretion in response to elevated blood glucose, decreased glucagon secretion, slowed gastric emptying, and increased satiety.	Alogliptin (*Nesina*) With metformin (*Kazano*) With pioglitazone (*Oseni*) Linagliptin (*Tradjenta*) With metformin (*Jentadueto*) With empagliflozin (*Glyxambi*) Saxagliptin (*Onglyza*) With metformin (*Kombiglyze XR*) Sitagliptin (*Januvia*) With metformin (*Janumet*, *Janumet XR*)	**Alogliptin** INITIAL: 25 mg PO once daily ($310) **Linagliptin** INITIAL: 5 mg PO once daily ($330) **Saxagliptin** INITIAL: 2.5 or 5 mg PO once daily ($325) **Sitagliptin** INITIAL: 100 mg PO once daily ($330)	• No hypoglycemia when used as monotherapy • Weight neutral • Generally well tolerated	• Dosage modification with renal impairment needed (sitagliptin, saxagliptin, alogliptin) • CYP3A4 interactions (saxagliptin, linagliptin) • May be associated with pancreatitis[6] • May worsen heart failure (saxagliptin)[7,13] • May cause severe joint pain[12]

Class/ Expected A1C Reduction[c]	**Specific Agents**	**Initial Dose[a] (Approximate cost for 30-day supply[b])**	**Advantages [a,1-3]**	**Disadvantages[a,1-3]**
Glucagon-like, peptide-1 (GLP-1) agonist or incretin mimetic 1% to 1.5%[3] MOA: Stimulation of GLP-1 receptors results in increased insulin secretion in response to elevated blood glucose, decreased glucagon secretion, slowed gastric emptying, and increased satiety. (GLP-1 is an incretin hormone.) For more information, see our *PL Chart, Comparison of GLP-1 Agonists*.	Albiglutide (*Tanzeum*) Dulaglutide (*Trulicity*) Exenatide (*Byetta*) Exenatide extended-release (*Bydureon*) Liraglutide (*Victoza*)	**Albiglutide** INTIAL: 30 mg SC once weekly ($325) **Dulaglutide** INITIAL: 0.75 mg SC once weekly ($490) **Exenatide** INITIAL: 5 mcg SC BID ($480) **Exenatide extended-release** INITIAL: 2 mg SC once weekly ($475) **Liraglutide** INITIAL: 0.6 mg SC once daily x 1 week, then increase to 1.2 mg SC once daily ($430)	• Lack of hypoglycemia when used as monotherapy • Weight loss • Reduces postprandial glucose values • In patients who need more than one or two antidiabetes agents, combination injectable therapies of basal insulin and a GLP-1 agonist is an efficient, emerging strategy.	• Headache • Nausea (often transient) • Diarrhea • Dosage modification with renal dysfunction needed (albiglutide, dulaglutide) • Avoid in severe renal impairment (exenatide) • May be associated with pancreatitis[6] • Associated with thyroid cell cancer in rodents • May be associated with renal insufficiency[8] • Injectable

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Class/ Expected A1C Reduction[c]	**Specific Agents**	**Initial Dose[a] (Approximate cost for 30-day supply[b])**	**Advantages [a,1-3]**	**Disadvantages[a,1-3]**
Insulin 1.5% to 3.5%[5]	Various. See our *PL Chart, Comparison of Insulins and Injectable Diabetes Meds*.	See our *PL Charts, Initiation and Adjustment of Insulin Regimens for Type 2 Diabetes* and *Comparison of Insulins and Injectable Diabetes Meds*.	• Effective in all patients • Reduced microvascular complications • Consider starting insulin, in combination with metformin therapy with or without other noninsulin therapies when the blood glucose is >300 mg/dL to 350 mg/dL and/or the A1C ≥10%. Insulin may be more effective than other therapies when hyperglycemia is severe, especially if the patient is symptomatic or has any catabolic features (e.g., weight loss, ketosis).	• Hypoglycemia • Weight gain • Injectable
Meglitinide 0.5% to 1%[3] MOA: Stimulates pancreatic insulin secretion.	Nateglinide (*Starlix*) Repaglinide (*Prandin*, others) With metformin (*PrandiMet*)	**Nateglinide** INITIAL: 60 to 120 mg PO TID with meals ($105) **Repaglinide** INITIAL: 0.5 mg PO TID with meals if A1C <8%, 1 or 2 mg TID with meals if A1C ≥8% ($50)	• Reduces postprandial glucose values • Can be used in place of sulfonylureas in patients with irregular meal schedules or in those who develop late hypoglycemia with a sulfonylurea	• Hypoglycemia if taken without food or if severe renal impairment • Weight gain • Frequent dosing • Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started[3]

Class/ Expected A1C Reduction[c]	**Specific Agents**	**Initial Dose[a] (Approximate cost for 30-day supply[b])**	**Advantages [a,1-3]**	**Disadvantages[a,1-3]**
Sodium-glucose co-transporter 2 (SGLT2) inhibitor or "flozins" 0.5% to 1%[1] MOA: Blocks glucose reabsorption in kidney, increases glucosuria.	Canagliflozin (*Invokana*) With metformin (*Invokamet*) Dapagliflozin (*Farxiga*) Empagliflozin (*Jardiance*) With linagliptin (*Glyxambi*) With metformin (*Synjardy*)	**Canagliflozin** INITIAL: 100 mg PO once daily ($340) **Dapagliflozin** INITIAL: 5 mg PO once daily ($340) **Empagliflozin** INITIAL: 10 mg PO once daily ($340)	• Lack of hypoglycemia • Weight loss • May reduce blood pressure	• Genital fungal infections (male and female) • Urinary tract infection • Increased urination • Hypotension • Increase LDL • Do not use if eGFR <45 mL/min/1.73m^2 (canagliflozin, empagliflozin) or <60 mL/min/1.73m^2 (dapagliflozin) • Fractures (rare, in susceptible patients).[4] Decrease in BMD (canagliflozin).[11] • May be associated with increased risk of bladder cancer (dapagliflozin) • Possible association with ketoacidosis[14]

Class/ Expected A1C Reduction[c]	**Specific Agents**	**Initial Dose[a] (Approximate cost for 30-day supply[b])**	**Advantages [a,1-3]**	**Disadvantages[a,1-3]**
Sulfonylurea–first generation 1% to 1.5%[3] MOA: Stimulates pancreatic insulin secretion.	Chlorpropamide (*Diabinese*, others) Tolazamide (*Tolinase*, others) Tolbutamide (*Orinase*, others)	**Chlorpropamide** INITIAL: 100 to 250 mg PO once daily (less than $20/month) **Tolazamide** INITIAL: 250 mg PO once daily ($48) **Tolbutamide** INITIAL: 1 g PO once daily ($70)	• Initially, good efficacy • Inexpensive	• Hypoglycemia more common compared with second-generation sulfonylureas[5] • Weight gain[5] • Reduced efficacy over time[5] • Avoid in patients with renal dysfunction or the elderly (chlorpropamide) • Use of second-generation sulfonylureas preferred over first-generation sulfonylureas • Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started[1]

Class/ Expected A1C Reduction[c]	**Specific Agents**	**Initial Dose[a] (Approximate cost for 30-day supply[b])**	**Advantages [a,1-3]**	**Disadvantages[a,1-3]**
Sulfonylurea-second generation 1% to 1.5%[3] MOA: Stimulates pancreatic insulin secretion.	Glyburide (*Diabeta*, *Glynase*, *Micronase*, others) With metformin (*Glucovance*) Glipizide (*Glucotrol*, *Glucotrol XL*, others) With metformin (*Metaglip*) Glimepiride (*Amaryl*, others) With metformin (*Amaryl M*) With pioglitazone (*Duetact*) With rosiglitazone (*Avandaryl*)	**Glyburide** INITIAL: 2.5 mg PO once daily (less than $10/month) **Glipizide** INITIAL: 5 mg PO once daily (less than $10/month) **Glimepiride** INITIAL: 1 mg PO once daily (less than $10/month)	• Initially, good efficacy • Inexpensive	• Hypoglycemia, especially with renal dysfunction (less with glimepiride versus glyburide)[5] • Weight gain (glyburide more than glipizide, glimepiride) • Reduced efficacy over time • For the elderly and those with hepatic or renal dysfunction, start with low doses and titrate up • Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started[1]

Class/ Expected A1C Reduction[c]	**Specific Agents**	**Initial Dose[a] (Approximate cost for 30-day supply[b])**	**Advantages [a,1-3]**	**Disadvantages[a,1-3]**
Thiazolidinedione (TZD) 1% to 1.5%[3] MOA: Increases insulin sensitivity in muscle and fat.	Pioglitazone (*Actos*) With metformin (*Actoplus Met* or *Actoplus Met XR*) With glimepiride (*Duetact*) With alogliptin (*Oseni*) Rosiglitazone (*Avandia*) With metformin (*Avandamet*) With glimepiride (*Avandaryl*)	**Pioglitazone** INITIAL: 15 mg PO once daily (less than $20) **Rosiglitazone** INITIAL: 4 mg PO once daily ($115)	• Lack of hypoglycemia when used as monotherapy • Improves HDL cholesterol • Reduced triglycerides (pioglitazone) • May reduce CVD (pioglitazone)	• Weight gain • Volume retention, congestive heart failure • Increased fracture risk • Increases LDL (rosiglitazone) • May possibly increase the risk of bladder cancer (pioglitazone)
Others – bile acid sequestrant 0.5% to 1%[3] MOA: May reduce hepatic glucose production, may increase incretin levels, and decreases GI glucose absorption.	Colesevelam (*Welchol*)	**Colesevelam** INITIAL: 3.75 g PO per day (taken as six tablets once daily, or three tablets BID, with meals) ($470)	• No hypoglycemia • Weight neutral • Safe in CVD • Lowers LDL cholesterol	• Constipation • Nausea, bloating • Increased triglycerides • Drug interactions
Others – dopamine agonist 0.5% to 1%[3] MOA: May centrally regulate metabolism, increase insulin sensitivity.	Bromocriptine (*Cycloset*)	**Bromocriptine** INITIAL: 0.8 mg PO once daily ($90)	• No hypoglycemia • Weight neutral	• Dizziness/syncope • Nausea

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a. **Information based on most current U.S. product information unless otherwise noted**: *Precose* (March 2015), *Glyset* (February 2015), *Symlin* (March 2015), *Glucophage* (March 2015), *Onglyza* (May 2013), *Januvia* (March 2015), *Tradjenta* (May 2014), *Byetta* (February 2015), *Bydureon* (March 2015), *Victoza* (March 2015), *Starlix* (January 2013), *Prandin* (March 2012), *Diabeta* (October 2013), *Glucotrol* (February 2011), *Amaryl* (February 2012), *Actos* (August 2012), *Avandia* (May 2012), *Welchol* (January 2014), *Cycloset* (March 2011), *Diabinese* (October 2013), tolazamide (Mylan; December 2009), tolbutamide (Mylan; February 2009), *Invokana* (March 2015), *Nesina* (June 2013), *Farxiga* (March 2015), *Jardiance* (August 2014), *Tanzeum* (March 2015), *Invokamet* (March 2015), *Trulicity* (March 2015).

b. Approximate prices based on WAC for 30-day supply (of generic product if available, generic prices may vary considerably). If WAC not available (chlorpropamide, tolazamide, tolbutamide), AWP for 30-day supply used.

c. A1C reductions are estimates using monotherapy.

Users of this PL Detail-Document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

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