

### Treating Type 2 Diabetes Mellitus:

**Key Message 3: Metformin should be used as a first-line medication in almost every patient with type 2 diabetes. If goal HbA1C is not achieved after 3 months of maximized metformin monotherapy (2g/day) and patient adherence has been confirmed, add a second agent based on the % of HbA1C lowering required for each patient to reach their goal**

**Calculate % of HbA1C lowering required to reach goal:  
Patient's Current HbA1C – Patient's Goal HbA1C = % of HbA1C lowering required**

Initiating Pharmacotherapy <sup>1,2</sup> :	Monotherapy	Dual Therapy
<b>ADA</b>	At time of diagnosis	HbA1C ≥ 9%
<b>AACE</b>	HbA1C < 7.5%	HbA1C ≥ 7.5%

**First Line Treatment Option + Lifestyle Modifications<sup>[1, 2]</sup>  
(medication classes listed in order of greatest HbA1C lowering potential to least)**

**Biguanide**

**Mechanism of Action:** Decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increase peripheral glucose uptake and utilization peripheral

Drug	Dosing	% of HbA1C Lowering potential	Side effects /Notes
Metformin (Glucophage) <sup>[3]</sup>	IR: 2000-2550mg divided BID to TID EX: 2000-2500mg divided BID	1 - 2 %	<p><b>BLACK BOX WARNINGS</b> Lactic acidosis – risk increased with hypoxic states, dehydration, hepatic/renal impairment, age ≥ 65 years, iodinated contrast media</p> <p><b>CONTRAINDICATIONS</b> Severe renal dysfunction (eGFR &lt;30 mL/minute/1.73 m<sup>2</sup>); acute or chronic metabolic acidosis with or without coma (including diabetic ketoacidosis)</p> <p><b>SIDE EFFECTS</b> GI side effects (diarrhea, upset stomach, indigestion, flatulence, nausea, metallic taste), lactic acidosis</p> <p><b>ADVANTAGES</b> Weight loss/neutral, ↓basal and postprandial glucose, ↓triglycerides, LDL and total cholesterol, low risk of hypoglycemia</p>

**Additional information on Metformin:**

Metformin GI disturbances are usually transient and the following tips can help minimize them<sup>3</sup>:

- ▶ Switch to extended-release tablets
- ▶ Take metformin with food
- ▶ Initiate metformin using slow titration schedule to reach the maximum recommended daily dose of 2,000mg
  - Advise patients to take the largest metformin dose with the biggest meal of the day.

**Metformin IR: Recommended dosing titration schedule:**

**Metformin ER: Recommended dosing titration schedule:**

SUN	MON	TUE	WED	THU	FRI	SAT
Week 1	500 mg once daily					
Week 2	500 mg twice daily					
Week 3	1,000 mg AM, 500 mg PM					
Week 4	1,000 mg twice daily					

SUN	MON	TUE	WED	THU	FRI	SAT
Week 1	500 mg once daily					
Week 2	1000 mg once daily					
Week 3	1,500 mg once daily					
Week 4	2,000 mg once daily					

**Metformin and Lactic Acidosis**

Contraindications to metformin use include renal impairment -- defined by the manufacturer as Scr levels at or exceeding 1.4 mg/dL in females and 1.5 mg/dL in males, or abnormal creatinine clearance -- as well as metabolic acidosis.<sup>3</sup> Although the concern exists that patients with poor renal function are at an increased risk of lactic acidosis, a review of studies shows a weak association between metformin use and development of lactic acidosis. There has been no evidence from prospective comparative trials or observational cohort studies that metformin is associated with an increased risk of lactic acidosis.<sup>4</sup>

Additional oral agents available to add to help patients achieve HbA1C goal + Metformin + Continued Lifestyle Modifications (medication classes listed in order of greatest HbA1C lowering potential to least)			
<b>Sulfonylurea</b>			
<b>Mechanism of Action:</b> Stimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites			
Drug	Dosing	% of HbA1C Lowering potential	Side effects /Notes
Glyburide (DiaBeta, Glynase) <sup>[5]</sup>	1.25 – 20mg daily MDD: 20mg/day  Glynase: 0.75 – 12mg daily MDD: 12mg/day	1 - 2 %	<b>WARNINGS</b> Hypoglycemia, possible sulfa allergy  <i>Glyburide:</i> Due weakly active metabolic that is renally excreted, avoid if eGFR <60 ml/min or > 65 years of age  <b>SIDE EFFECTS</b> Weight gain, nausea, hypoglycemic  <b>ADVANTAGES</b> low cost, extensive experience
Glipizide (Glucotrol, Glucotrol XL)	IR: 2.5 – 20mg daily or BID MDD: 40mg/day  ER: 5-10mg daily MDD: 20mg/day		
Glimepiride (Amaryl) <sup>[6]</sup>	1 – 4mg daily MDD: 8mg/day		
<b>Thiazolidinediones</b>			
<b>Mechanism of Action:</b> decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output			
Rosiglitazone (Avandia) <sup>[7]</sup>	4 – 8mg daily	0.7 - 1.5 %	<b>BLACK BOX WARNINGS</b> Cause or exacerbate congestive heart failure  <b>CONTRAINDICATIONS</b> New York Heart Association (NYHA) Class III or IV heart failure  <b>WARNINGS</b>

Pioglitazone (Actos) <sup>[8]</sup>	15 – 45mg daily		<p>Obtain liver function tests before initiation and continue to monitor</p> <p><i>Pioglitazone</i>: linked with an increased risk of bladder cancer</p> <p><i>Rosiglitazone</i>: associated with increased risk of myocardial ischemic events</p> <p><b>SIDE EFFECTS</b> CHF, edema, bone fractures, upper respiratory tract infection, headache, sinusitis, myalgia, and pharyngitis, Interaction with CYP2C8 drugs</p>
<b>DDP-4 Inhibitors</b>			
<b>Mechanism of Action:</b> increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation			
Sitagliptin (Januvia) <sup>[9]</sup>	100mg daily 50mg daily if eGFR < 45 mL/min/1.73m <sup>2</sup> 25mg daily if eGFR < 30 mL/min/1.73m <sup>2</sup>	0.5 -1.0%	<p><b>WARNINGS</b> Pancreatitis, arthralgia, hypersensitivity including anaphylaxis, angioedema and/or severe dermatologic reaction (SJS)</p> <p><i>Saxagliptin</i> and <i>Sitagliptin</i>: may exacerbate underlying myocardial dysfunction</p> <p><i>Alogliptin</i>: hepatotoxicity, use with caution in patient with liver disease</p> <p><b>SIDE EFFECTS</b> Headache, nasopharyngitis, URI, UTI, peripheral edema</p> <p><b>ADVANTAGES</b> low risk of hypoglycemia, weight neutral</p>
Linagliptin (Tradjenta) <sup>[10]</sup>	5mg daily		
Saxagliptin (Onglyza) <sup>[11]</sup>	2.5 -5mg daily 2.5mg daily if eGFR < 45 mL/min/1.73m <sup>2</sup>		
Alogliptin (Nesina) <sup>[12]</sup>	25mg daily 12.5mg daily for CrCl <60 mL/min 6.25mg daily for CrCl < 30 mL/min		
<b>SGLT2 Inhibitors</b>			
<b>Mechanism of Action:</b> inhibits SGLT2 in the proximal renal tubules, which reduces reabsorption of filtered glucose, lowers the renal threshold for glucose, and increases excretion of glucose			
Canagliflozin (Invokana) <sup>[13]</sup>	100 – 300mg daily AM	0.7 – 1.0%	<p><b>BLACK BOX WARNINGS</b> <i>Canagliflozin</i>: Increased risk lower limb amputation. Before initiating, consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers</p> <p><b>CONTRAINDICATIONS</b> severe renal impairment (eGFR &lt; 30 mL/min/1.73m<sup>2</sup>)</p> <p><b>SIDE EFFECTS</b> ↑ serum potassium, ↑ thirst, UTI, polyuria</p> <p><b>ADVANTAGES</b> Low risk of hypoglycemia, weight loss, slight reduction in BP</p>
Dapagliflozin (Farxiga) <sup>[14]</sup>	5 – 10mg daily AM, with or without food		
Empagliflozin (Jardiance) <sup>[15]</sup>	10 – 25mg daily AM or without food		
<b>Alpha – Glucosidase Inhibitor</b>			
<b>Mechanism of Action:</b> delays hydrolysis of carbohydrates to glucose in small intestine, delaying glucose absorption			
Acarbose (Precose) <sup>[16]</sup>	25mg TID at the start of each main meal. Titrate to 100mg TID if needed.  MDD ≤60kg: 50mg TID MDD >60kg: 100mg TID	0.4-0.8%	<p><b>CONTRAINDICATIONS</b> inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who have conditions that may deteriorate as a result of increased gas formation in the intestine</p> <p><b>SIDE EFFECTS</b> GI (abdominal pain, diarrhea and flatulence)</p> <p><b>ADVANTAGES</b> low risk of hypoglycemia, weight neutral, decreases Post Prandial glucose</p>
Miglitol (Glyset) <sup>[17]</sup>	25mg TID at the start of each main meal. Titrate to 100mg TID if needed.  MDD: 100mg TID		

## Other Non-Insulin Injectable

### Glucagon-Like Peptide 1 Agonists

**Mechanism of Action:** enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying.

Drug	Dosing	% of HbA1C Lowering potential	Side effects /Notes
Exenatide IR (Byetta) <sup>[17a]</sup>	Inject subcutaneously within 60 minutes prior to morning and evening meals.  5mcg BID for 1 month → Increase to 10mcg BID  NOT recommended in CrCl <30mL/min or ESRD	>0.8-1.5 %	<p><b>BLACK BOX WARNING</b> All GLP-1 agonists (except for exenatide IR and lixisenatide): risk of thyroid C-cell tumors</p> <p><b>CONTRADINDICATION</b> All GLP-1 agonists (except for exenatide IR and lixisenatide) are contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN2).</p> <p><b>WARNINGS</b> Acute pancreatitis</p> <p>GLP-1 receptor agonist slow gastric emptying, the use is not recommended in patients with preexisting severe GI disease</p> <p><i>Exenatide ER:</i> serious injection-site reactions with or without subcutaneous nodules have been reported</p> <p><i>Liraglutide:</i> increased resting report has been reported. Monitor is recommended</p> <p><b>SIDE EFFECTS</b> nausea, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia</p>
Exenatide ER (Bydureon, Bydureon BCISE) <sup>[18, 19]</sup>	Inject 2 mg subcutaneously once weekly, at any time of day and with or without meals		
Liraglutide (Victoza) <sup>[20]</sup>	Inject subcutaneously once daily at any time of day, independently of meals  0.6mg QD for 1 week → Increase to 1.2mg QD (may increase to 1.8mg QD if needed)		
Dulaglutide (Trulicity) <sup>[21]</sup>	Inject 0.75mg subcutaneously once weekly at any time of day (may increase to 1.5mg once weekly if needed)		
Lixisenatide (Adlyxin) <sup>[22]</sup>	Inject 0.75mg subcutaneously once weekly at any time of day (may increase to 1.5mg once weekly if needed)		

Key: **wt** - weight, **GLP-1 Receptor Agonist** - Glucagon-like peptide-1 receptor agonists, **GI** - gastrointestinal, **TZDs** - thiazolidines, **CHF** - congestive heart failure, **DPP-4 Inhibitors** - dipeptidyl Peptidase-4 Inhibitors, **SGLT2 Inhibitor** - sodium-glucose co-transporter 2 inhibitors, \* - anticipated HbA1C lowering potential and cost

REFERENCES:

1. "American Diabetes Association Standards Of Medical Care In Diabetes- 2017." *Diabetes Care* 40.Supplement 1.
2. "AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY – CLINICAL PRACTICE GUIDELINES FOR DEVELOPING A DIABETES MELLITUS COMPREHENSIVE CARE PLAN – 2015." *AACE.com*. N.p., 2017. Web. 25 Sept. 2017.
3. *Glucophage*® [package insert]. Bristol-Myers Squibb Company. 2017.
4. Philbrick AM, Ernst ME, McDanel DL, Ross MB, Moores KG. Metformin use in renal dysfunction: is a serum creatinine threshold appropriate? *Am J Health Syst Pharm*. 2009;66(22):207-2023.
5. *Diabeta*® [package insert]. Sanofi-aventis. 2009.
6. *Amaryl*® [package insert]. Sanofi-aventis US LLC. 2009
7. *Avandia*® [package insert]. GlaxoSmithKline. 2007.
8. *Actos*® [package insert]. Takeda Pharmaceuticals America Inc. 2011.
9. *Januvia*® [package insert]. Merck & Co, Inc. 2010.
10. *Tradjenta*® [package insert]. Boehringer Ingelheim Pharmaceuticals, Inc. 2014.
11. *Onglyza*® [package insert]. Bristol-Myers Squibb Company. 2013.
12. *Nesina*® [package insert]. Takeda Pharmaceuticals America. 2013.
13. *Invokana*® [package insert]. Janssen Pharmaceuticals, Inc. 2013.
14. *Farxiga*® [package insert] Bristol-Myers Squibb Company. 2014.
15. *Jardiance*® [package insert]. Boehringer Ingelheim Pharmaceuticals, Inc. 2014.
16. *Precose*® [package insert]. Bayer HealthCare Pharmaceuticals Inc. 2011.
17. *Glyset*® [package insert]. Pfizer. 2012.17a) *Byetta*® [package insert]. Amylin Pharmaceuticals, Inc. 2013.
18. *Bydureon*® [1package insert]. Amylin Pharmaceuticals, Inc 2015.
19. *Bydureon BCise (exenatide)* [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals. 2017.
20. *Victoza*® [package insert]. Novo Nordisk. 2010.
21. *Trulicity*® [package insert]. Eli Lilly and Company. 2014
22. *Adlyxin (lixisenatide)* [prescribing information]. Bridgewater, NJ: Sanofi-Aventis US LLC. 2016.