

## Therapeutic Class Overview

### Sulfonylureas

#### INTRODUCTION

- In the United States (US), diabetes mellitus affects more than 30 million people and is the 7<sup>th</sup> leading cause of death (*Centers for Disease Control and Prevention [CDC] 2018*).
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is characterized by elevated fasting and postprandial glucose concentrations (*American Diabetes Association [ADA] 2019[a]*). It is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications (*ADA 2019[b]*).
  - Complications of T2DM include hypertension, heart disease, stroke, vision loss, nephropathy, and neuropathy (*ADA 2019[a]*).
- In addition to dietary and lifestyle management, T2DM can be treated with insulin, one or more oral medications, or a combination of both. Many patients with T2DM will require combination therapy (*Garber et al 2019*).
- Classes of oral medications for the management of blood glucose levels in patients with T2DM focus on increasing insulin secretion, increasing insulin responsiveness, or both, decreasing the rate of carbohydrate absorption, decreasing the rate of hepatic glucose production, decreasing the rate of glucagon secretion, and blocking glucose reabsorption by the kidney (*Garber et al 2019*).
- Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin (*Garber et al 2019*).
- SFUs are the oldest of the oral antidiabetic medications, and all agents are available generically. The SFUs can be divided into 2 categories: first-generation and second-generation.
- The first-generation SFUs are acetohexamide, chlorpropamide, tolazamide, and tolbutamide. Acetohexamide has been discontinued from the U.S. market and will not be further discussed in this review. Chlorpropamide, tolazamide and tolbutamide are all available as generics; the branded products (Diabinese, Tolinase, and Orinase, respectively) have been discontinued by the manufacturers.
- The second-generation SFUs are glimepiride, glipizide, and glyburide. The second-generation agents have structural characteristics that allow them to be given in much lower doses than the first-generation agents. The branded products Diabeta and Micronase have been discontinued by their respective manufacturers, but generic glyburide is still available.
- The combination products consist of an SFU and metformin (glyburide/metformin and glipizide/metformin) or an SFU and a TZD (glimepiride/pioglitazone), which also have generic formulations available. Of note, the brands Metaglip (glipizide/metformin) and Glucovance (glyburide/metformin) have been discontinued. Additionally, Avandaryl (glimepiride/rosiglitazone) has been discontinued, but not for efficacy or safety reasons. A generic formulation is not yet available but has received Food and Drug Administration (FDA) approval. This review will focus on the single entity and combination oral SFUs listed in Table 1.
- Medispan class: Antidiabetics, Sulfonylureas; Antidiabetics, Antidiabetic Combinations

**Table 1. Medications Included Within Class Review**

| Drug                     | Generic Availability |
|--------------------------|----------------------|
| <b>First-generation</b>  |                      |
| chlorpropamide           | ✓                    |
| tolazamide               | ✓                    |
| tolbutamide              | ✓                    |
| <b>Second-generation</b> |                      |
| Amaryl (glimepiride)     | ✓                    |
| glyburide                | ✓                    |
| Glucotrol (glipizide)    | ✓                    |

| Drug   | Generic Availability |
|--|----------------------|
| Glucotrol XL (glipizide extended-release [ER]) | ✓                    |
| Glynase (micronized glyburide)                 | ✓                    |
| <b>Combination products</b>                    |                      |
| Duetact (glimepiride/pioglitazone)             | ✓                    |
| glipizide/metformin                            | ✓                    |
| glyburide/metformin                            | ✓                    |

(Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019)

## INDICATIONS

**Table 2. FDA-Approved Indications**

| Indication  | 1 <sup>st</sup> generation |            |             | 2 <sup>nd</sup> generation |           |           | Combinations                 |                         |                         |
|---|----------------------------|------------|-------------|----------------------------|-----------|-----------|------------------------------|-------------------------|-------------------------|
|   | chlorpropamide             | tolazamide | tolbutamide | glimepiride                | glipizide | glyburide | glimepiride/<br>pioglitazone | glipizide/<br>metformin | glyburide/<br>metformin |
| Adjunct to diet and exercise to improve glycemic control in adults with T2DM  | ✓                          | ✓          | ✓           | ✓                          | ✓         | ✓         |                              | ✓                       | ✓                       |
| Adjunct to diet and exercise to improve glycemic control in adults with T2DM who are already treated with a TZD and an SFU or who have inadequate glycemic control on a TZD alone or an SFU alone |                            |            |             |                            |           |           | ✓                            |                         |                         |

(Prescribing information: Amaryl 2018, chlorpropamide 2009, Duetact 2017, glipizide and metformin 2017, glyburide 2017, glyburide/metformin 2017, Glucotrol 2018, Glucotrol XL 2018, Glynase 2017, tolazamide 2009, tolbutamide 2009)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## CLINICAL EVIDENCE SUMMARY

- Second-generation SFUs have comparable efficacy for the treatment of T2DM (Bell et al 2004, Inzucchi et al 2002). Some evidence suggests that glimepiride may have less of an impact on ischemic preconditioning than glyburide and may be the preferred agent in patients with coronary heart disease; however, contrasting evidence suggests that there is no difference between agents (Andersson et al 2011, Evans et al 2008, Lee et al 2003, Pantalone et al 2010). Other studies show that therapy with glipizide and glyburide resulted in comparable HbA1c reductions, and similar reductions in HbA1c were observed with patients on glimepiride and glyburide therapy (Birkeland et al 1994, Kitabchi et al 2000, Sami et al 1996).
- A systematic review and meta-analysis of 31 DB randomized controlled trials (RCTs) evaluated the efficacy of SFUs in reducing hemoglobin A1C (HbA1c). Included studies evaluated glimepiride, glipizide, glyburide, tolbutamide, or tolazamide as monotherapy or add-on therapy. The duration of the included trials ranged from 12 weeks to 3 years, with a median duration of 16 weeks. In 9 monotherapy trials, the placebo-adjusted reduction in HbA1c with SFUs was 1.51% (95% CI, 1.25 to 1.78). In 4 add-on therapy trials, SFUs reduced HbA1c by 1.62% (95% CI, 1.0 to 2.24). In 17 trials with patients on insulin therapy, the addition of an SFU was associated with an HbA1c reduction of 0.46% (95% CI, 0.24 to 0.69) and a reduced insulin dose (Hirst et al 2013).

- A meta-analysis demonstrated that glyburide was not associated with a higher risk of cardiovascular (CV) events when compared to other SFUs, meglitinides, or insulin. However, glyburide was associated with a 52% higher risk of experiencing greater than 1 episode of hypoglycemia (*Gangji et al 2007*). Additional meta-analyses supported this evidence. Bolen et al compared several endpoints (eg, mortality, microvascular endpoints, macrovascular endpoints) among the following agents: second-generation SFUs, biguanides, TZDs, meglitinides, and alpha-glucosidase inhibitors. Results demonstrated that there was no definitive evidence on the comparative effectiveness of the agents on all-cause mortality, CV mortality or morbidity, peripheral arterial disease, neuropathy, retinopathy, or nephropathy. TZDs, metformin, and repaglinide improved glycemic control to the same degree as SFUs (*Bolen et al 2007*). Pantalone et al and Andersson et al also compared overall mortality among several second-generation SFUs. No statistically significant difference in the risk of overall mortality was observed among these agents. However, study results suggest that glimepiride may be the preferred SFU in those with underlying coronary artery disease (*Andersson et al 2011, Pantalone et al 2010*).
- In a double-blind (DB) randomized trial, treatment with metformin showed a significant reduction in the recurrence of composite CV events compared to glipizide (*Hong et al 2013*). In an observational study, the use of glyburide, glipizide, and rosiglitazone was associated with significantly higher mortality rates than metformin therapy (*Wheeler et al 2013*).
- Several head to head studies were conducted to evaluate the efficacy of SFUs compared to a GLP-1 agonist. Each therapy in most instances was added to existing drugs to improve glycemic control. Overall, reduction in HbA1c from baseline and improvement in glycemic control were significantly greater with the GLP-1 agonist compared to glimepiride (*Ahrén et al 2014, Gallwitz et al 2012, Garber et al 2009, Garber et al 2011, Nauck et al 2009*). In similarly designed studies, the efficacy and safety of an SFU was compared to a DPP-4 inhibitor. Overall, reductions in mean HbA1c from baseline were similar in the DPP-4 inhibitor (alogliptin, linagliptin, sitagliptin, saxagliptin) and SFU (glimepiride, glipizide) study groups (*Arechavaleta et al 2011, Del Prato et al 2014, Gallwitz et al 2012, Goke et al 2010, Rosenstock et al 2013, Seck et al 2010*). In a study comparing alogliptin to glipizide, more patients taking glipizide experienced hypoglycemic episodes compared to patients taking alogliptin (*Del Prato et al 2014, Rosenstock et al 2013*). In a 52-week extension study, patients taking saxagliptin + metformin had similar glycemic control compared to patients taking glipizide + metformin. However, the saxagliptin group had a lower incidence of hypoglycemia and less weight gain (*Goke et al 2013*).
- A meta-analysis by Amate et al compared the efficacy and safety of metformin and a DPP-4 inhibitor versus metformin and glimepiride as a second-line treatment. The results revealed a 12% greater decrease in HbA1c and a higher proportion of patients achieving HbA1c <7% in the metformin with glimepiride group (*Amate et al 2015*). Another meta-analysis compared metformin with an SFU to metformin with a DPP-4 inhibitor. The results revealed a statistically significant reduction in HbA1c levels for the SFU group during the first 12 weeks of therapy, but no difference between the 2 groups following 52 to 104 weeks of treatment. The proportion of patients reaching HbA1c <7% was not statistically different between the 2 groups (*Mishriky et al 2015*). A meta-analysis by Hou et al investigated the efficacy and safety of metformin with an SFU versus metformin with sitagliptin when used for at least 12 weeks. The results revealed no statistically significant differences between the 2 groups with regard to decrease in HbA1c levels and proportion of patients achieving HbA1c <7% (*Hou et al 2015*). Results of all meta-analyses revealed greater weight gain and more hypoglycemia in patients taking metformin with an SFU compared to patients on metformin with a DPP-4 inhibitor.
- A network meta-analysis of controlled trials comparing 2 or more SFUs assessed all-cause mortality and CV mortality. In 18 studies (N = 167,327), all-cause mortality was lowest with glimepiride, followed by glipizide, glyburide, tolbutamide, and chlorpropamide. Glimepiride was associated with a significantly lower risk of mortality than glyburide, and glipizide was associated with a similar mortality rate to glyburide. Similar associations were observed for CV mortality in 13 studies (N = 145,916). Compared to glyburide, the RR of CV-related death was 0.79 (95% credible interval [CrI], 0.57 to 1.11) for glimepiride, 1.01 (95% CrI, 0.72 to 1.43) for glipizide, 1.11 (95% CrI, 0.79 to 1.55) for tolbutamide, and 1.45 (95% CrI, 0.88 to 2.44) for chlorpropamide (*Simpson et al 2015*).
- A meta-analysis of 8 studies compared CV outcomes with metformin plus an SFU and metformin plus a DPP-4 inhibitor. The relative risk (RR) of nonfatal CV events (0.71, 95% confidence interval [CI] 0.56 to 0.90), CV mortality (0.58, 95% CI 0.41 to 0.82), and all-cause mortality (0.72, 95% CI 0.59 to 0.87) were all significantly lower with metformin plus a DPP-4 inhibitor. The RR of fatal CV events was similar with both treatment combinations (*Wang et al 2017*).
- A network meta-analysis of 170 RCTs (N = 166,371) evaluated differences in 4-point major adverse cardiovascular events (MACE) (composite of CV death, nonfatal MI, nonfatal stroke, and unstable angina) and all-cause mortality. Compared to SFUs, SGLT2 inhibitors, insulin, GLP-1 receptor agonists, and DPP-4 inhibitors were associated with

significantly lower rates of MACE. For all-cause mortality, SFUs were associated with more deaths than SGLT2 inhibitors and insulin. The ranking of CV risk was linearly correlated with the ranking of severe hypoglycemia risk, and SFUs were associated with the highest risks for both outcomes (Zhuang et al 2018).

- A head to head study was conducted to evaluate the efficacy and safety of glyburide when compared to nateglinide in T2DM with 2 hour postprandial glucose levels  $\geq 11.1$  mmol/L. Study results revealed that nateglinide led to greater reductions in postprandial glucose excursions compared to glyburide (Bellomo et al 2011).
- Clinical trials comparing the SFUs to the SGLT2 inhibitors have suggested that the SGLT2 inhibitors are noninferior to glipizide or glimepiride and are associated with less hypoglycemia and weight gain (Nauck et al 2011, Nauck et al 2014, Ridderstrale et al 2014).
- The effectiveness of the combination SFUs was demonstrated primarily through clinical trials designed to compare individual SFU agents in combination with other antidiabetic agents (ie, metformin). A significant improvement in glycemic control was observed when an SFU was administered as combination therapy compared to monotherapy (Garber et al 2002, Goldstein et al 2003, Marre et al 2002). In 2 studies where glyburide monotherapy and metformin monotherapy were compared to a combination of glyburide and metformin, the reductions in HbA1c were significantly greater with the combination (Garber et al 2002, Marre et al 2002). A similar outcome was seen when glipizide monotherapy and metformin monotherapy were compared to the combination of glipizide and metformin (Goldstein et al 2003). The addition of basal insulin to combination therapy with glimepiride and metformin resulted in a significant improvement in overall glycemic control compared with combination glimepiride and metformin (Park et al 2014).
- Another set of studies consisted of retrospective analyses that looked at glyburide and metformin as individual agents given concurrently compared to a combination product of glyburide and metformin (Blonde et al 2003, Duckworth et al 2003, Gottschalk et al 2007). These studies provided only mean doses of the individual agents and the combination products, making it difficult to determine if equivalent doses of the individual agents given concurrently were equivalent to the combination products. Thus, it is not clear if there is any advantage of the combination formulation over the individual agents when given at an equivalent dose. Finally, a meta-analysis compared the safety of SFUs in combination with metformin to metformin monotherapy. While combination therapy was more effective than metformin alone in improving HbA1c and reducing gastrointestinal effects, it had the disadvantage of decreasing high-density lipoproteins and increasing the risk of hypoglycemia and nervous system adverse events (Zhang et al 2013).
- A systematic review evaluated the safety and efficacy of antidiabetic classes (ie, biguanides, TZDs, SFUs, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists) in 216 studies of monotherapy or combination therapy for T2DM. (Bolen et al 2016).
  - For monotherapy, metformin, TZDs, and SFUs were associated with similar reductions in HbA1c in the short term (high strength of evidence). Compared to DPP-4 inhibitors, metformin was more effective in lowering HbA1c (difference,  $-0.4\%$ ). Differences in HbA1c reduction between SFUs, TZDs, DPP-4 inhibitors, and SGLT2 inhibitors as add-on therapy to metformin were either not statistically significant or not clinically meaningful ( $< 0.3\%$ ) (moderate strength of evidence).
  - In general, significant between-group differences were observed when comparing classes expected to increase weight (ie, SFUs, TZDs, insulin) to classes expected to decrease weight (ie, metformin, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 agonists). SFUs were associated with less weight gain than TZDs, but more weight gain than metformin and GLP-1 agonists (moderate strength of evidence). Patients with an SFU added to metformin therapy experienced significantly more weight gain compared to patients who remained on metformin alone (high strength of evidence) and patients with a DPP-4 inhibitor or SGLT2 inhibitor added to metformin (high strength of evidence).
  - Compared to metformin, SFU monotherapy was associated with a 50 to 70% higher RR of CV mortality (absolute risk difference, 0.1 to 2.9% in RCTs; moderate strength of evidence).
  - Overall, the risk of mild, moderate, or total hypoglycemia was higher with SFUs alone and in combination with metformin than with any other monotherapies and metformin-based combinations. Patients receiving SFU monotherapy had a higher risk of severe hypoglycemia than patients receiving metformin or TZD monotherapy (moderate strength of evidence). As add-on therapy to metformin, SFUs were associated with a greater risk of severe hypoglycemia than DPP-4 or SGLT2 inhibitors (moderate strength of evidence).
- Three retrospective, propensity-matched, new-user cohort studies (N = 246,558,805) with replication across 8 sites evaluated patients receiving SFUs, DPP-4 inhibitors, or TZDs as add-on therapy to metformin. No significant differences were observed between classes in the reduction of HbA1c levels to  $\leq 7\%$  or the incidence of kidney disorders. Compared to DPP-4 inhibitors, SFUs were associated with an increased risk for myocardial infarction (hazard ratio [HR], 1.12; 95% CI, 1.02 to 1.24) and eye disorders (HR, 1.15; 95% CI, 1.11 to 1.19) (Vashisht et al 2018).

## CLINICAL GUIDELINES

### Overview

- Professional society guidelines are consistent in recommending metformin as the optimal first-line pharmacologic therapy for treatment-naïve patients with T2DM, unless the patient has contraindications or intolerance. SFUs are among the second-line options for subsequent therapy. All guidelines emphasize individualized therapy based upon patient-specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes (ADA 2019, Copeland et al 2013, Davies et al 2018, Garber et al 2019).
- A 2018 American College of Cardiology expert consensus decision pathway on CV risk reduction in patients with T2DM and atherosclerotic CV disease (ASCVD) suggests adding an SGLT2 inhibitor or GLP-1 receptor agonist that has demonstrated beneficial CV outcomes to other guideline-directed therapy for diabetes (specifically, metformin). Among the SGLT2 inhibitors with CV outcome data at the time that the pathway was written (canagliflozin and empagliflozin), empagliflozin was the preferred SGLT2 inhibitor based on the available evidence and overall risk to benefit ratio (Das et al 2018).
- **ADA/European Association for the Study of Diabetes (EASD): Management of Hyperglycemia in Type 2 Diabetes, 2018** (Davies et al 2018)
  - The goals of T2DM therapy are to prevent or delay complications and maintain quality of life, which requires glycemic control, CV risk factor management, regular follow-up, and a patient-centered approach to enhance patient engagement in self-care activities. Careful consideration of patient-specific factors and preferences must inform the process of individualizing treatment goals and strategies.
  - Due to new evidence of benefit with specific agents in the reduction of mortality, heart failure (HF), and progression of renal disease, the overall approach to glucose-lowering medication in T2DM for the ADA/EASD consensus report was updated in 2018. A history of CVD, chronic kidney disease (CKD), and heart failure should be taken into consideration early in the process of treatment selection. Additionally, the guideline recommends early consideration of weight, hypoglycemic risk, treatment cost, and other patient-related factors that may influence the choice of drug therapy.
    - Among patients with T2DM who have established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven CV benefit are recommended as part of glycemic management.
    - For patients with ASCVD with concomitant HF, SGLT2 inhibitors are recommended.
    - For patients with T2DM and CKD (with or without ASCVD), an SGLT2 inhibitor shown to reduce CKD progression should be considered. If SGLT2 inhibitors are contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression should be considered.
  - **Initial monotherapy:** Metformin remains the preferred drug for initial monotherapy based on its efficacy, safety, tolerability, low cost, and extensive clinical experience.
  - **Add-on to metformin:** The selection of a second agent added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established ASCVD and other comorbidities such as HF or CKD; the risk for specific AEs, particularly hypoglycemia and weight gain; as well as safety, tolerability, and cost.
  - **Intensification beyond 2 medications:** Intensification of treatment beyond dual therapy to maintain glycemic targets requires consideration of the impact of medication side effects on comorbidities, as well as the burden of treatment and cost.
  - **Addition of injectable medications:** For patients who require the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are preferred over insulin. For patients with extreme and symptomatic hyperglycemia, insulin is recommended.
  - **Beyond basal insulin:** Patients who are unable to maintain glycemic targets on basal insulin in combination with oral medications can have treatment intensified with GLP-1 receptor agonists, SGLT2 inhibitors, or prandial insulin.
- **ADA: Standards of Medical Care in Diabetes – 2019** (ADA 2019)
  - **Pharmacological therapy for T2DM:**
    - Metformin (if not contraindicated and if tolerated) is the preferred initial pharmacological agent for T2DM (level A).
    - Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated (level A).

- Dual therapy should be considered in patients with newly diagnosed T2DM who have HbA1c  $\geq$  1.5% above their glycemic target (level E).
- Early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels ( $>$  10%) or blood glucose levels ( $>$  300 mg/dL) are very high (level E).
- A patient-centered approach should be used to guide the choice of pharmacologic therapy. Considerations include comorbidities (ASCVD, HF, CKD), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (level E).
- In patients with T2DM and established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with demonstrated CVD benefit are recommended as part of the antihyperglycemic regimen (level A).
- In patients with T2DM and established ASCVD with a high risk of or existing heart failure, SGLT2 inhibitors are preferred (level C).
- In patients with T2DM and CKD, use of SGLT2 inhibitors or GLP-1 receptor agonists shown to reduce the risk of CKD progression, CV events, or both should be considered (level C).
- In most patients who require the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are preferred over insulin (level B).
- The medication regimen should be reevaluated at regular intervals (every 3 to 6 months) and adjusted as needed to incorporate new patient factors (level E).
- Initial therapy
  - Metformin should be initiated at the time T2DM is diagnosed if there are no contraindications.
  - For patients with contraindications or intolerance to metformin, initial therapy with an SGLT2 inhibitor, GLP-1 receptor agonist, DPP-4 inhibitor, TZD, SFU (2nd generation), or insulin should be considered based on patient factors.
- Combination therapy
  - Dual therapy is recommended for patients who do not achieve their HbA1c goal after 3 months of monotherapy.
  - For patients without ASCVD or CKD, an agent from any of the 6 preferred classes (SFU, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin) can be added to metformin, with the choice of agent based on drug-specific effects (ie, avoidance of adverse effects such as hypoglycemia and weight gain) and patient factors (ie, cost and personal preference).
  - For patients with ASCVD, HF, or CKD, the best choice for add-on therapy is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated benefit.
  - Similar considerations are applied in patients who require a third agent to achieve glycemic goals.

**Table 3. ADA Factors to Consider for Antihyperglycemic Therapies in T2DM**

| Class*                                     | Efficacy     | Hypoglycemia | Weight                              | ASCVD  | CHF   | Route | DKD   | Additional considerations   |
|--|--------------|--------------|-------------------------------------|--|---|-------|---|---|
| <b>Metformin</b>                           | High         | No           | Neutral (potential for modest loss) | Potential benefit  | Neutral                                       | Oral  | Neutral                                     | GI AEs common<br>B12 deficiency   |
| <b>SGLT2i</b>                              | Intermediate | No           | Loss                                | Benefit:<br>canagliflozin,<br>empagliflozin  | Benefit:<br>canagliflozin,<br>empagliflozin   | Oral  | Benefit:<br>canagliflozin,<br>empagliflozin | Boxed warning for<br>amputation: canagliflozin<br>Genitourinary infections                                |
| <b>GLP-1ra</b>                             | High         | No           | Loss                                | Neutral:<br>lixisenatide<br>Benefit:<br>liraglutide ><br>semaglutide ><br>exenatide ER | Neutral                                       | SQ    | Benefit:<br>liraglutide                     | Boxed warning for<br>thyroid C-cell tumors<br>(liraglutide, albiglutide,<br>dulaglutide, exenatide<br>ER) |
| <b>DPP-4i</b>                              | Intermediate | No           | Neutral                             | Neutral  | Potential risk:<br>saxagliptin,<br>alogliptin | Oral  | Neutral                                     | Potential risk of acute<br>pancreatitis<br>Joint pain   |
| <b>TZD</b>                                 | High         | No           | Gain                                | Potential<br>benefit:<br>pioglitazone  | Increased risk                                | Oral  | Neutral                                     | Boxed warning for CHF<br>(pioglitazone,<br>rosiglitazone)   |
| <b>SFU (2<sup>nd</sup><br/>generation)</b> | High         | Yes          | Gain                                | Neutral  | Neutral                                       | Oral  | Neutral                                     | FDA special warning on<br>increased risk of CV  |

Data as of March 15, 2019 KAL/CME

Page 6 of 13

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

|                |         |     |      |         |         |    |         |  |
|----------------|---------|-----|------|---------|---------|----|---------|--|
|                |         |     |      |         |         |    |         | mortality based on studies of an older SFU (tolbutamide) |
| <b>Insulin</b> | Highest | Yes | Gain | Neutral | Neutral | SQ | Neutral | Injection site reactions                                 |

Abbreviations: AE = adverse event; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CV = cardiovascular; DKD = diabetic kidney disease; DPP-4i = dipeptidyl peptidase 4 inhibitor; ER = extended-release; GI = gastrointestinal; GLP-1ra = glucagon-like peptide-1 receptor agonist; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SQ = subcutaneous; T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones

\* Other antidiabetic drugs not shown in above table (eg, inhaled insulin, alpha-glucosidase inhibitors (AGIs), colesevelam, bromocriptine, and pramlintide) may be tried in specific situations; however, considerations include modest efficacy in T2DM, frequency of administration, potential for drug interactions, cost, and/or side effects.

• **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) - Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm (Garber et al 2019)**

○ Founding principles of the Comprehensive Type 2 Diabetes Management Algorithm:

- Lifestyle optimization is essential for all patients with diabetes.
- Minimizing the risk of both severe and non-severe hypoglycemia is a priority. Minimizing risk of weight gain is also a priority.
- The HbA1c target should be individualized based on numerous factors, such as age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia or adverse consequences from hypoglycemia, patient motivation, and adherence. A target HbA1c  $\leq 6.5\%$  is considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time.
- Glycemic control targets include fasting and post-prandial glucose as determined by self-monitoring of blood glucose.
- The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves. Medication attributes include antihyperglycemic efficacy, mechanism of action, risk of inducing hypoglycemia, risk of weight gain, other AEs, tolerability, ease of use, likely adherence, cost, and safety or risk reduction in heart, kidney, or liver disease. Patient-specific considerations include initial A1C, duration of T2DM, and obesity status.
  - The choice of therapy depends on the individual patient's cardiac, cerebrovascular, and renal status.
- Combination therapy is usually required and should involve agents with complementary mechanisms of action.
- Therapy must be evaluated frequently (eg, every 3 months) until the patient is stable, using multiple criteria (eg, HbA1c, self-monitoring of blood glucose records, lipid and blood pressure levels, hypoglycemia events, AEs).

○ Glycemic control algorithm for T2DM:

- In patients with recent-onset T2DM or mild hyperglycemia (HbA1c  $< 7.5\%$ ), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended. For patients with ASCVD or CKD, GLP-1 receptor agonists and SGLT2 inhibitors with proven benefits may be preferred.
  - Other acceptable alternatives to metformin include DPP-4 inhibitors and TZDs; AGIs, SFUs, and meglitinides may also be appropriate as monotherapy for select patients.
- In patients who do not achieve their HbA1c goal after 3 months of monotherapy or patients who present with HbA1c  $\geq 7.5\%$ , dual therapy should be started by adding 1 of the following agents to metformin (in order of preference): GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, TZD, basal insulin, colesevelam, bromocriptine quick release (QR), AGI, SFU, or meglitinide.
- If dual therapy does not achieve the HbA1c goal in 3 months, triple therapy should be started by adding 1 of the following agents to metformin plus a second-line agent (in order of preference): GLP-1 receptor agonist, SGLT2 inhibitor, TZD, basal insulin, DPP-4 inhibitor, colesevelam, bromocriptine QR, AGI, SFU, or meglitinide.
- If triple therapy fails to achieve the HbA1c goal in 3 months, then the patient should proceed to or intensify insulin therapy.
- In patients with entry HbA1c  $> 9.0\%$ , dual therapy or triple therapy is recommended if the patient is asymptomatic. If the patient is symptomatic, insulin therapy alone or in combination with other agents is recommended.

○ SFU-specific information:

- The SFUs have relatively potent HbA1c-lowering effects, but they lack durability and are associated with weight gain and hypoglycemia. SFUs have the highest risk of serious hypoglycemia of any noninsulin therapy, and

analyses of large datasets have raised concerns regarding the CV safety of this class when the comparator is metformin, which may itself have cardioprotective properties.

**Table 4. AACE/ACE Profiles of Antidiabetic Medications**

|                         | Hypoglycemia       | Weight      | Renal/GU   | GI       | Cardiac   | Bone                   | Ketoacidosis  |
|-------------------------|--------------------|-------------|--|----------|---|------------------------|---------------|
| <b>Metformin</b>        | Neutral            | Slight loss | eGFR < 30: contraindicated   | Moderate | Neutral   | Neutral                | Neutral       |
| <b>GLP-1ra</b>          | Neutral            | Loss        | Possible benefit: liraglutide<br>Exenatide not indicated<br>CrCl < 30                | Moderate | Liraglutide FDA approved for prevention of MACE   | Neutral                | Neutral       |
| <b>SGLT2i</b>           | Neutral            | Loss        | Genital mycotic infections<br>Not indicated eGFR < 45<br><b>Possible CKD benefit</b> | Neutral  | Empagliflozin FDA approved to reduce CV mortality<br><b>Canagliflozin FDA approved to reduce MACE</b> | <b>Neutral</b>         | DKA can occur |
| <b>DPP-4i</b>           | Neutral            | Neutral     | Dose adjustment necessary (except linagliptin)<br>Albuminuria reduction              | Neutral  | Alogliptin, saxagliptin:<br>Possible increased HHF  | Neutral                | Neutral       |
| <b>AGI</b>              | Neutral            | Neutral     | Neutral  | Moderate | Neutral   | Neutral                | Neutral       |
| <b>TZD</b>              | Neutral            | Gain        | Neutral  | Neutral  | Moderate CHF risk<br>May reduce stroke risk   | Moderate fracture risk | Neutral       |
| <b>SFU</b>              | Moderate/severe    | Gain        | More hypoglycemia risk   | Neutral  | Possible ASCVD risk   | Neutral                | Neutral       |
| <b>Meglitinide</b>      | Mild               | Gain        | More hypoglycemia risk   | Neutral  | Possible ASCVD risk   | Neutral                | Neutral       |
| <b>Colesevelam</b>      | Neutral            | Neutral     | Neutral  | Mild     | ASCVD benefit   | Neutral                | Neutral       |
| <b>Bromocriptine QR</b> | Neutral            | Neutral     | Neutral  | Moderate | Safe  | Neutral                | Neutral       |
| <b>Insulin</b>          | Moderate to severe | Gain        | More hypoglycemia risk   | Neutral  | CHF risk  | Neutral                | Neutral       |
| <b>Pramlintide</b>      | Neutral            | Loss        | Neutral  | Moderate | Neutral   | Neutral                | Neutral       |

Abbreviations: AGI = alpha-glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CrCl = creatinine clearance; CV = cardiovascular; DKA = diabetic ketoacidosis; DPP-4i = dipeptidyl peptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; GI = gastrointestinal; GLP-1ra = glucagon-like peptide-1 receptor agonist; GU = genitourinary; HHF = hospitalization for heart failure; MACE = major adverse cardiovascular events; QR = quick release; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TZD = thiazolidinedione

#### SAFETY SUMMARY

- The American Geriatrics Society recommends avoidance of long-acting sulfonylureas (chlorpropamide, glimepiride, and glyburide) in older adults (high quality of evidence; strong recommendation) (*Fick et al 2019*).
  - Chlorpropamide has a prolonged half-life in older adults, which increases the risk for prolonged hypoglycemia and syndrome of inappropriate antidiuretic hormone (SIADH).
  - Glimepiride and glyburide have a higher risk of severe, prolonged hypoglycemia in older adults.

#### • Contraindications:

- Patients with diabetic ketoacidosis or diabetic coma
- Patients with type 1 diabetes mellitus
- Hypersensitivity to drug or its components
- Amaryl (glimepiride), Glucotrol XL: Patients who have a history of an allergic reaction to sulfonamide derivatives including cutaneous reactions with or without pruritus such as angioedema and Stevens-Johnson syndrome
- Duetact: Patients with New York Heart Association Class III or IV heart failure
- Glyburide, glyburide/metformin, Glynase: Concomitant administration with Tracleer (bosentan)
- Glyburide/metformin, glipizide/metformin: Renal disease or renal dysfunction

#### • Boxed Warnings:

Data as of March 15, 2019 KAL/CME

Page 8 of 13

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.



- Duetact: TZDs, including pioglitazone and rosiglitazone, cause or exacerbate congestive heart failure in some patients.
- Glyburide/metformin: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation.
- **Warnings/Precautions:**
  - The metabolism and excretion of these drugs may be slowed in patients with impaired renal and/or hepatic function.
  - There is an association between use of an SFU (tolbutamide) and increased CV mortality.
  - Post-marketing data showed that glimepiride can be associated with angioedema, Stevens-Johnson syndrome, and anaphylaxis.
  - All SFUs are capable of producing severe hypoglycemia.
  - Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with SFUs can lead to hemolytic anemia.
  - Other warnings/precautions for TZDs and metformin can be found in the product labeling.
- **Adverse events:**
  - Constipation, diarrhea, hypoglycemia, nausea, photosensitivity, rash, and vomiting are some of the most common adverse effects.
  - Weight gain
  - Chlorpropamide has unique adverse effects, including disulfiram-like reaction and a reaction identical to SIADH.
  - Adverse events for TZDs and metformin can be found in the product labeling.
- **Drug interactions:**
  - ACE inhibitors - may cause a temporary increase in insulin sensitivity, increasing the risk for hypoglycemia.
  - MAO inhibitors - may enhance the hypoglycemic action of SFUs through an unknown mechanism.
  - Salicylates, nonsteroidal anti-inflammatory agents - can reduce plasma glucose levels and enhance insulin secretion, adding to the hypoglycemic effects of SFUs.
  - Thiazide diuretics, atypical antipsychotics, corticosteroids, oral contraceptives, protease inhibitors, calcium channel blockers - may increase fasting blood glucose levels, resulting in decreased glycemic control.
  - Sulfonamides, quinolones, fluconazole - may impair the metabolism of certain SFUs and enhance the hypoglycemic effects of SFUs.
  - Colesevelam - maximum plasma concentration and total exposure to the SFU is reduced when colesevelam is coadministered with certain SFUs. Therefore, the SFU should be administered at least 4 hours prior to colesevelam.
  - Beta-blockers, clonidine – may either increase or decrease the glucose-lowering effect of SFUs, and may block signs and symptoms of hypoglycemia.
  - Chlorpropamide has a unique interaction with alcohol, which may cause a disulfiram-like reaction and increase the risk for hypoglycemia.

## DOSING AND ADMINISTRATION

- SFUs are typically administered with meals. When dosed once daily, SFUs are given with breakfast or the first main meal of the day.

**Table 5. Dosing and Administration**

| Drug                     | Available Formulations | Route | Usual Recommended Frequency              | Comments                              |
|--------------------------|------------------------|-------|--|---------------------------------------|
| <b>First-generation</b>  |                        |       |  |                                       |
| chlorpropamide           | Tablets                | Oral  | Once daily                               |                                       |
| tolazamide               | Tablets                | Oral  | Once daily                               | Twice daily dosing for doses > 500 mg |
| tolbutamide              | Tablets                | Oral  | Once daily or divided throughout the day | Administered without regard to meals  |
| <b>Second-generation</b> |                        |       |  |                                       |

Data as of March 15, 2019 KAL/CME

Page 9 of 13

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

| Drug   | Available Formulations   | Route | Usual Recommended Frequency          | Comments   |
|--|--------------------------|-------|--------------------------------------|--|
| Amaryl (glimepiride)                           | Tablets                  | Oral  | Once daily                           |  |
| glyburide                                      | Tablets                  | Oral  | Once daily<br>> 10 mg: twice daily   | Micronized and conventional formulations of glyburide are not bioequivalent<br>Avoid use in patients with moderate to severe renal impairment or renal failure |
| Glucotrol (glipizide)                          | Tablets                  | Oral  | Once daily<br>> 15 mg: divided doses |  |
| Glucotrol XL (glipizide extended-release [ER]) | Extended-release tablets | Oral  | Once daily                           |  |
| Glynase (micronized glyburide)                 | Tablets                  | Oral  | Once daily<br>> 6 mg: twice daily    | Micronized and conventional formulations of glyburide are not bioequivalent  |
| <b>Combination products</b>                    |                          |       |                                      |  |
| Duetact (glimepiride/pioglitazone)             | Tablets                  | Oral  | Once daily                           |  |
| glipizide/metformin                            | Tablets                  | Oral  | Once or twice daily                  | Contraindicated for use in patients with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m <sup>2</sup>   |
| glyburide/metformin                            | Tablets                  | Oral  | Once or twice daily                  | Contraindicated for use in patients with eGFR < 30 mL/min/1.73 m <sup>2</sup>  |

See the current prescribing information for full details

## CONCLUSION

- The SFUs are FDA-approved for the treatment of T2DM. SFUs stimulate the release of insulin by binding to the SFU receptor on pancreatic  $\beta$ -cells and increase basal and postprandial insulin secretion; therefore, they are useful only in patients with some  $\beta$ -cell function. SFUs are the oldest of the oral antidiabetic medications. All single-entity agents and combination therapy agents with pioglitazone or metformin are available generically.
- The SFUs can be divided into 2 categories: first-generation and second-generation. The first-generation SFUs consist of chlorpropamide, tolazamide, and tolbutamide. The second-generation SFUs consist of glimepiride, glipizide, and glyburide. The second-generation agents have structural characteristics that allow them to be given in much lower doses than the first-generation agents. In general, the SFUs differ in their pharmacokinetic parameters; however, they are equally effective when administered in equipotent doses.
- Second-generation agents are generally more potent and may have a better safety profile than first-generation SFUs. All SFUs have similar effectiveness and lower HbA1c by approximately 1 to 2%.
- The SFUs are contraindicated in patients with type 1 diabetes or diabetic ketoacidosis.
- The labeling for each SFU contains a special warning for increased CV mortality based on an older study of tolbutamide. Other key warnings include hypoglycemia, secondary failure, and SFU-induced hemolytic anemia in patients with G6PD deficiency.
  - AEs associated with the SFU class include gastrointestinal disturbances, allergic skin reactions, and hematologic AEs.
  - Chlorpropamide is associated with unique AEs, including SIADH, hyponatremia, and disulfiram-like reaction when used with alcohol.
- **The American Geriatrics Society recommends avoidance of long-acting sulfonylureas (chlorpropamide, glimepiride, and glyburide) in older adults due to the increased risk of AEs, including prolonged hypoglycemia (Fick et al 2019).**

- According to current clinical guidelines for the management of T2DM, metformin is the preferred initial pharmacological agent for T2DM. The SFUs are among the recommended second- or third-line treatment options for patients who are not candidates for metformin or who failed to achieve glycemic goals on metformin therapy. **SGLT2 inhibitors and GLP-1 receptor agonists with proven benefit are preferred over SFUs for patients with T2DM and ASCVD, CKD, or HF.** When SFUs are added to ongoing treatment, use of the second-generation agents is recommended (ADA 2019, Garber et al 2019).

## REFERENCES

- Ahren B, Johnson SL, Stewart M, et al. Harmony 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. *Diabetes Care*. 2014;37:2141-2148.
- Amaryl prescribing information. Sanofi-Aventis US, LLC. Bridgewater, NJ. December 2018.
- Amate JM, Lopez-Cuadrado T, Almendo N, et al. Effectiveness and safety of glimepiride and iDPP4 associated with metformin and in second-line pharmacotherapy of type 2 diabetes mellitus: systematic review and meta-analysis. *Int J Clin Pract*. 2015;69(3):292-304.
- American Diabetes Association (ADA). Diabetes Basics: Type 2. ADA Web site. <http://www.diabetes.org/diabetes-basics/type-2>. Accessed March 15, 2019[a].
- American Diabetes Association. Standards of Medical Care in Diabetes—2019. *Diabetes Care*. 2019[b];42(Suppl 1). doi: 10.2337/dc19-S009.
- Andersson et al. Comparable long-term mortality risk associated with individual sulfonylureas in diabetes patients with heart failure. *Diabetes Res Clin Pract*. 2011 Oct;94(1):119-25.
- Archavaleta R1, Seck T, Chen Y, et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab*. 2011 Feb;13(2):160-8. doi: 10.1111/j.1463-1326.2010.01334.x.
- Bell DSH. Practical considerations and guidelines for dosing sulfonylureas as monotherapy or combination therapy. *Clin Ther*. 2004;26:1714-27.
- Bellomo Damato A, Stefanelli G, Laviola L, et al. Nateglinide provides tighter glycemic control than glyburide in patients with Type 2 diabetes with prevalent postprandial hyperglycemia. *Diabet Med*. 2011 May;28(5):560-6
- Birkeland KI, Furueth K, Melander A, et al. Long-term randomized placebo-controlled double-blind therapeutic comparison of glipizide and glyburide. Glycemic control and insulin secretion during 15 months. *Diabetes Care*. 1994 Jan;17(1):45-9.
- Blonde L, Wogen J, Kreilick C, et al. Greater reductions in A1C in type 2 diabetic patients new to therapy with glyburide/metformin tablets as compared to glyburide coadministered with metformin. *Diabetes Obes Metab*. 2003;5(6):424-31.
- Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann of Int Med*. 2007;147(96):386-400.
- Bolen S, Tseng E, Hutfless S, et al. Diabetes medications for adults with type 2 diabetes: an update. *AHRQ Comparative Effectiveness Reviews*. 2016 Apr;16-EHC013-EF.
- Centers for Disease Control and Prevention (CDC). Diabetes quick facts. Updated May 2018. Available at: <https://www.cdc.gov/diabetes/basics/quick-facts.html>. Accessed March 15, 2019.
- Chlorpropamide prescribing information. Mylan Pharmaceuticals. Morgantown, WV. December 2009.
- Das SR, Everett BM, Birtcher KK, et al. 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2018;72(24):3200-3223. doi: 10.1016/j.jacc.2018.09.020.
- Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018;41(12):2669-2701. doi: 10.2337/dci18-0033.
- Del Prato S, Camisasca R, Wilson C, et al. Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a two-year study. *Diabetes Obes Metab*. 2014;16(12):1239-46.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. <https://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed March 15, 2019.
- Duckworth W, Marcelli M, Padden M, et al. Improvements in glycemic control in type 2 diabetes patients switched from sulfonylurea coadministered with metformin to glyburide-metformin tablets. *J Managed Care Pharm*. 2003;9(3):256-62.
- Duetact prescribing information. Takeda Pharmaceuticals America, Inc. Deerfield, IL. December 2017.
- Evans JMM, Ogston SA, Reimann F, et al. No differences in mortality between users of pancreatic-specific and non-pancreatic-specific sulphonylureas: a cohort analysis. *Diabetes Obes Metab* 2008;10:350-2.
- Fick DM, Semla TP, Steinman M, et al; the 2019 American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2019 Jan 29. doi: 10.1111/jgs.15767.
- Gallwitz B, Guzman J, Dotta F, et al. Exenatide twice daily versus glimepiride for prevention of glycemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label randomized controlled trial. *Lancet*. 2012; 379:2270-78.
- Gallwitz B, Rosenstock J, Rauch T, et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomized, double-blind, non-inferiority trial. *Lancet*. 2012 Aug 4;380(9840):475-83.
- Gangji AS, Cukierman T, Gerstein HC, et al. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. *Diabetes Care*. 2007;30(2):389-94.
- Garber A, Henry R, Ratner R, et al. Liraglutide vs glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomized, 52-weeks, phase III, double-blind, parallel-treatment trial. *Lancet*. 2009;373:473-81.
- Garber A, Henry RR, Ratner R, et al. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. *Diabetes Obes Metab*. 2011 Apr;13(4):348-56.

- Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2019 Executive Summary. *Endocr Pract.* 2019;25(1):69-100.
- Garber AJ, Larsen L, Schneider SH, et al. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. *Diabetes Obes Metab.* 2002;4(3):201-8.
- Glipizide and metformin prescribing information. Teva Pharmaceuticals USA, Inc. North Wales, PA. January 2017.
- Glucotrol prescribing information. Roerig, division of Pfizer, Inc. New York, NY. March 2018.
- Glucotrol XL prescribing information. Roerig, division of Pfizer, Inc. New York, NY. August 2018.
- Glyburide and metformin prescribing information. Actavis Pharma, Inc. Parsippany, NJ. May 2017.
- Glyburide prescribing information. Mylan Pharmaceuticals Inc. Morgantown, WV. October 2017.
- Glynase prescribing information. Pharmacia & Upjohn Company, division of Pfizer, Inc. New York, NY. October 2017.
- Göke B, Gallwitz B, Eriksson J, et al. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomized controlled trial. *Int J Clin Pract.* 2010 Nov;64(12):1619-31.
- Goke B, Gallwitz B, Eriksson JG, et al. Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial. *Int J Clin Pract.* 2013 April;67(4): 307–16.
- Goldstein BJ, Pans M, Rubin CJ. Multicenter, randomized, double-masked, parallel-group assessment of simultaneous glipizide/metformin as second-line pharmacologic treatment for patients with type 2 diabetes mellitus that is inadequately controlled by a sulfonylurea. *Clin Ther.* 2003;25(3):890-903.
- Gottschalk M, Danne T, Vlainic A, Cara JF. Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes: a randomized, single-blind comparative study. *Diabetes Care.* 2007 Apr;30(4):790-4.
- Hirst JA, Farmer AJ, Dyar A, et al. Estimating the effect of sulfonylurea on HbA1c in diabetes: a systematic review and meta-analysis. *Diabetologia.* 2013 May;56(5):973-84. doi: 10.1007/s00125-013-2856-6.
- Hong J, Zhang Y, Lai Sh, Lv A, Su Q, Dong Y, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. *Diabetes Care.* 2013;36(5):1304–11.
- Hou L, Zhao T, Liu Y, Zhang Y. Efficacy and safety of sitagliptin compared with sulfonylurea therapy in patients with type 2 diabetes showing inadequately controlled glycosylated hemoglobin with metformin monotherapy: a meta-analysis. *Exp Ther Med.* 2015;(9):1528-1536.
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2015;38(1):140-149.
- Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA.* 2002;287:360-72.
- Kitabchi AE, Kaminska E, Fisher JN et al. Comparative efficacy and potency of long-term therapy with glipizide or glyburide in patients with type 2 diabetes mellitus. *Am J Med Sci.* 2000;319(3):143-8.
- Lee TM, Chou TF. Impairment of myocardial protection in type 2 diabetic patients. *J Clin Endocrinol Metab.* 2003;88:531-7.
- Marre M, Howlett H, Lehert P, et al. Improved glycemic control with metformin-glibenclamide combined tablet therapy (Glucovance) in type 2 diabetic patients inadequately controlled on metformin. *Diabet Med.* 2002;19(8):673-80.
- Mishriky BM, Cummings DM, Tanenberg R. The efficacy and safety of DPP4 inhibitors compared to sulfonylureas as add-on therapy to metformin in patients with Type 2 diabetes: A systematic review and meta-analysis. *Diabetes Res Clin Pract.* 2015 Aug;109(2):378-88. doi: 10.1016/j.diabres.2015.05.025.
- Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes. *Diabetes Care.* 2009;32:84-90.
- Nauck MA, Del Prato S, Duran-Garcia A, et al. Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizide as add-on therapies in patients whose type 2 diabetes mellitus is inadequately controlled with metformin. *Diabetes Obes Metab.* 2014;16(11):1111-20.
- Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin. *Diabetes Care.* 2011;34:2015-2022.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Accessed March 15, 2019.
- Pantalone et al. The risk of overall mortality in patients with type 2 diabetes receiving glipizide, glyburide, or glimepiride monotherapy: a retrospective analysis. *Diabetes Care.* 2010 Jun;33(6):1224-9.
- Park CY, Kang JG, Chon S, et al. Comparison between the therapeutic effect of metformin, glimepiride and their combination as an add-on treatment to insulin glargine in uncontrolled patients with type 2 diabetes. *PLoS ONE.* 2014;9(3): e87799. doi:10.1371/journal.pone.0087799.
- Qaseem A, Barry MJ, Humphrey LL, et al for the Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2017;166:279-290.
- Ridderstrale M, Andersen KR, Zeller C, et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomized, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endocrinol.* 2014;2:691-700.
- Rosenstock J, Wilson C, Fleck P. Alogliptin versus glipizide monotherapy in elderly type 2 diabetes mellitus patients with mild hyperglycaemia: a prospective, double-blind, randomized, 1-year study. *Diabetes Obes Metab.* 2013;15(10):906-14.
- Sami T, Kabadi UM, Moshiri S. The effect on metabolic control of second-generation sulfonylurea drugs in patients with NIDDM after secondary failure to first-generation agents. (non-insulin-dependent diabetes mellitus). *J Fam Pract.* 1996;43(4):370-4.
- Seck et al. Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. *Int J Clin Pract.* 2010 Apr;64(5):562-76.
- Simpson SH, Lee J, Choi S, et al. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. *Lancet Diabetes Endocrinol.* 2015 Jan;3(1):43-51. doi: 10.1016/S2213-8587(14)70213-X.
- Tolazamide prescribing information. Mylan Pharmaceuticals Inc. Morgantown, WV. December 2009.
- Tolbutamide prescribing information. Mylan Pharmaceuticals Inc. Morgantown, WV. February 2009.
- Vashisht R, Jung K, Schuler A, et al. Association of hemoglobin A1c levels with use of sulfonylureas, dipeptidyl peptidase 4 inhibitors, and thiazolidinediones in patients with type 2 diabetes treated with metformin: analysis from the Observational Health Data Sciences and Informatics Initiative. *JAMA Network Open.* 2018;1(4):e181755. doi:10.1001/jamanetworkopen.2018.1755.



- Wang F, He Y, Zhang R, Zeng Q, Zhao X. Combination therapy of metformin plus dipeptidyl peptidase-4 inhibitor versus metformin plus sulfonylurea and their association with a decreased risk of cardiovascular disease in type 2 diabetes mellitus patients. *Medicine (Baltimore)*. 2017 Sep;96(36):e7638. doi: 10.1097/MD.0000000000007638.
- Wheeler S, Moore K, Forsberg CW, et al. Mortality among veterans with type 2 diabetes initiating metformin, sulfonylurea or rosiglitazone monotherapy. *Diabetologia*. 2013;56:1934–43.
- Zhang F, Xiang H, Fan Y et al. The effects of sulfonylureas plus metformin on lipids, blood pressure, and adverse events in type 2 diabetes: a meta-analysis of randomized controlled trials. *Endocrine*. 2013;44:648-658.
- Zhuang XD, He X, Yang DY, et al. Comparative cardiovascular outcomes in the era of novel anti-diabetic agents: a comprehensive network meta-analysis of 166,371 participants from 170 randomized controlled trials. *Cardiovasc Diabetol*. 2018 Jun 5;17(1):79. doi: 10.1186/s12933-018-0722-z.

Publication Date: March 26, 2019