Therapeutic Class Overview
Biguanides

INTRODUCTION

- Diabetes mellitus affects more than 30 million people in the United States. More than 84 million American adults have prediabetes, with 90% of this population unaware that they have the condition (*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. 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 (*American Diabetes Association [ADA] 2019, CDC 2018*).
- Complications of T2DM include heart disease, stroke, vision loss, kidney disease, and lower-limb amputations. It is the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness and the seventh leading cause of death in the United States (*CDC 2018*).
- Medical costs for patients with diabetes are double the costs for patients without diabetes (*CDC 2018*).
- Classes of oral medications for the management of blood glucose levels in patients with T2DM may exert their effects through various mechanisms, including decreasing hepatic glucose production, increasing insulin secretion, increasing insulin sensitivity, decreasing the rate of carbohydrate absorption, decreasing glucagon secretion, and blocking glucose reabsorption by the kidney (*Davies et al 2018*).
- Key pharmacologic options for T2DM include sulfonylureas, biguanides, thiazolidinediones (TZDs), meglitinides (or glinides), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and insulin (*Davies et al 2018*). Many patients with T2DM will require combination therapy (*Garber et al 2018*).
- Metformin, the sole available biguanide, is thought to have several mechanisms of action. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged.
- In addition to diabetes, metformin is used off-label for management of women with polycystic ovarian syndrome (PCOS), a condition that affects approximately 6% to 10% of women (*Azziz 2017, Legro et al 2013*).
- Although metformin is the sole biguanide in the class, it is available in various dosage forms including tablets, several forms of extended-release tablets, and an oral solution. This review includes the single-ingredient metformin products. Metformin is also available in combination products with several other classes of antihyperglycemic drugs; however, the combination products are not included in this review.
- Medispan class: Biguanides

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Glucophage (metformin tablets)	✔
Glucophage XR (metformin tablets, extended release)	✔
Fortamet (metformin tablets, extended release)	✔
Glumetza (metformin tablets, extended release)	✔
Riomet (metformin oral solution)	✔ *

*Authorized generic

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Glucophage	Glucophage XR	Fortamet	Glumetza	Riomet
Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with T2DM	✔				✔
Adjunct to diet and exercise to improve glycemic control in adults with T2DM		✔	✔	✔	

(*Prescribing Information: Fortamet 2018, Glucophage/Glucophage XR 2018, Glumetza 2018, Riomet 2018*)

- 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 EFFICACY SUMMARY

- The effectiveness of metformin in T2DM as monotherapy and in combination with other oral antidiabetic agents and/or insulin has been demonstrated through many clinical trials. Most trials evaluated a number of glycemic outcomes such as hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG). Other metabolic outcomes often reported were body weight, body mass index (BMI), effects on insulin secretion, and effects on lipid parameters. However, results from recent cardiovascular outcomes trials of patients with T2DM are moving away from a glucocentric approach, since drugs that lower HbA1c to similar levels may have different effects on patient outcomes. Furthermore, the diabetes field is moving away from its historical reliance on surrogate markers and toward studies that assess outcomes such as heart disease and mortality to identify drugs that achieve the goals of diabetes care (*Lipska and Krumholz 2017*).
- A number of trials have demonstrated the effectiveness of metformin compared to placebo (*Douek et al 2005, Jones et al 2002, Kooy et al 2009, Wulffele et al 2002*). More often, metformin has been studied in comparison to an alternative antihyperglycemic drug, either as monotherapy or in various combination regimens (*Aschner et al 2010, Bailey et al 2010, Bosi et al 2009, Cryer et al 2005, Defronzo et al 1995, Derosa et al 2010, Fonseca et al 2012, Gottschalk et al 2007, Henry et al 2012, Jadzinsky et al 2009, Kahn et al 2006, Lewin et al 2007, Lund et al 2009, Neutel et al 2013, Pavo et al 2003, Russell-Jones et al 2012, Stewart et al 2006, United Kingdom Prospective Diabetes Study [UKPDS] Group 1998, Weissman et al 2005*).
- A large meta-analysis estimated the effect of metformin on HbA1c to be approximately 1.1% in monotherapy trials, 0.95% in trials adding metformin to other oral therapies, and 0.6% in trials adding metformin to insulin (*Hirst et al 2012*).
- A number of trials and analyses have evaluated cardiovascular and other diabetes outcomes (*Boussageon et al 2012, Hemmingsen et al 2012, Johnson et al 2005, Kooy et al 2009, Lamanna et al, 2011*). Trial results have not always been in agreement for these outcomes. A landmark study often cited in the literature is UKPDS 34, which compared metformin therapy to conventional treatment (primarily diet alone) on diabetes-related cardiovascular and other clinical outcomes, diabetes-related death, and all-cause mortality in overweight patients with T2DM. The study demonstrated a significantly reduced risk of these 3 outcomes in the group treated with metformin. However, the investigators also evaluated the use of metformin when added to sulfonylurea compared to sulfonylurea alone, and found contrary results: patients treated with metformin had an increased risk of diabetes-related death and all-cause mortality (*UKPDS Group 1998*).
- Since UKPDS 34 was published, several other studies and meta-analyses have sought to gather more information on cardiovascular and other patient-relevant outcomes. Overall, the evidence supporting a potential cardiovascular benefit for metformin is not robust (*Fitchett et al 2017*). A retrospective trial compared metformin to sulfonylureas and their combination for a composite endpoint of fatal or nonfatal cardiovascular-related events, and the trial demonstrated that patients in the metformin monotherapy group had a lower risk of the composite cardiovascular endpoint compared to sulfonylurea monotherapy (*Johnson et al 2005*). A Cochrane meta-analysis and systematic review evaluated metformin compared to non-pharmacologic and other pharmacologic interventions for T2DM, and it was concluded that metformin

showed a significant benefit compared to chlorpropamide, glyburide, or insulin for all-cause mortality and for any diabetes-related outcome (a composite measure evaluating a large number of outcomes such as sudden death, myocardial infarction, heart failure, stroke, amputation, retinopathy, and blindness) (*Saenz et al 2005*); this review has since been withdrawn from publication due to multiple changes like new publications, methods and standards since its publication. In contrast, a prospective study with a 4.3-year follow-up that compared insulin plus metformin to insulin plus placebo failed to demonstrate a significant benefit for metformin for a composite macrovascular and microvascular endpoint. In this trial, a small benefit was seen for metformin on an aggregate macrovascular endpoint, but this failed to reach statistical significance after adjusting for changes in body weight (*Kooy et al 2009*). Several meta-analyses have failed to conclusively demonstrate a cardiovascular benefit with metformin (*Boussageon et al 2012, Hemmingsen et al 2012, Lamanna et al 2011*). Some investigators noted that significant differences were found for some outcomes, but these differences did not persist when data from UKPDS 34 was excluded (*Boussageon et al 2012, Lamanna et al 2011*).

- In addition to these outcomes, a number of studies evaluated the use of different dosage forms of metformin. Metformin is available in several different formulations, which include metformin immediate-release tablets and solution, as well as 3 sustained-release formulations. Metformin solution was found to have an equivalent rate and extent of absorption as metformin immediate-release tablets. Clinical studies reported comparable changes in HbA1c between the immediate-release formulations and sustained-release formulations (*Fujioka et al 2003, Schwartz et al 2006*).

CLINICAL GUIDELINES

- Current guidelines recommend that metformin, along with lifestyle intervention, should be the initial pharmacologic therapy for T2DM in the absence of specific contraindications.
  - According to the ADA and a joint consensus report by the ADA and the European Association for the Study of Diabetes (EASD), dual therapy or triple therapy can be considered in patients not achieving their HbA1c goal on metformin monotherapy (*ADA 2019, Davies et al 2018*). Choice of add-on therapy should be determined based on 1) whether the patient has established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD); and 2) whether there is a compelling need to minimize hypoglycemia or a compelling need to minimize weight gain or promote weight loss in patients without established ASCVD or CKD.
    - If ASCVD predominates, a GLP-1 receptor agonist with proven cardiovascular disease (CVD) benefit or an SGLT2 inhibitor with proven CVD benefit (if estimated glomerular filtration rate [eGFR] is adequate) is recommended.
    - If heart failure or CKD predominates, an SGLT2 inhibitor with evidence of reducing heart failure and/or CKD progression is preferred if the eGFR is adequate. If the SGLT2 inhibitor is not tolerated or contraindicated, or if the eGFR is less than adequate, a GLP-1 receptor agonist with proven CVD benefit is recommended.
    - In patients without established ASCVD or CKD:
      - If there is a compelling need to minimize hypoglycemia, recommendations include a DPP-4 inhibitor, a GLP-1 receptor agonist, an SGLT2 inhibitor, or a TZD.
      - If there is a compelling need to minimize weight gain or promote weight loss, a GLP-1 receptor agonist with good efficacy for weight loss or an SGLT2 inhibitor is recommended.
    - The early introduction of insulin should be considered if there is evidence of ongoing catabolism (eg, weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels or blood glucose levels are very high (> 10% or ≥ 300 mg/dL, respectively).
    - In most patients who need the greater glucose-lowering effect of an injectable medication (ie, HbA1c is above target despite dual/triple therapy), GLP-1 receptor agonists are preferred to insulin. Insulin should be considered as the first injectable if the HbA1c is very high (> 11%), in the presence of symptoms or evidence of catabolism, or if type 1 diabetes is a possibility.
  - According to the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE), the choice of diabetes therapies must be individualized based on attributes specific to the patient and the medication (*Garber et al 2018*). Metformin is recommended as the preferred initial agent for monotherapy in patients with an entry HbA1c < 7.5%; however, monotherapy with other agents may be considered. Combination therapies including metformin plus 1 or 2 additional agents are recommended for patients with an entry HbA1c ≥ 7.5%. Several options for dual- and triple-therapy are presented in a hierarchy, with GLP-1 receptor agonists and SGLT2 inhibitors listed as the top 2 options to be added. In patients with an entry HbA1c > 9%, dual- or triple therapy should be considered if patients are asymptomatic, and insulin considered if patients are symptomatic.

- Metformin is also utilized to treat women with PCOS. The Endocrine Society guideline recommends using metformin in women with PCOS and T2DM or impaired glucose tolerance and as a second-line therapy in women with PCOS and menstrual irregularity who cannot tolerate hormonal contraceptives. Metformin has no benefit in improving hirsutism, acne, or infertility (*Legro et al 2013*).
- See the individual guidelines for additional details on subsequent therapy and patient-specific considerations.

SAFETY SUMMARY

- Metformin has a strong safety record when used according to guidelines. A main safety concern is lactic acidosis. However, a 2010 Cochrane Review including 347 studies failed to identify any cases of fatal or non-fatal lactic acidosis caused by metformin (*Salpeter et al 2010*).
- Contraindications:
  - Severe renal impairment (eGFR < 30 mL/min/1.73 m^2)
  - Known hypersensitivity to metformin hydrochloride
  - Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma
- Boxed warnings:
  - Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias.
    - Risk factors include renal impairment, concomitant use of certain drugs, age ≥ 65 years, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment.
    - Symptoms include malaise, myalgias, respiratory distress, somnolence, and abdominal pain.
    - If lactic acidosis is suspected, metformin should be discontinued and general supportive measures should be instituted in a hospital setting. Prompt hemodialysis is recommended.
- Warnings:
  - Vitamin B_{12} levels: Low vitamin B_{12} levels have been observed in some patients on metformin, possibly due to reduced B_{12} absorption. Monitoring of hematologic parameters annually, and vitamin B_{12} levels at 2 to 3 year intervals, is advised.
  - Hypoglycemia: May occur with insufficient caloric intake, strenuous exercise or with other drugs that lower glucose. A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with metformin.
  - There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with metformin.
- Adverse drug events:
  - The most common are gastrointestinal in nature: diarrhea, flatulence, nausea and vomiting.
- Drug Interactions:
  - Carbonic anhydrase inhibitors (eg, topiramate, zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with metformin may increase the risk for lactic acidosis. More frequent monitoring should be considered.
  - Drugs that reduce metformin clearance: Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (eg, ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Benefits and risks of concomitant use should be considered.
  - Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake.
  - Medications affecting glycemic control (eg, thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid): The co-administered drug may lead to loss of glycemic control; thus the patient should be closely observed.
- Special populations:
  - Renal insufficiency: In April 2016, the FDA issued a Drug Safety Communication requiring a change to metformin labeling in order to convey that metformin may be safely used in patients with mild to moderate renal impairment. The FDA also recommended that a better estimate of renal function (ie, eGFR) be used in place of blood creatinine as a measure of renal function. These recommendations have resulted in updates to the product labeling (*FDA 2017*).

- Metformin is contraindicated in patients with an eGFR < 30 mL/minute/1.73 m^2. Initiation is not recommended in patients with eGFR between 30 and 45 mL/minute/1.73 m^2. In patients taking metformin whose eGFR falls below 45 mL/min/1.73 m^2, the benefit and risk of continuing therapy should be assessed.

- Hepatic impairment: Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Metformin is not recommended in patients with hepatic impairment.
- Pregnancy: Limited data with metformin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes mellitus in pregnancy.
- Lactation: Limited published studies report that metformin is present in human milk. There is insufficient information to determine the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Glucophage	Tablets	Oral	Twice daily	With meals. May be used in children 10 to 16 years of age in addition to adults.
Glucophage XR	Extended-release tablets	Oral	Once daily	With evening meal. Safety and effectiveness in pediatric patients have not been established. Should not be crushed or chewed.
Fortamet	Extended-release tablets	Oral	Once daily	With evening meal. Safety and effectiveness in pediatric patients have not been established. Should not be cut, crushed, or chewed.
Glumetza	Extended-release tablets	Oral	Once daily	With evening meal. Safety and effectiveness in pediatric patients have not been established. Should not be split, crushed, or chewed.
Riomet	Oral solution	Oral	Twice daily	With meals. May be used in children 10 to 16 years of age in addition to adults.

See the current prescribing information for full details.

CONCLUSION

- Metformin is a well-established medication for the treatment of T2DM. Treatment guidelines are consistent in their recommendation that metformin be considered a first-line treatment for T2DM in the absence of contraindications.
- Metformin has been shown to be effective as monotherapy, in combination with other oral antidiabetic agents, and in combination with insulin.

- Consistent benefits are seen with metformin for HbA1c and FPG. A large meta-analysis estimated the effect of metformin on HbA1c to be approximately 1.1% in monotherapy trials, 0.95% in trials adding metformin to other oral therapies, and 0.6% in trials adding metformin to insulin (*Hirst et al 2012*).
- Despite strong efficacy on metabolic outcomes in T2DM, data on cardiovascular outcomes and mortality have not consistently demonstrated a benefit with metformin.
- Metformin is used off-label as a second-line agent in women with PCOS and menstrual irregularities if they do not tolerate hormonal contraceptives (*Legro et al 2013*).
- Metformin has a strong safety record when used according to guidelines. A main safety concern is lactic acidosis. However, a 2010 Cochrane Review including 347 studies failed to identify any cases of fatal or non-fatal lactic acidosis caused by metformin (*Salpeter et al 2010*).
- The most common adverse effects associated with metformin are gastrointestinal.
- Metformin is available in several dosage forms for dose individualization and patient convenience. Several products (Glucophage, Glucophage XR, Glumetza, and Fortamet) are available generically. Riomet is available as a brand and an authorized generic.

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