Therapeutic Class Overview
Biguanides

INTRODUCTION

- Diabetes mellitus affects more than 29 million people in the U.S. About 86 million American adults have prediabetes, with 90% of this population unaware that they have the disease (CDC, 2016).
- 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], 2016[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, 2016[b]).
- Complications of T2DM include heart disease, stroke, vision loss, kidney disease, and amputations of toes, feet or legs. It is the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness and the seventh leading cause of death in the U.S. (CDC, 2016).
- More than 20% of health care spending is for people with diagnosed diabetes (CDC, 2016).
- 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, 2017).
- 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; and blocking glucose reabsorption by the kidney (Inzucchi et al, 2015).
- Pharmacologic options for type 2 diabetes include sulfonylureas, biguanides, thiazolidinediones, 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 (ADA, 2017[b]).
- Metformin, the sole 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 (GLUCOPHAGE prescribing information, 2009).
- Metformin is also used off-label for management of women with polycystic ovarian syndrome (PCOS), a condition that affects about 6 to 7% of women in the reproductive age group (DynaMed 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	Manufacturer	FDA Approval Date	Generic Availability
GLUCOPHAGE® (metformin tablets)	Bristol Myers Squibb	03/03/1995	✔
GLUCOPHAGE® XR (metformin tablets, extended release)	Bristol Myers Squibb	10/13/2000	✔
FORTAMET® (metformin tablets, extended release)	Andrx Labs LLC	04/28/2004	✔
GLUMETZA® (metformin tablets, extended release)	Salix	06/03/2005	✔
RIOMET® (metformin oral solution)	Sun Pharm Inds LTD	09/11/2003	-

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

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 children with T2DM	✔				✔
Adjunct to diet and exercise to improve glycemic control in adults with T2DM		✔	✔	✔	

(Prescribing Information: FORTAMET, 2012; GLUCOPHAGE/GLUCOPHAGE XR, 2017; GLUMETZA, 2016; RIOMET, 2014)

Information on indications, safety, and dosing 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. In a recently published JAMA opinion paper, however, the authors noted that 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 had different effects on patient outcomes. Furthermore, the diabetes field is moving away from its historical reliance on surrogate markers and toward studies that asses outcome 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; UKPDS Group, 1998; Weissman et al, 2005).

- 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; Saenz et al, 2005). 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 three 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. 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 meta-analysis 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). However, 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 be statistically significant after adjusting for changes in body weight (Kooy et al, 2009). Several more recent 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 three sustained-release formulations. Metformin solution was found to have an equivalent rate and extent of absorption as metformin immediate-release tablets (RIOMET prescribing information, 2014). Clinical studies reported comparable changes in HbA1c between the immediate-release formulations and sustained-release formulations (Fujioka et al, 2003; Schwartz et al, 2006).
- Current guidelines recommend that metformin, along with lifestyle intervention, should be the initial pharmacologic therapy in the absence of specific contraindications (ADA, 2017[b]; Copeland et al, 2013; Garber et al, 2017; Inzucchi et al, 2015; Qaseem et al, 2017).
- Metformin is 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).
- Metformin was explored as a weight loss agent in an analysis that has shown its effectiveness. However, Canadian guidelines on the management of adults who are obese and overweight advise against use of metformin for this indication due to adverse events and trial designs with confounders (Canadian Task Force et al, 2015).

SAFETY SUMMARY

- Contraindications:
    - Renal disease or renal dysfunction (e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women or abnormal creatinine clearance).
    - Severe renal impairment (estimated glomerular filtration rate [eGFR] below 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:

- Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. Post-marketing cases, including fatal cases, of lactic acidosis associated with metformin have been reported.
    - Reported cases have occurred primarily in diabetic patients with significant renal insufficiency.
    - The risk of lactic acidosis increases with increasing age (age ≥ 65 years), use of intravascular iodinated contrast agents or certain other interacting medications, surgery and other procedures that involve withholding food and fluids, hypoxic states (e.g., acute congestive heart failure, cardiovascular collapse [shock], acute myocardial infarction, sepsis), excessive alcohol intake, and hepatic impairment.
    - If acidosis is suspected, metformin should be discontinued and the patient hospitalized immediately.

- Warnings:
    - Hypoxic states: Cardiovascular collapse (shock), congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may cause prerenal azotemia. When such events occur in patients on metformin, the drug should be promptly discontinued.
    - Alcohol intake: alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while taking metformin.
    - Vitamin B_{12} levels: Low vitamin B_{12} levels have been observed in some patients on metformin, possibly due to reduced B_{12} absorption. Annual monitoring of hematologic parameters is advised.
    - Impaired hepatic function: Avoid metformin in patients with clinical or laboratory evidence of hepatic disease.
    - Hypoglycemia: May occur with insufficient caloric intake, strenuous exercise or with other drugs that lower glucose.
- Adverse drug events:
    - The most common are gastrointestinal in nature: diarrhea, flatulence, nausea and vomiting.
- Drug Interactions:
    - Cationic drugs (e.g., amiloride, cimetidine, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interacting with metformin by competing for common renal tubular transport systems. Careful patient monitoring and dose adjustment of metformin and/or the interfering drug is recommended.
    - Medications affecting glycemic control (e.g., 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.
    - Carbonic anhydrase inhibitors (e.g., topiramate, zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. The risk of lactic acidosis may increase.
    - Discontinue metformin either at the time of, or prior to, iodinated contrast imaging procedures in patients with eGFR between 30 and 60 mL/min/1.73 m^2, patients with a history of liver disease, alcoholism, or heart failure, or patients who will be administered intra-arterial iodinated contrast. Renal function should be re-evaluated 48 hours after the imaging procedure and metformin may be restarted if stable.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
GLUCOPHAGE (metformin	Tablet: 500 mg,	Adults: Usual starting dose is 500 mg twice daily or 850	Dosing is varied. Start at a low dose and	Give in divided doses with meals.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
tablets)	850 mg, 1,000 mg	mg once daily. Dose increases should be made in increments of 500 mg weekly or 850 mg every two weeks in divided doses. Patients can also be titrated from 500 mg twice daily to 850 mg twice daily after two weeks. Pediatrics (age 10 to 16 years): Usual starting dose is 500 mg twice a day. Dosage increases should be made in increments of 500 mg weekly.	escalate slowly. Maximum daily dose is 2,550 mg in adults and 2,000 mg in children 10 to 16 years of age.	
GLUCOPHAGE XR (metformin tablets, extended release)	Extended-release tablets: 500 mg, 750 mg	Usual starting dose is 500 mg daily. Dose increases should be made in increments of 500 mg weekly.	Dosing is varied. Start at a low dose and escalate slowly. Maximum daily dose is 2,000 mg in adults.	Give once daily with evening meal. Swallow whole, never crush or chew.
FORTAMET (metformin tablets, extended release)	Extended release tablets: 500 mg, 1,000 mg	Usual starting dose is 1,000 mg daily, although 500 mg may be used when clinically appropriate. Dose increases should be made in increments of 500 mg weekly.	Dosing is varied. Start at a low dose and escalate slowly. Maximum daily dose is 2,500 mg in adults.	Take with full glass of water once daily with evening meal. Do not cut, crush or chew.
GLUMETZA (metformin tablets, extended release)	Extended release tablets: 500 mg, 1,000 mg	Usual starting dose is 500 mg daily. Dose increases should be made in 500 mg increments every one to two weeks.	Dosing is varied. Start at a low dose and escalate slowly. Maximum daily dose is 2,000 mg in adults.	Give once daily with evening meal. Swallow whole, never split, crush or chew. For a missed dose, patients should not take two doses in one day but instead should resume their usual dose with the next scheduled dose.
RIOMET (metformin oral solution)	Oral solution: 500 mg/5 mL	Adults: Usual starting dose is 500 mg (5 mL) twice a day or 850 mg (8.5 mL) once a day. Dose increases should be made in increments of 500 mg (5 mL) weekly or 850 mg (8.5 mL) every two weeks. Patients can also be titrated from 500 mg (5 mL) twice a day to 850 mg (8.5 mL) twice a day after two weeks.	Dosing is varied. Start at a low dose and escalate slowly. Maximum daily dose is 2,550 mg (25.5 mL) in adults and 2,000 mg (20 mL) in children 10 to 16 years of age.	Give in divided doses with meals.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		Pediatrics (age 10 to 16 years): Usual starting dose is 500 mg (5 mL) twice a day. Dosage increases should be made in increments of 500 mg (5 mL) weekly.		

SPECIAL POPULATIONS

Table 4 provides information on the use of metformin in special populations. A key distinction between products is that the safety and efficacy of metformin tablets and oral solution have been demonstrated in children 10 to 16 years of age, while this has not been demonstrated for metformin extended-release tablets.

- In April 2016, the Food and Drug Administration (FDA) issued a Drug Safety Communication requiring a change to metformin labeling in order to reflect that metformin may be safely used in patients with mild to moderate renal impairment (FDA, 2016). Changes have not yet been reflected in all the most recently revised labeling for each product; however, recommendations from the FDA have been incorporated in the GLUMETZA and GLUCOPHAGE prescribing information listed in Table 4. The FDA also recommended that a better estimate of renal function (i.e., eGFR) be used in place of blood creatinine as a measure of renal function.
- A systematic review evaluated glibenclamide (glyburide), metformin and insulin in 15 studies (N=2,509) for the treatment of gestational diabetes (Balsells et al, 2015). Glyburide was associated with higher birth weight, (7 studies; pooled mean difference 109 g; 95% CI, 35.9 to 181; P=0.003; I^2=0%) and more macrosomia (6 studies; pooled risk ratio 2.62; 95% CI, 1.35 to 5.08; P=0.004; I^2=34%) and neonatal hypoglycemia (7 studies; pooled risk ratio 2.04; 95% CI, 1.30 to 3.20; P=0.002; I^2=0%) compared to insulin. Compared to insulin, metformin was associated with lower maternal weight gain (4 studies; pooled mean difference -1.14 kg; 95% CI, -2.22 to -0.06; P=0.04; I^2=64%), lower gestational age at delivery (6 studies; pooled mean difference -0.16 weeks; 95% CI, -0.3 to -0.02; P=0.03; I^2=0%), and more preterm birth (5 studies; pooled risk ratio 1.5; 95% CI, 1.04 to 2.16; P=0.03; I^2=0%). In comparisons of metformin and glyburide, metformin was associated with lower maternal weight gain (1 study; pooled mean difference -2.06 kg; 95% CI, -3.98 to -0.14; P=0.04), less macrosomnia (2 studies; pooled risk ratio 0.33; 95% CI, 0.13 to 0.81; P=0.02; I^2=0%), and fewer large for gestational age newborns (1 study; pooled risk ratio 0.44; 95% CI, 0.21 to 0.92; P=0.03). Authors concluded that glyburide should not be used for the treatment of gestational diabetes, and metformin may be an oral option.
- A multicenter randomized controlled trial showed that metformin reduced progression to diabetes by 40% in women with a history of gestational diabetes mellitus over a 10 year period (Aroda et al, 2015).

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Metformin tablets (GLUCO-PHAGE) and oral solution (RIOMET)	Because aging is associated with reduced renal function, metformin should be used with caution as age increases. Do not initiate in patients ≥80 years of age unless	Safety and efficacy have been established in pediatric patients ages 10 to 16 years.	Contraindicated in renal disease/ dysfunction as suggested by serum creatinine ≥1.5 mg/dL in males and ≥1.4 mg/dL in females or abnormal CrCL (RIOMET). Contraindicated in	Pharmacokinetic studies have not been conducted in patients with hepatic insufficiency. Because impaired hepatic function may limit the ability to clear lactate, metformin should	Pregnancy Category B; not recommended for use in pregnancy* Unknown. Excreted into milk in animal studies. A decision should be made to discontinue nursing or discontinue the

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	measurement of CrCL demonstrates that renal function is not reduced.		patients with eGFR < 30 mL/min/1.73 m^2. Discontinue if eGFR < 30 mL/min/1.73 m^2. Initiation not recommended in patients with eGFR between 30 to 45 mL/min/1.73 m^2.	generally be avoided in patients with hepatic disease.	drug.
Metformin extended release tablets (FORTAMET, GLUCO-PHAGE XR)	See metformin tablets/oral solution.	Safety and effectiveness have not been established.	See metformin tablets/oral solution.	See metformin tablets/oral solution.	Pregnancy Category B; not recommended for use in pregnancy* See metformin tablets/oral solution.
Metformin extended release tablets (GLUMETZA)	Dosing in elderly should be cautious and usually start low. Renal function should be assessed more frequently.	Safety and effectiveness have not been established.	Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. Discontinue if eGFR < 30 mL/min/1.73 m^2. Initiation not recommended in patients with eGFR between 30 to 45 mL/min/1.73 m^2. Assess benefit and risk of therapy in patients whose eGFR falls below 45 mL/min/1.73 m^2.	See metformin tablets/oral solution.	Pregnancy Category B; not recommended for use in pregnancy* Unknown. Excreted into milk in animal studies.

CrCL=creatinine clearance; eGFR=estimated glomerular filtration rate

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.

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).
- A benefit of metformin is its association with weight loss or maintenance, as opposed to several other antidiabetic drug categories associated with weight gain.

- 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; the prescribing information reports post-marketing cases of metformin-associated 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 (diarrhea and nausea/vomiting).
- Metformin is available in several dosage forms for dose individualization and patient convenience. Several products (GLUCOPHAGE, GLUCOPHAGE XR, GLUMETZA, and FORTAMET) are available generically, while RIOMET remains brand name only at this time.

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