Hypoglycemics, Metformins
Therapeutic Class Review (TCR)

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Magellan Rx MANAGEMENT℠

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
glipizide/ metformin[1]	generic	▪ Initial therapy to improve glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise ▪ Second-line therapy in type 2 diabetics who have not achieved adequate glycemic control with a sulfonylurea or metformin alone
glyburide/ metformin (Glucovance®)[2]	generic, BMS	▪ Initial therapy to improve glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise ▪ Second-line therapy in type 2 diabetics who have not achieved adequate glycemic control with a sulfonylurea or metformin alone ▪ In combination with a TZD in patients who do not have adequate glycemic control with Glucovance alone
metformin (Glucophage®)[3]	generic, BMS*	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise in patients 10 years of age and older (including in combination with a sulfonylurea or insulin)
metformin ER (Fortamet™ ER)[4]	generic, Shionogi	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise
metformin ER (Glumetza™ ER)[5]	generic, Santarus	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise (including in combination with a sulfonylurea or insulin)
metformin XR (Glucophage XR®)[6]	generic, BMS*	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise (including in combination with a sulfonylurea or insulin)
metformin oral solution (Riomet™)[7]	generic, Ranbaxy/Sun	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise in patients 10 years of age and older (including in combination with a sulfonylurea or insulin for ages 17 and older)

* BMS has made a business decision to discontinue Glucophage 500 mg, 850 mg, and 1,000 mg and Glucophage XR 500 mg and 750 mg. Products may remain until supply is depleted.

OVERVIEW

It is estimated that 30.3 million Americans have diabetes.[8] In type 2 diabetes, insulin function may be impaired by defective insulin secretion and/or insulin resistance (decreased insulin sensitivity). Insulin resistance is typically the first to occur, leading to increased circulating insulin levels in the blood as a result of the decreased response from muscle tissues. Increasing rates of obesity support the projection that cases of diabetes will continue to grow. Diabetes causes a significant economic burden, both in terms of direct and indirect costs, to society. It is also responsible for increased morbidity and mortality. Adequate glycemic control is crucial to minimize chronic complications; the long-term effects of type 2 diabetes include renal failure due to diabetic nephropathy, impaired vision due to diabetic retinopathy, loss of sensation and/or pain from diabetic neuropathy, and cardiovascular disease.[9]

The primary objective of diabetes management is to achieve and maintain glycemic control and modify interventions when therapeutic goals are not being met. For most patients with type 2 diabetes, the initial treatment involves lifestyle changes. Lifestyle changes usually include healthier diets, increased exercise, and weight loss. Insulin sensitivity can be restored with continued practice of the lifestyle changes. If lifestyle modifications are not sufficient, oral medications are typically introduced. Oral drugs affect the insulin pathway by stimulating insulin production, regulating glucose release from the

liver, and attenuating insulin resistance. When necessary, insulin therapy and other injectable drugs can be added to the treatment regimen.

The UK Prospective Diabetes Study (UKPDS) investigated whether intensive glucose control with metformin had any specific advantage or disadvantage. Intensive glucose control with metformin decreased the risk of diabetes-related endpoints in overweight diabetic patients and was associated with less weight gain and fewer hypoglycemic attacks than were insulin and sulfonylureas.[10] A 10-year follow-up to UKPDS revealed that patients treated with metformin continued to have significant risk reductions for any diabetes-related end point, as well as significant risk reductions for myocardial infarction (MI) and all-cause death.[11] Metformin has also proven to be as effective as a sulfonylurea at controlling blood glucose levels. Metformin reduces HbA1c by 1.5% to 2% and fasting plasma glucose (FPG) levels by about 20% or 60 to 70 mg/dL.[12] Metformin also has favorable effects on serum triglycerides, total cholesterol and LDL-C, and a possible modest increase in HDL-C.[13]

The American Diabetes Association (ADA) Standards of Medical Care in Diabetes position statement, updated in 2019, recommends HbA1c < 7%, as a reasonable target for most nonpregnant patients. More stringent HbA1c goals (< 6.5%) for select patients (e.g., those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease [CVD]) may be considered if this can be achieved without significant hypoglycemia.[14] Less-stringent HbA1c goals (< 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain. For pediatric patients, the ADA recommends a target HbA1c < 7.5% for all age groups and HbA1c target of 6% to 6.5% for pregnant women, which can be relaxed or tightened depending on hypoglycemia risk during pregnancy. Metformin is recommended for the treatment of type 2 diabetes, along with lifestyle interventions at the time of diagnosis, unless metformin is contraindicated.[15] If metformin cannot be used, another initial agent could be chosen from the following classes based on patient factors: sulfonylurea (SU), thiazolidinedione (TZD), DPP-4 inhibitor, sodium-glucose cotransporter-2 (SGLT2) inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, or basal insulin. In patients *without* atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD), if initial therapy at maximal tolerated doses does not achieve or maintain the hemoglobin A1c (HbA1c) target after 3 months, an agent from a different class (listed above) should be added. In patients *with* ASCVD or CKD, the addition of an agent with known cardiovascular (CV) or renal benefit (select GLP-1 agonist or select SLGT2 inhibitor) is preferred. Therapy should be individualized based on the needs, preferences, and tolerances of each patient. In addition, aggressive management of cardiovascular risk factors (e.g., blood pressure and lipid therapy, antiplatelet treatment, and smoking cessation) should be part of multifactorial risk reduction approach.[16]

The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) 2019 diabetes management algorithm for T2DM and the 2015 guidelines for developing a diabetes care plan.[17,18] In order to minimize the risk of diabetes related complications, the algorithm specifies a target HbA1c ≤ 6.5% if it can be reached without substantial hypoglycemia or other adverse effect. A target HbA1c > 6.5% may be individualized for patients with concurrent serious illness and a high risk of hypoglycemia. Patients are stratified based on their current HbA1c levels to monotherapy, dual therapy, or triple therapy. The choices of medications are prioritized according to safety, risk of hypoglycemia, efficacy, simplicity, anticipated degree of patient adherence, and cost. These guidelines state HbA1c targets should be individualized and take into account residual life expectancy, duration of disease, cardiovascular disease risk factors, and comorbid conditions; the

patient's psychological, social, and economic status should also be considered. For the patient with an HbA1c < 7.5%, it is possible that a single agent might achieve the HbA1c goal of 6.5%. Metformin is the cornerstone of therapy and is usually the most appropriate initial choice for monotherapy, unless contraindicated. Agents as alternative monotherapy or as add-on therapy, listed in order of strength of recommendation, include GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, and then TZDs.

The American College of Physicians (ACP) revised their guidelines in 2017.[19] They also recommend metformin as first-line therapy and state a sulfonylurea, TZD, SGLT-2 inhibitor, or a DPP-4 inhibitor are preferred second-line treatments. These guidelines are also endorsed by the American Academy of Family Physicians (AAFP). In 2018, the ACP developed a statement to guide clinicians in selecting targets for pharmacologic treatment of type 2 diabetes, including recommending a goal HbA1c level between 7% and 8% in most patients.[20] In addition, they state that clinicians should consider deintensifying pharmacologic therapy in patients who achieve HbA1c levels < 6.5%, treat patients to minimize symptoms related to hyperglycemia, and avoid targeting an HbA1c level in patients with a life expectancy < 10 years due to advanced age because the harms outweigh the benefits in this population.

Results of meta-analyses confirm the role of metformin in therapy. In a 2016 random-effects network meta-analysis of 301 clinical trials evaluating the role of various classes of antidiabetic drugs, there were no significant differences between classes in the risk of cardiovascular or all-cause mortality. Metformin was associated with either lower or no significant difference in HbA1c compared to other drug classes, and all drugs were estimated to be effective when added on to metformin therapy.[21] Findings from a similar meta-analysis of 204 studies also support metformin as first-line therapy, citing relative safety and beneficial effects on HbA1c, weight, and cardiovascular mortality.[22]

PHARMACOLOGY

Metformin, a biguanide, decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Glyburide and glipizide, the sulfonylurea components in combination products in this class, lower blood glucose by stimulating the release of insulin from the pancreas.

PHARMACOKINETICS

Metformin has a bioavailability of 50% to 60%. Bioavailability decreases with increasing doses due to a decrease in absorption rather than a change in elimination. Metformin is eliminated by the kidney (greater than 90% within 24 hours) with no hepatic metabolism. The half-life is approximately 6.2 hours. Tubular secretion plays a role in elimination, as the elimination rate of metformin is approximately 3.5 times greater than the creatinine clearance.[23]

The glipizide and metformin components of glipizide/metformin are bioequivalent to coadministered Glucotrol® and Glucophage.[24]

The pharmacokinetics of metformin in the combined product, Glucovance, are similar to the pharmacokinetics of metformin as a single agent. The pharmacokinetics of glyburide as a combination product are different than those of glyburide as the Micronase® product. The area under the plasma concentration time curve (AUC) was greater for glyburide in the combination product, Glucovance, versus glyburide as the Micronase product.[25]

The rate and extent of absorption of metformin oral solution (Riomet) was found to be comparable to that of metformin tablets under fasting or fed conditions.[26]

Metformin ER (Fortamet ER) uses single-composition osmotic technology. Upon ingestion, the drug is dissolved inside the tablet and slowly released through laser-drilled ports. Drug release is dependent on a constant osmotic gradient and continues until this gradient is no longer present.[27]

Metformin ER (Glumetza ER) is a polymer-based oral drug delivery system.[28] The tablets swell in the stomach allowing increased gastric retention time for delivery of metformin at a designed rate.

Metformin XR (Glucophage XR) is a dual hydrophilic matrix consisting of polymers that hydrate and swell after contact with the GI tract. Drug diffusion is independent of pH and provides a slow release of metformin.[29]

CONTRAINDICATIONS/WARNINGS[30,31,32,33,34,35,36]

Any product containing metformin is contraindicated in patients with any of the following: renal disease or severe renal dysfunction (estimated glomerular filtration rate [eGFR] below 30 mL/minute/1.73 m^2), acute or chronic metabolic acidosis including diabetic ketoacidosis, acute myocardial infarction, septicemia, pregnancy, or known hypersensitivity to metformin or other ingredients in the drug formulation. Metformin products once carried a contraindication in congestive heart failure patients but that has now been removed. Patients with congestive heart failure still have a higher risk of lactic acidosis.

Lactic acidosis is a rare, but potentially fatal, complication of metformin therapy, and symptoms may be subtle with only nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Discontinue use in patients with an eGFR between 30 and 60 mL/minute/1.73 m^2 before an iodinated contrast imaging procedure and in patients with a history of liver disease, alcoholism, or heart failure.

Caution should be used with metformin in patients experiencing hypoxic states or undergoing surgical procedures and in patients with hepatic impairment or with excessive alcohol intake. Initiating metformin in patients with an eGFR between 30 to 45 mL/minute/1.73 m^2 is not recommended. Due to the age-related decline of renal function, do not titrate metformin to the upper dosage range in elderly patients (> 80 years of age) even for patients with eGFR levels within the normal range.

Notably, previous warnings for metformin were based on estimated creatinine clearance (CrCl); however, in 2016, the FDA issued a MedWatch regarding use of metformin in patients with reduced renal function and stated that adjustments should be based on eGFR as it takes into account additional patient parameters.[37]

DRUG INTERACTIONS[38,39,40,41,42,43]

Exercise caution when using with drugs that are known to exacerbate hyperglycemia.

Cationic drugs such as amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin that are eliminated by renal tubular secretion have a theoretical potential interaction with metformin by competing for common renal tubular transport systems. No specific dosing changes are recommended. Increased metformin plasma concentrations are seen with concurrent administration of cimetidine, furosemide, and nifedipine. No specific dosing changes are recommended. Contrast agents increase the risk of metformin-induced lactic acidosis.

The same drug interactions can occur with glipizide/metformin or glyburide/metformin as with each individual agent. Consult package inserts for detailed information.

ADVERSE EFFECTS

Drug	Diarrhea	Headache	Nausea/ Vomiting	Abdominal Pain	Dizziness
glipizide/metformin 5/500 mg[44] n=87	18.4	12.6	8	5.7	nr
glipizide 5 mg n=84	13.1	6	6	8.3	nr
metformin 500 mg n=75	17.3	5.3	8	6.7	nr
glyburide/metformin (Glucovance)[45] n=642	17	8.9	7.6	6.9	5.5
glyburide n=324	6.2	11.4	5.2	3.1	5.6
metformin n=312	20.5	9.3	12.2	8	3.8
metformin (Glucophage)[46] n=141	53.2	5.7	25.5	6.4	nr
placebo n=145	11.7	4.8	8.3	4.8	
metformin ER (Fortamet ER)[47] n=424	16.7	4.7	8.5	nr	nr
metformin IR n=430	11.9	5.1	7.4		
metformin ER (Glumetza ER) + sulfonylurea[48] n=431	12.5	nr	6.7	nr	nr
placebo + sulfonylurea n=144	5.6		4.2		
metformin ER (Glucophage XR)[49] n=781	9.6	nr	6.5	nr	nr
placebo n=195	2.6		1.5		

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. nr = not reported

Adverse effects for metformin solution are similar to those for metformin.

Monitoring

Monitor renal function (eGFR) initially and annually. Monitor when renal function may be compromised (hypoxic states or surgical procedures) or when concomitant drug therapy may interfere with drug clearance. Monitor FPG periodically and HbA1c every 3 months to determine if treatment goals are met.

With long-term metformin use, periodic assessments of B12 levels should be performed and B12 supplementation should be provided as needed.[50]

SPECIAL POPULATIONS[51,52,53,54,55,56,57]

Pediatrics

Metformin (Glucophage, Riomet) can be used in patients 10 years of age and older according to the prescribing information. Other metformin-containing products have not been evaluated in pediatric patients.

Pregnancy

All products in this review are rated Pregnancy Category B except for metformin solution and glipizide/metformin combination which are Pregnancy Category C.

Renal Impairment

As renal clearance rate declines, elimination of metformin is reduced proportionally. GFR should be estimated at least annually in all patients taking metformin, and metformin should only be used in patients meeting eGFR recommendations described above. In patients at increased risk for the development of renal impairment, such as the elderly, renal function should be assessed more frequently.

Geriatrics

Metformin (Glucophage, Riomet) should not be initiated in patients ≥ 80 years of age unless eGFR is not severely reduced. Metformin should be titrated carefully in older patients. Due to reduced renal function in patients of advanced age and thereby increased risk of lactic acidosis, geriatric patients should be monitored more frequently than younger patients for reduced renal function and managed appropriately.

DOSAGES

Drug	Parameters	Initial Dosage	Availability
glipizide/metformin[58]	First-line therapy for FPG < 280 mg/dL	2.5 mg/250 mg daily with a meal	2.5 mg/250 mg 2.5 mg/500 mg 5 mg/500 mg tablets
	First-line therapy for FPG 280 to 320 mg/dL	2.5 mg/500 mg twice daily with meals	
	Second-line therapy	2.5 mg/500 mg or 5 mg/500 mg twice daily with meals	
glyburide/metformin (Glucovance)[59]	Initial therapy	1.25 mg/250 mg once or twice a day with meals	1.25 mg/250 mg, 2.5 mg/500 mg, 5 mg/500 mg tablets
	Initial therapy with HbA1c > 9% or FPG > 200 mg/dL	1.25 mg/250 mg twice daily with meals	
	Second-line therapy	2.5 mg/500 mg or 5 mg/500 mg twice daily with meals	
metformin (Glucophage)[60]	Initial therapy	500 mg twice daily or 850 mg daily with meals	500 mg, 850 mg, 1,000 mg tablets
metformin ER (Fortamet ER)[61]	Initial therapy	1,000 mg daily with evening meal	500 mg, 1,000 mg tablets
metformin ER (Glumetza ER)[62]	Initial therapy	1,000 mg daily with evening meal	500 mg, 1,000 mg tablets
metformin XR (Glucophage XR)[63]	Initial therapy	500 mg daily with evening meal	500 mg, 750 mg tablets
metformin oral solution (Riomet)[64]	Initial therapy	500 mg (5 mL) twice daily or 850 mg (8.5 mL) daily with meals	100 mg/mL oral solution

Combination therapy

Once metformin is used at maximum daily dose and hyperglycemia is not controlled, changing therapy to metformin XR 1,000 mg twice daily with meals is an alternative. If an adequate response is not seen within 2 to 3 months, initiate combination therapy with other antidiabetic agents.

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

The literature review of significant trials comparing agents within this therapeutic class is complete as of February 25, 2019.

glipizide/metformin

In a multicenter, double-blind trial, 247 patients were randomized to glipizide 30 mg, metformin 500 mg, or glipizide/metformin 5/500 mg for 18 weeks.[65] Maximum doses allowed were glipizide 30 mg, metformin 2,000 mg, and glipizide/metformin 20/2,000 mg. Patients were generally obese (mean BMI=31.3 kg/m^2), had moderate to severe hyperglycemia (mean HbA1c 8.7%), and had a mean duration of diabetes of 6.5 years. Glipizide/metformin tablets controlled the HbA1c level more effectively than did either glipizide or metformin monotherapies (mean treatment differences, in favor of glipizide/metformin, of -1.06% and -0.98%, respectively, p<0.001). Glipizide/metformin tablets also reduced the fasting plasma glucose (FPG) level and the 3-hour postprandial glucose area under the concentration-time curve more effectively than did either monotherapy, without increasing the fasting insulin level. The greatest blood glucose control with glipizide/metformin tablets was achieved at a mean daily dose of glipizide/metformin 17.5/1,747 mg compared with mean doses of glipizide 30 mg or metformin 1,927 mg.

glyburide/metformin (Glucovance)

In a placebo-controlled, double-blind, multicenter study, 806 patients with type 2 diabetes and HbA1c greater than 7% were randomized to 4 weeks of therapy with glyburide 2.5 mg, metformin 500 mg, glyburide/metformin 1.25/250 mg, glyburide/metformin 2.5/500 mg, or placebo once daily.[66] Doses could be titrated over the next 8 weeks based on glycemic response up to a maximum of 4 tablets per day. At 20 weeks, patients taking the combination therapy had greater reductions in HbA1c levels (-1.48% and -1.53%, respectively) compared with glyburide (-1.24%; both p<0.001), metformin (-1.03%; p=0.016 and 0.004, respectively), or placebo (0.21%; both p<0.001). FPG and postprandial glucose were reduced significantly more in the glyburide/metformin groups. These effects were achieved with lower doses of each agent in the combination therapy. Higher incidences of gastrointestinal effects were noted in the metformin groups versus glyburide alone and placebo.

In a multicenter, double-blind trial of 486 patients with type 2 diabetes who were treatment-naïve, therapy was initiated with glyburide/metformin 1.25/250 mg, metformin 500 mg, or glyburide 2.5 mg.[67] After 16 weeks, patients in the glyburide/metformin group had superior mean reductions in HbA1c from baseline (-2.27% versus metformin –1.53% and glyburide –1.9%; p=0.0003). Glyburide/metformin also significantly reduced FPG and 2-hour postprandial glucose values compared with either monotherapy. The final mean doses of glyburide/metformin (3.7/735 mg) were lower than those of metformin (1,796 mg) and glyburide (7.6 mg).

metformin (Glucophage)

In a study to evaluate the effect of metformin in intensive blood glucose control with insulin or sulfonylureas, 753 patients with newly-diagnosed type 2 diabetes were randomized to diet alone (n=411) or intensive blood glucose control with metformin (n=342).[68] Patients were followed for a mean duration of 10.7 years for the occurrence of any diabetes-related clinical endpoint, diabetes-related deaths, and all-cause mortality. The metformin group was also compared to patients on chlorpropamide (n=265), glyburide (n=277), or insulin (n=409) for the same endpoints. The median HbA1c in the metformin group was 7.4% compared with 8% in the diet alone group. Metformin patients had relative risk reductions of 32% (p=0.002) for any diabetes-related endpoint, 42% (p=0.017) for diabetes-related death, and 36% (p=0.011) for all-cause mortality compared to the diet alone group. Compared to the other pharmacologic therapies, metformin had a greater effect on any diabetes-related endpoint (p=0.0034), all-cause mortality (p=0.021), and stroke (p=0.032). The findings of this study help substantiate the use of metformin as a first line agent in the treatment of type 2 diabetes mellitus.

metformin XR (Glucophage XR)

A multicenter, double-blind trial enrolled 217 patients with type 2 diabetes who had HbA1c values less than or equal to 8.5% and mean fasting glucose concentrations of <200 mg/dL while receiving metformin 500 mg twice daily for 8 weeks.[69] Patients were randomly assigned to metformin XR 1,000 or 1,500 mg once daily or metformin 500 mg twice daily for 24 weeks. All 3 treatment groups had similar changes in HbA1c at weeks 12 and 24 compared to baseline. At week 12, the mean change from baseline in HbA1c was -0.15% for metformin, -0.23% for metformin XR 1,000 mg, and -0.04% for metformin XR 1,500 mg.

In Protocol 1 of a randomized, double-blind, placebo-controlled study, 240 patients were randomized to receive metformin XR 1,000 mg once daily or placebo.[70] In Protocol 2, 742 patients were randomized to receive metformin XR 500 mg once daily, 1,000 mg once daily, 1,500 mg once daily, 2,000 mg once daily, 1,000 mg twice daily, or placebo. The primary endpoint in each study was the change from baseline in HbA1c at 12 weeks (Protocol 1) or 16 weeks (Protocol 2). Metformin XR reduced HbA1c in Protocol 1 with mean treatment differences for 1,000 mg once daily versus placebo of -0.7% at 12 weeks and -0.8% at 24 weeks (p<0.001 for each). In Protocol 2, a clear dose-response relationship was evident at doses up to 1,500 mg with treatment differences versus placebo of -0.6% (500 mg once daily), -0.7% (1,000 mg once daily), -1% (1,500 mg once daily), and -1% (2,000 mg once daily). Efficacy of metformin XR 2,000 mg once daily and 1,000 mg twice daily were similar. More patients achieved HbA1c less than 7% with metformin XR versus placebo in Protocol 1 (29% versus 14% at 12 weeks) and with once daily metformin XR in Protocol 2 (up to 36% versus 10% at 16 weeks). Total

cholesterol and LDL-C improved ($p<0.05$, $p<0.001$) in metformin XR groups in Protocol 2. Metformin XR was well tolerated.

metformin XR (Glucophage XR) versus metformin (Glucophage)

An international, randomized, double-blind study compared the efficacy and safety of metformin extended-release (XR) and metformin immediate-release (IR) in pharmacotherapy-naive, adult patients (≥ 18 years old) who had type 2 diabetes and inadequate glycemic control (HbA1c, 7% to 9.2%) with diet and lifestyle advice alone (n=589).[71] After a 4-week single-blind placebo lead-in subjects were randomized 1:1 to receive metformin XR 2000 mg once daily or metformin IR twice daily with meals for 24 weeks. Dosage was titrated from 500 mg to 2000 mg daily over the first 3 weeks, with adjustments up or down allowed. The primary endpoint was change in HbA1c after 24 weeks. The adjusted mean changes after 24 weeks in the XR versus IR groups were −0.93% and −0.96%, respectively, for HbA1c, −21.1 and −20.6 mg/dL, respectively, for FPG, and −24.7 and −27.1 mg/dL, respectively, for mean daily glucose. Overall there was similar efficacy with metformin XR and metformin IR; however, the IR formulation required more dose titration before achieving similar final dosages, possibly due to initial intolerance of the higher peak concentrations.

SUMMARY

Metformin is an effective agent for the management of hyperglycemia in patients with type 2 diabetes mellitus. Metformin (Glucophage, Riomet) are FDA-approved in pediatric patients. The metformin immediate-release and extended-release formulations provide similar effects on HbA1c and fasting plasma glucose (FPG) with once daily dosing to enhance patient compliance.

The combination of glyburide/metformin has been shown to significantly decrease HbA1c and FPG more than either agent alone. Adverse effects of the combination product were not significantly different than either agent used alone. The other combination product, glipizide/metformin, also has been shown to be more effective than either agent used alone with adverse effect profiles similar to each individual agent. The combination products allow for using fewer tablets per day and may provide an incentive for increased adherence.

Clinical practice guidelines recommend metformin as the drug of choice for first-line oral treatment of patients with type 2 diabetes. Multiple other agents are available for the treatment of type 2 diabetes, and are appropriate as add-on therapy when goals are not achieved using a single medication. Thiazolidinediones and sulfonylureas (e.g., glipizide, glyburide) should be used with caution as they are generally considered less safe than glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter type 2 (SGLT2) inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors, or alpha-glucosidase inhibitors.

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