Hypoglycemics, Sulfonylureas Review

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FDA-Approved Indications[1,2,3,4,5,6]

Drug	Manufacturer	FDA-approved Indications (for type 2 diabetes)
glimepiride (Amaryl®)	generic	♦ Monotherapy as an adjunct to diet and exercise to enhance glycemic control ♦ Combination with insulin or metformin
glipizide (Glucotrol®)	generic	♦ Monotherapy as an adjunct to diet to enhance glycemic control ♦ Combination with insulin ♦ Combination with other blood glucose-lowering agents
glipizide extended-release (Glucotrol XL®)	generic	♦ Monotherapy as an adjunct to diet to enhance glycemic control ♦ Combination with insulin ♦ Combination with other blood glucose-lowering agents
glyburide (Diabeta®, Glynase® PresTab®, Micronase®)	generic	♦ Monotherapy as an adjunct to diet to enhance glycemic control ♦ Combination with insulin or metformin

Overview

Approximately 17.9 million people in the United States have been diagnosed with diabetes mellitus.[7] In type 2 diabetes, insulin function can be impaired by two pathways: defective insulin secretion and 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.

The initial effects of type 2 diabetes do not have visible symptoms. This leads to delays in diagnosis of this condition. There are about 5.7 million people living with undiagnosed diabetes, according to the American Diabetic Association.[8] 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 vascular disease.

The 2010 ADA Standards of Medical Care in Diabetes recommend a hemoglobin A_1c (HbA_1c) goal of less than seven percent for most patients.[9] These updated guidelines also include the use of HbA_1c greater than or equal to 6.5 percent as a diagnostic indicator of diabetes. An additional category has been added to identify patients at risk for developing diabetes in the future as those with a HbA1c between 5.7 and 6.4 percent with impaired fasting glucose or impaired glucose tolerance.

For most patients with Type 2 diabetes, the initial treatment involves lifestyle changes. This usually includes 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 2009 revision to the ADA Consensus Statement on the Medical Management of Hyperglycemia in Type 2 Diabetes stratifies its treatment recommendations into Tier 1 and Tier 2 recommendations, based on the documented and relative effectiveness of the interventions. Tier 1 interventions represent the most effective, well-established strategies, whereas Tier 2 interventions represent less well-validated therapies.[10] Consistent with the 2010 ADA Standards of Medical Care in Diabetes, lifestyle modifications and initiation of metformin (Glucophage®) are considered Tier 1 interventions and the first step in managing hyperglycemia in patients with type 2 diabetes.[11] In the event lifestyle interventions and metformin fail to produce or maintain glycemic goals, the 2009 consensus treatment algorithm recommends the initiation of one of the Tier 1, Step 2 strategies.[12] The Step 2 strategies consist of adding either a sulfonylurea or basal insulin to the Step 1 interventions. This review focuses on the second-generation sulfonylureas: glyburide, glipizide, and glimepiride (Amaryl).[13] While hypoglycemia is a major adverse effect of sulfonylureas, glyburide is associated with the greatest risk for hypoglycemia. For this reason, the guidelines note that if a sulfonylurea is to be initiated in a patient, one other than glyburide should be chosen.

Pharmacology

Sulfonylureas enhance response of beta cells in the pancreatic islet to glucose. These agents bind to the plasma membrane of functioning beta cells, resulting in a decrease in potassium permeability that increases membrane depolarization and therefore causes an influx of calcium ions. Increased intracellular calcium leads to secretion of insulin and subsequent lowering of blood glucose. The exact mechanism of how sulfonylureas lower blood sugar on a chronic basis is unknown.

Pharmacokinetics[14,15,16,17,18,19]

Drug	Bioavailability (%)	Onset (hr)	Half-Life (hr)	Metabolism	Excretion (%)
glimepiride (Amaryl)[20]	100	2-3	9	1 active and 1 inactive metabolite	urine: 60 feces: 40
glipizide/ER (Glucotrol/XL)[21,22]	100	1.5-2 (glipizide) 2-3 (glipizide ER)	2-4	inactive metabolites	urine: 80 feces: 10
glyburide (Diabeta, Glynase PresTab, Micronase)[23,24,25]	significant	2-4	4-10	weakly active metabolites	urine: 50 feces: 50

Contraindications/Warnings[26,27,28,29,30,31]

The sulfonylureas have a class warning stating the increased risk of cardiovascular mortality when compared to diet alone or diet plus insulin. The warning is based on the study that evaluated the long-term effectiveness of glucose-lowering medications in the prevention or delaying of vascular complications. The first-generation sulfonylurea, tolbutamide (Orinase®) was found to have an increased incidence of cardiovascular mortality despite the early discontinuation of the study. Due to the findings of this study, all sulfonylureas have this warning in the package insert. Data to support this association are limited and have not been confirmed by the UKPDS. These agents are also contraindicated in patients with sulfonamide allergy, diabetic ketoacidosis with or without coma, and type 1 diabetes.

Use caution in using glipizide ER (Glucotrol XL) in patients with severe gastrointestinal narrowing. The tablet is insoluble and is excreted in the feces. Patients with altered GI transit times which result in slowing of peristalsis may have an altered pharmacokinetic profile.

Patients with impaired renal or hepatic function may be at increased risk for hypoglycemia with glipizide ER (Glucotrol XL) and glyburide (Diabeta, Glynase, Micronase). Use caution with glimepiride (Amaryl) in renal impairment.

Drug Interactions[32,33,34,35,36,37]

As a class, the sulfonylureas may be affected by concurrent therapy. When drugs that exacerbate hyperglycemic or hypoglycemic effects are added or discontinued, close monitoring of blood glucose is recommended.

Adverse Effects

Drug	Asthenia	Dizziness	Headache	Nausea
glimepiride (Amaryl)[38] n=746	1.6	1.7	1.5	1.1
(placebo n=294)	(1)	(0.3)	(1.4)	(0)
glipizide ER (Glucotrol XL®)[39] n=278	10.1	6.8	8.6	< 3
(placebo n=69)	(13)	(5.8)	(8.7)	(nr)
glyburide (Diabeta, Glynase PresTab, Micronase)[40,41,42]	nr	reported	reported	1.8

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Similar adverse events are reported for glipizide (Glucotrol) and glipizide ER (Glucotrol XL).

All sulfonylureas can cause hypoglycemia. Increased risk is seen in patients with impaired renal or hepatic function, adrenal or pituitary insufficiency, malnourishment or debilitation, after

prolonged exercise, after alcohol use, or when diabetic drugs are used in combination. Hypoglycemia can be more pronounced in the elderly with impaired hepatic or renal function. Glyburide (Diabeta, Glynase, Micronase) can cause a higher incidence of hypoglycemia than glipizide or glimepiride (Amaryl).[43]

Special Populations[44,45,46,47,48,49]

Pediatrics

Safety and efficacy have not been established in the pediatric population.

Pregnancy

Glimepiride (Amaryl) and glipizide (Glucotrol, Glucotrol XL) products are Pregnancy Category C, and glyburide (Diabeta, Glynase, Micronase) products are Category B.

Other

In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic episodes with all of these agents.

Dosages[50,51,52,53,54,55]

Drug	Initial Dosage	Maximum Dose	Dosage Forms
glimepiride (Amaryl)	1-2 mg daily with first meal	8 mg daily	1, 2, 4 mg tablets
glipizide (Glucotrol)	5 mg daily with first meal	40 mg daily in divided doses	5, 10 mg tablets
glipizide ER (Glucotrol XL)	5 mg daily with first meal	20 mg daily	2.5, 5, 10 mg tablets
glyburide (Diabeta, Glynase PresTab, Micronase)	Diabeta, Micronase 2.5-5 mg daily with first meal Glynase PresTab 1.5-3 mg daily with first meal	Diabeta, Micronase 20 mg daily Glynase PresTab 12 mg daily	Diabeta, Micronase 1.25, 2.5, 5 mg tablets Glynase PresTab 1.5, 3, 6 mg tablets

Regular non-micronized glyburide (Diabeta, Micronase) tablets cannot be used interchangeably with micronized glyburide (Glynase PresTab) formulations.

Switching patients on immediate release glipizide (Glucotrol) to glipizide ER (Glucotrol XL)

Patients on immediate release glipizide may be switched to Glucotrol XL at the nearest equivalent dose given once daily. Patients may also start on Glucotrol XL 5 mg and be titrated to the appropriate dose.

Clinical Trials

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved 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 percent 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.

glimepiride (Amaryl)

In poorly controlled patients with type 2 diabetes on diet therapy alone, a randomized, placebo-controlled study of glimepiride was conducted.[56] The titration period was over ten weeks with glimepiride (n=123) doses of 1 to 8 mg daily or placebo (n=126) followed by 12 weeks of monitoring of FPG, HbA_1c, and two-hour postprandial glucose. Glimepiride lowered FPG by 46 mg/dL, HbA_1c by 1.4 percent, and two-hour postprandial glucose by 72 mg/dL more than placebo. No clinically important increases in fasting insulin or C-peptide levels were observed. Sixty-nine percent of patients in the glimepiride group achieved HbA_1c levels less than 7.2 percent. Both therapies were well tolerated.

In a study to evaluate the efficacy and safety of various doses of glimepiride, 416 patients with type 2 diabetes were randomized in a double-blind manner to glimepiride 8 mg daily, 4 mg twice daily, 16 mg daily, 8 mg twice daily, or placebo.[57] All patients participated in a three-week washout period followed by the fixed dose regimen. After 14 weeks, FPG, two-hour postprandial blood glucose, and HbA_1c were similar in all treatment groups whereas the placebo group experienced increases in all values ($p \leq 0.001$). No significant differences in glycemic control among doses or intervals were observed. All groups tolerated therapy well. Researchers concluded that maximum effectiveness is obtained with glimepiride 8 mg daily.

glimepiride (Amaryl) and glyburide (non-micronized)

In a one-year randomized, double-blind, parallel-group, multicenter study of 577 patients, subjects were randomized to receive glimepiride 1 mg or glyburide 1.25 mg once daily.[58] Doses were titrated to achieve a FPG of 90 to 150 mg/dL. Decreases from baseline to the completion of the study in FPG and HbA_1c were similar between both groups. Incidence of hypoglycemia was 12 percent with glimepiride and 17 percent with glyburide.

glipizide ER (Glucotrol XL)

In a safety, efficacy, and dose-response study of glipizide using the gastrointestinal therapeutic system (GITS), 347 patients with type 2 diabetes were enrolled in a two-phase prospective, randomized, double-blind, placebo-controlled, multicenter trial.[59] In the first phase of the trial,

143 patients received 5, 20, 40, or 60 mg daily glipizide GITS daily and were followed for 16 weeks including the washout, placebo, and titration phases. In the second phase of the trial, doses included glipizide GITS 5, 10, 15, or 20 mg daily or placebo for 204 patients. All doses of glipizide GITS produced significant reductions in HbA_1c and FPG compared to placebo. Postprandial insulin and C-peptide levels were significantly higher in the treatment groups compared to placebo. No weight gain or changes in lipid profiles were noted in this short-term trial. Researchers concluded that maximum efficacy was seen with glipizide GITS 20 mg daily.

Summary

The sulfonylureas are efficacious, safe, well tolerated, and have the added convenience of once daily dosing. In addition to insulin and thiazolidinediones, sulfonylureas are possible treatment options after failure of metformin to adequately treat hyperglycemia. Glyburide (Diabeta, Glynase, Micronase) can cause more hypoglycemia as it has a longer half-life, particularly in elderly with impaired renal or hepatic function. Glimepiride (Amaryl) may possibly augment peripheral tissue insulin sensitivity; however, this is still unproven. Glipizide ER (Glucotrol XL) is not a suitable agent for patients with GI motility problems including strictures, obstructions, or severe narrowing. Regular non-micronized glyburide (Diabeta, Micronase) tablets cannot be used interchangeably with micronized glyburide (Glynase PresTab) formulations. These agents are easily titrated to achieve appropriate glycemic control as monotherapy or in combination with other antidiabetic therapies.

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