



expertise in action™

## **Indiana Medicaid Therapeutics Committee** **Therapeutic Class Review Summary**

### **Therapeutic Class:**

Antidiabetic Agents, Oral

### **Overview:**

Six different classes of oral antidiabetic agents include: sulfonylureas (SU), biguanides,  $\alpha$ -glucosidase inhibitors (AGI), nonsulfonylurea insulin secretagogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, and thiazolidinediones (TZDs). Each class has a unique mechanism of action. Sulfonylureas stimulate insulin secretion from  $\beta$  cells in the pancreas. Biguanides decrease hepatic glucose production. Alpha-glucosidase inhibitors (AGI) work on the brush border of the small intestine and delay intestinal carbohydrate absorption. Nonsulfonylurea insulin secretagogues work similarly to sulfonylureas; however, due to their quick onset and short duration of action, these agents target postprandial hyperglycemia. DPP-4 inhibitors are believed to exert their effects by slowing the inactivation of incretin hormones. Finally, thiazolidinediones improve insulin sensitivity and increase glucose uptake. The orally inhaled insulin, Exubera<sup>®</sup>, was recently discontinued due to limited use.

Sulfonylureas are the oldest oral hypoglycemic agents and were developed in the 1950s. The mean reduction in HbA<sub>1c</sub> with sulfonylurea treatment is approximately 1% to 2%. The literature supports that sulfonylureas improve long-term microvascular outcomes in patients with type 2 diabetes. Though the second-generation sulfonylureas (ie, glyburide, glipizide, and glimepiride) are generally more potent than, and as efficacious as the first generation agents (i.e., chlorpropamide, tolbutamide, acetohexamide, and tolazamide), the older products are associated with a higher risk of hypoglycemia. Increased cardiovascular mortality has been documented with tolbutamide treatment, but has not been noted with other sulfonylureas. Glimepiride, the newest addition, binds with cardiac tissue to a lesser extent and may reduce ischemic conditions; however, there are no clinical trials to validate this hypothesis. Glimepiride has also demonstrated a lower incidence of hypoglycemia and weight gain compared to other sulfonylureas in clinical trials. All sulfonylureas are available generically.

Biguanides were developed in the 1950s in Europe, but not approved by the FDA until 1994 (metformin). Currently, metformin (Glucophage<sup>®</sup>, Riomet<sup>™</sup>) and its sustained release formulations (ie, Glucophage<sup>®</sup> XR, Fortamet<sup>®</sup>, and Glumetza<sup>™</sup>) are the only biguanides available. The mean reduction in HbA<sub>1c</sub> with metformin treatment is approximately 1% to 2%. Clinical data indicate that metformin improves both macro- and microvascular outcomes in type 2 diabetic patients.<sup>19</sup> Compared with sulfonylureas, metformin provides the same glycemic control with a lower incidence of hypoglycemia. In addition, metformin does not cause weight gain and is the preferred agent for obese patients. Due to the risk of lactic acidosis, there are many contraindications associated

with the use of metformin. Also, the most common adverse effects are gastrointestinal related. Metformin is available generically in both immediate-release and sustained-release solid dosage forms. Riomet™, an oral liquid formulation of metformin, is also available.

Alpha-glucosidase inhibitors delay the absorption of carbohydrates and reduce postprandial hyperglycemia. With an average HbA<sub>1c</sub> lowering effect of 0.5% to 1%, the overall efficacy in glycemic control of  $\alpha$ -glucosidase inhibitors is less than that of sulfonylureas or metformin. The STOP-NIDDM trial was the first prospective intervention study that showed treatment with an alpha-glucosidase inhibitor (acarbose) in patients with impaired glucose tolerance was associated with a significant reduction in cardiovascular events and hypertension. However, the dosing schedule of alpha-glucosidase inhibitors is complicated and needs to be tailored to mealtimes. Though gastrointestinal side effects are common with the alpha-glucosidase inhibitors, hypoglycemia is not a concern. The medications in this class include acarbose (Precose®) and miglitol (Glyset®). Both agents are FDA-approved for use as monotherapy or in combination with sulfonylureas. Acarbose is additionally approved for use in combination with insulin or metformin.

Nonsulfonylurea insulin secretagogues are distinguished from the sulfonylureas by their short half-lives. They cause brief episodic stimulation of insulin secretion; therefore, these drugs target postprandial hyperglycemia. The short duration of action necessitates frequent administration but results in fewer incidences of hypoglycemia. The overall efficacy in glycemic control is similar to sulfonylureas with a mean HbA<sub>1c</sub> reduction of 1% to 2%. Based on the DECODE study, postprandial glucose intolerance is related to the adverse outcome of cardiovascular complications; however, there are no data on the effectiveness of nonsulfonylurea insulin secretagogues in reducing microvascular or macrovascular complications with type 2 diabetes. The medications included in this class are nateglinide (Starlix™) and repaglinide (Prandin®). Both agents are FDA-approved for use as monotherapy or in combination with metformin or a thiazolidinedione.

Sitagliptin (Januvia™), and recently approved saxagliptin (Onglyza™) are dipeptidyl peptidase-4 (DPP-4) inhibitors, which prolong actions of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) via inhibition of the dipeptidyl peptidase-4 enzyme. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Common side effects associated with use of sitagliptin include upper respiratory tract infection, nasopharyngitis, and headache. Saxagliptin and sitagliptin may be used as monotherapy or as combination therapy with metformin or a thiazolidinedione. Treatment with DPP-4 inhibitors lowers HbA<sub>1c</sub> by approximately 0.6% to 0.8%.



Thiazolidinediones are agonists for the peroxisome proliferator-activated receptor (PPAR) gamma, which regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. Thiazolidinediones improve insulin sensitivity and generally modify other components of the metabolic syndrome, such as dyslipidemia, vascular procoagulant state, and blood pressure. Treatment with thiazolidinediones lowers HbA<sub>1c</sub> by approximately 0.5% to 1.4%.

In August 2007, a boxed warning was added to the pioglitazone and rosiglitazone labels regarding the risk of congestive heart failure. The prescribing information for these agents also indicates these drugs should not be used by individuals with New York Heart Association (NYHA) Class III and IV heart failure as thiazolidinediones can cause fluid retention, which may exacerbate or lead to heart failure. Additionally, combining pioglitazone or rosiglitazone with insulin is not recommended since concomitant therapy of thiazolidinediones with insulin increases the risk of edema and heart failure. Treatment with thiazolidinediones is also associated with weight gain. Liver enzyme monitoring is recommended prior to initiation of thiazolidinedione therapy and periodically thereafter.

Also in 2007, the results of a study published in the *New England Journal of Medicine* suggested that rosiglitazone increases the risk of myocardial infarction compared to placebo or other type 2 diabetes medications. However, since this publication, the FDA concluded that the risk of heart attacks with rosiglitazone does not seem to be different than with other oral diabetes medications. Despite the FDA's conclusion regarding rosiglitazone, Avandia® was excluded as a recommendation in a consensus algorithm recently released by the American Diabetes Association and European Association for the Study of Diabetes. It was concluded that, while both rosiglitazone and pioglitazone can cause fluid retention, heart failure, and bone fractures, advantages of pioglitazone over rosiglitazone include a neutral effect on cardiovascular disease outcomes and a more positive effect on lipid profiles. Consequently, pioglitazone (Actos®) remains a possible second-step medication after metformin.

Combination therapy with different drug classes may be necessary given patients with type 2 diabetes are often inadequately controlled on monotherapy. Oral combination agents include the following: glipizide/metformin (Metaglip™), glyburide/metformin (Glucovance®), pioglitazone/metformin (Actoplus Met™), rosiglitazone/metformin (Avandamet™), pioglitazone/glimepiride (Duetact™), rosiglitazone/glimepiride (Avandaryl™), sitagliptin/metformin (Janumet™), and repaglinide/metformin (Prandimet™). The pharmacokinetic profiles of the combination drugs are the same as the individual drugs. Glyburide/metformin and glipizide/metformin tablets are available generically.

	<b>Generic Name</b>	<b>Brand Name</b>	<b>Manufacturer</b>
Sulfonylurea	Acetohexamide	Dymelor® (brand no longer marketed)	Various
	Chlorpropamide	Diabinese®	Various
	Glimepiride	Amaryl®	Various
	Glipizide	Glucotrol®, Glucotrol® XL	Various
	Glyburide	Diabeta®, Glynase®, Micronase®, Glynase® PresTab®	Various
	Tolazamide	Tolinase®	Various
	Tolbutamide	Orinase®	Various
Biguanide	Metformin	Glucophage®, Glucophage® XR, Fortamet®, Glumetza™, Riomet™	Various
α-Glucosidase inhibitors	Acarbose	Precose®	Various
	Miglitol	Glyset®	Pfizer
Nonsulfonylurea insulin secretagogues	Nateglinide	Starlix™	Novartis, various
	Repaglinide	Prandin®	Novo Nordisk
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	Saxagliptin	Onglyza™	Bristol-Myers Squibb
	Sitagliptin	Januvia™	Merck
Thiazolidinediones	Pioglitazone	Actos®	Takeda
	Rosiglitazone	Avandia®	GlaxoSmithKline
Combinations	Glipizide/Metformin	Metaglip™	Various
	Glyburide/Metformin	Glucovance®	Various
	Pioglitazone/Metformin	Actoplus Met™	Takeda
	Rosiglitazone/Metformin	Avandamet™	GlaxoSmithKline
	Pioglitazone/Glimepiride	Duetact™	Takeda
	Rosiglitazone/ Glimepiride	Avandaryl™	GlaxoSmithKline
	Sitagliptin/Metformin	Janumet™	Merck
	Repaglinide/Metformin	Prandimet™	Novo Nordisk

### Summary:

Because all sulfonylureas are equally efficacious, the generic sulfonylureas provide a wide range of selection for clinicians. Additionally, metformin reduces adverse microvascular and macrovascular outcomes, and sustained-release metformin has decreased dosing frequency. The advantage of α-glucosidase inhibitors and nonsulfonylurea insulin secretagogues over sulfonylurea and metformin is the superior control of postprandial plasma glucose. Sitagliptin and saxagliptin are the newest treatment option for patients with diabetes and may be used either as monotherapy or in combination therapy. The thiazolidinediones improve insulin sensitivity and cause hypoglycemia less frequently than alternative therapies. Finally, the combination hypoglycemic agents provide convenient dosing and have the same pharmacokinetic profiles as the individual agents. The cost of the combination products should be compared with the cost of each individual drug when determining their inclusion on the PDL.