Indiana Medicaid Therapeutics Committee
Therapeutic Class Review Summary

Therapeutic class:
Antidiabetic Agents, Oral

Overview:
There are six different classes of oral antidiabetic agents: sulfonylureas (SU), biguanides, α-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 β 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 similary 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. Thiazolidinediones improve insulin sensitivity and increase glucose uptake. The orally inhaled insulin, Exubera®, was recently discontinued.

Sulfonylureas are the oldest oral hypoglycemic agents and were developed in the 1950s. The mean reduction in HbA_{1c} with sulfonylurea treatment is about 1% to 2%. Based on the results of the UK Prospective Diabetes Study (UKPDS), sulfonylureas improve long-term microvascular outcomes in patients with type 2 diabetes. The second-generation sulfonylureas (ie, glyburide, glipizide, and glimepiride) are generally more potent and efficacious as the first generation agents (ie, chlorpropamide, tolbutamide, acetohexamide, and tolazamide). Increased cardiovascular mortality was documented with tolbutamide treatment, but it has not been noted with other sulfonylureas. The newest addition, glimepiride, 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®, Riomet™) and its sustained release formulations (ie, Glucophage® XR, Fortamet®, and Glumetza™) are the only biguanides available. The mean reduction in HbA_{1c} with metformin treatment is about 1% to 2%. Based on the analysis of the UKPDS, metformin improves both macro- and microvascular outcomes in type 2 diabetic patients.[19] Compared with sulfonylureas, metformin provides the same glycemic control with a lower incidence of hypoglycemia. In addition, metformin does not cause weight gain. It is the preferred agent for obese patients. However, because of the risk of lactic acidosis, there are many contraindications associated with the use of metformin. Both immediate-release and sustained-release metformin are available generically in solid dosage forms. The most common adverse

effects are gastrointestinal related. Riomet™, an oral liquid formulation containing 100 mg of metformin per milliliter, is also available.

Alpha-glucosidase inhibitors delay the absorption of carbohydrates and reduce postprandial hyperglycemia. With an average HbA_{1c} lowering effect of 0.5% to 1%, the overall efficacy in glycemic control of α-glucosidase inhibitors is less than that of sulfonylureas or metformin. The recently published STOP-NIDDM trial was the first prospective intervention study showing that treatment with an alpha-glucosidase inhibitor (acarbose) in patients with impaired glucose tolerance was associated with a significant reduction in cardiovascular events and hypertension. The dosing schedule of alpha-glucosidase inhibitors is complicated and needs to be tailored to mealtimes. Gastrointestinal side effects are common, but hypoglycemia is not a concern. Acarbose (Precose®) and miglitol (Glyset®) are two brand name drugs in this class. The FDA approved both medications for use as monotherapy or in combination with sulfonylureas. Acarbose obtained additional approval 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_{1c} 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. Nateglinide (Starlix™) and repaglinide (Prandin®) are two brand name drugs in this class. The FDA has approved the use of this class of drugs as monotherapy or in combination with metformin or a thiazolidinedione.

Sitagliptin (Januvia™), the only dipeptidyl peptidase-4 (DPP-4) inhibitor available, is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Sitagliptin use results in prolonged 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. The intestines release incretin hormones throughout the day and levels are increased in response to a meal. 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. Sitagliptin may be used as monotherapy or as combination therapy with metformin or a peroxisome proliferator-activated receptor gamma agonist (e.g., thiazolidinediones). Treatment with sitagliptin lowers HbA_{1c} 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 beneficially modify other components of the metabolic syndrome, such as dyslipidemia, vascular procoagulant state, and blood pressure. Treatment with thiazolidinediones lowers HbA_{1c} 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. In addition, the American Diabetes Association recently issued a consensus statement indicating the authors do not view the clinical trial data regarding the potential risk of myocardial infarction with rosiglitazone as definitive. The consensus statement also indicates that the increased risk of heart failure and fractures with the thiazolidinediones does not warrant their removal as a possible second-step medication after metformin, considering that these agents cause hypoglycemia less frequently than alternative second-step therapies. A Medication Guide has been developed to provide information regarding the safe use of rosiglitazone.

Combination therapy with different drug classes may be necessary considering 50% of patients with type 2 diabetese were inadequately controlled with monotherapy after 3 years (UKPDS 49). The oral combination agents are glipizide/metformin (Metaglip™), glyburide/metformin (Glucovance®), pioglitazone/metformin (Actoplus Met™), rosiglitazone/metformin (Avandamet™), pioglitazone/glimepiride (Duetact™), rosiglitazone/glimepiride (Avandaryl™), and sitagliptin/metformin (Janumet™). The pharmacokinetic profiles of the combination drugs are the same as the individual drugs. Glyburide/metformin and glipizide/metformin tablets are available generically.

	Generic Name	Brand Name	Manufacturer
Sulfonylurea	Acetohexamide	Dymelor® (brand no longer marketed)	Various
	Chlorpropamide	Diabinese®	Various
	Glimepiride	Amaryl®	Various
	Glipizide	Glucotrol®, Glucotrol®XL	Various

	Generic Name	Brand Name	Manufacturer
	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
	Repaglinide	Prandin®	Novo Nordisk
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	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

Summary:
Because all sulfonylureas are equally efficacious, the generic sulfonylureas provide a wide range of selection for clinicians. 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 is the newest treatment option for patients with diabetes and may be used either as monotherapy or in combination therapy. Finally, the thiazolidinediones improve insulin sensitivity and cause hypoglycemia less frequently than alternative therapies. 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.