

Indiana Medicaid Therapeutics Committee Therapeutic Class Review Summary

Therapeutic class:

Biguanides and Other Antidiabetic Agents

Overview:

There are five different classes of oral antidiabetic agents: sulfonylureas (SU), biguanides, α -glucosidase inhibitors (AGI), nonsulfonylurea insulin secretagogues, 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. The mechanism of action of nonsulfonylurea insulin secretagogues is similar to sulfonylureas; however, because of their quick onset and short duration of action, these agents target postprandial hyperglycemia. Thiazolidinediones are discussed in separate review. 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.

Combination therapy with different drug classes may be necessary because 50% of patients with type 2 diabetes 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[™]), and 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), generics | Various |
| | Chlorpropamide | Diabinese [®] , generics | Various |
| | Glimepiride | Amaryl [®] , generics | Various |
| | Glipizide | Glucotrol [®] , Glucotrol [®] XL, generics | Various |
| | Glyburide | Diabeta [®] , Glynase [®] , Micronase [®] , Glynase [®] PresTab [®] , generics | Various |
| | Tolazamide | Tolinase [®] , generics | Various |
| | Tolbutamide | Orinase [®] , generics | Various |

| | Generic Name | Brand Name | Manufacturer |
|---------------------------------------|----------------------------|---|---------------------|
| Biguanide | Metformin | Glucophage [®] , generics, Glucophage [®] XR, Fortamet [®] , Glumetza [™] , generics, Riomet [™] | Various |
| α-Glucosidase inhibitors | Acarbose | Precose [®] | Bayer |
| | Miglitol | Glyset [®] | Pfizer |
| Nonsulfonylurea insulin secretagogues | Nateglinide | Starlix [™] | Novartis |
| | Repaglinide | Prandin [®] | Novo Nordisk |
| Combinations | Glipizide/Metformin | Metaglip [™] , generics | Various |
| | Glyburide/Metformin | Glucovance [®] , generics | 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 the sulfonylureas are equally efficacious, the generic sulfonylureas provide a wide range of selection for clinicians. Metformin reduces adverse microvascular and macrovascular outcomes, and the 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. Cost and utilization should be considered when selecting preferred agents from these two classes. The combination hypoglycemic agents provide convenient dosing, and they 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 for PDL.