

# Wyoming Drug Utilization Review

## A General Overview of Oral Hypoglycemics for Type 2 Diabetes

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Type 2 diabetes is a disease marked by high levels of blood glucose due to the body's resistance to the action of insulin and insufficient insulin production. Type 2 diabetes accounts for approximately 90% to 95% of all diagnosed cases of diabetes.<sup>1</sup> The incidence of type 2 diabetes is growing and is now considered an epidemic. Risk factors for type 2 diabetes include: older age, obesity, family history of type 2 diabetes, history of gestational diabetes (diabetes during pregnancy), impaired glucose metabolism, physical inactivity, and race/ethnicity. Goals of therapy in diabetes mellitus are directed at reducing symptoms of hyperglycemia, reducing the onset and progression of retinopathy, nephropathy, and neuropathy complications, and improving quality of life. Many people with type 2 diabetes control their blood glucose by adhering to a healthy diet, exercising, and taking an oral hypoglycemic medication.

A number of studies have demonstrated that control of blood glucose with oral agents can reduce the morbidities associated with diabetes.<sup>1</sup> Oral hypoglycemic agents are initiated at the diagnosis of type 2 diabetes to achieve glycemic control goals (hemoglobin A1c (HbA1c) less than 7) with healthy diet and exercise.<sup>2</sup> Currently, six classes of oral hypoglycemic agents are approved for the treatment of type 2 diabetes: biguanides, sulfonylureas, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, and dipeptidyl peptidase 4 (DPP-4) inhibitors. The selection of oral hypoglycemic agents for type 2 diabetic patients should be based on effectiveness, safety, tolerability, and cost.

**Biguanides:** Metformin (Glucophage®) is a first line agent in therapy that works by improving insulin sensitivity (increases peripheral glucose uptake and utilization), decreases liver glucose production, and decreases intestinal absorption of glucose.<sup>3</sup> The expected reduction in HbA1c with metformin is 1.5% to 2%. Metformin is initiated at the time of diagnosis of type 2 diabetes at 500 mg once or twice daily (with breakfast and/or dinner) in addition to lifestyle modifications (healthy diet and exercise).<sup>4</sup> The dose can be increased to 850 to 1,000 mg if gastrointestinal adverse effects have not occurred. The maximum dose is 2,550 mg daily in adults and 2,000 mg daily in patients that are between the ages of 10 and 16.<sup>3</sup> Metformin is contraindicated in patients with a serum creatinine greater than 1.5mg/dL and greater than 1.4mg/dL for males and females respectively, and in patients with a creatinine clearance less than 60-70 ml/minute.<sup>3</sup> Side effects of metformin include nausea, diarrhea, abdominal pain, and the possibility of lactic acidosis. Some benefits seen in patients that take metformin include: weight loss, improved lipid profiles, and no risk for hypoglycemia.<sup>5</sup>

**Sulfonylureas:** There are two generations of sulfonylureas that are available for use in type 2 diabetes. Second generation sulfonylureas are preferred over first generation agents due to fewer drug interactions and adverse effects.<sup>5</sup> First generation agents include: acetohexamide (Dymelor®), chlorpropamide (Diabinese®), tolazamide (Tolinase®), and tolbutamide (Apo-Tolbutamide®). Second generation agents include: glyburide (Micronase®), glipizide (Glucotrol®), and glimepiride (Amaryl®).

Sulfonylureas are considered first or second line agents in therapy that work by stimulating the release of endogenous insulin from the pancreas.<sup>3</sup> The expected reduction in HbA1c with sulfonylureas is 1.5% to 2%. This class of medication is dosed 30 minutes before meals (peak medication levels then coincide with the hyperglycemic response to meal) in 1 or 2 divided doses every day.<sup>5</sup> Glyburide is contraindicated in renally impaired patients because the active metabolites are excreted renally. Glipizide and glimepiride do not have active metabolites that are excreted renally and are preferred in patients who are renally impaired.<sup>5</sup> Side effects of sulfonylureas include: hypoglycemia and weight gain. The advantages of sulfonylureas include once daily dosing and lower cost due to generic availability.

**Thiazolidinediones:** Rosiglitazone (Avandia®) and pioglitazone (Actos®) are second line agents in therapy that work

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## WY-DUR Board Meeting Update

The DUR Board met for its bimonthly business meeting on January 31, 2008. Highlights of this meeting include:

- The Board approved the final criteria for insomnia criteria. The criteria can be viewed at [www.uwyo.edu/DUR](http://www.uwyo.edu/DUR).
- The Psychiatry Advisory Board requested that the Board consider some additional changes to the anti-depressant criteria. The Board accepted their recommendations to remove immediate release bupropion and venlafaxine from the step therapy. Bupropion SR was moved to step one and Effexor XR was moved to step two. The final criteria can be viewed at [www.uwyo.edu/DUR](http://www.uwyo.edu/DUR).

- At the request of a local provider, the Board added cancer-related neuropathic pain as an approved indication for Lyrica.
- The Preferred Drug List Advisory Committee will meet June 4, 2008 and October 15, 2008. There will be no meeting in April.

The next DUR Board meeting will be held March 27, 2008 in Laramie. Topics for discussion will include newly approved medications, combination drugs, DDAVP utilization, and asthma. An agenda will be posted approximately two weeks prior to the meeting.

## Public Health Advisory

### Important Information on Chantix (varenicline)

<http://www.fda.gov/cder/drug/advisory/varenicline.htm>

FDA is issuing this public health advisory to alert patients, caregivers, and healthcare professionals to important changes to Chantix prescribing information. Chantix is a medicine used to help patients stop smoking.

At the request of FDA, Pfizer, the manufacturer of Chantix, has updated the Chantix prescribing information to include warnings about the possibility of severe changes in mood and behavior in patients taking Chantix. FDA is highlighting the following related important safety information on Chantix:

- **Patients should tell their doctor about any history of psychiatric illness prior to starting Chantix.** Chantix may cause worsening of a current psychiatric illness even if it is currently under control and may cause an old psychiatric illness to reoccur.
- **Healthcare professionals, patients, patients' families, and caregivers should be alert to and monitor for changes in mood and behavior in patients treated with Chantix.** Symptoms may include anxiety, nervousness, tension, depressed mood, unusual behaviors and thinking about or attempting suicide. **In most cases, neuropsychiatric symptoms developed during Chantix treatment, but in others, symptoms developed following withdrawal of varenicline therapy.**
- **Patients taking Chantix should immediately report changes in mood and behavior to their doctor.**
- **Patients taking Chantix may experience vivid, unusual, or strange dreams.**
- **Patients taking Chantix may experience impairment of the ability to drive or operate heavy machinery.**

While Chantix has demonstrated clear evidence of efficacy, it is important to consider these safety concerns and alert patients that they are possible.

## Label Changes to Zyprexa and Symbyax

In October, Eli Lilly and Company announced updates to the Warnings section of the labeling for Zyprexa and Symbyax. Results of pooled analyses of clinical trials and information from the CATIE and CAFÉ trials indicated that olanzapine has a greater association with increased glucose levels than other atypical antipsychotics. In addition, olanzapine appears to cause greater increases in total cholesterol, LDL cholesterol and triglycerides than placebo, regardless of cholesterol levels at baseline. The updated labeling also emphasizes the importance of weight monitoring. While studies of olanzapine use in adolescents are included in the labeling, Eli Lilly and Company notes that olanzapine is not currently approved for use in children under the age of 18 years old. **The American Diabetes Association has published guidelines with recommendations for monitoring glucose, weight and lipid levels in patients being treated with an atypical antipsychotic.**

## Federal Upper Limit

Due to a preliminary injunction that is preventing the Center for Medicare and Medicaid Services (CMS) from moving forward with implementing the final rule concerning calculating the Federal Upper Limit (FUL) of certain drugs based on the Average Manufacturer Prices (AMPs), Wyoming Medicaid can't move forward with making any type of reimbursement decisions until a final determination on the rule is rendered. Pharmacies will be kept informed of any reimbursement decisions through Equality Care provider bulletins.

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by increasing peripheral insulin sensitivity. The expected reduction in HbA1c with thiazolidinediones is 0.5% to 1.4%. Advantages with this class of medication are no hypoglycemia and once daily dosing. However, rosiglitazone can be dosed up to twice daily. Side effects include weight gain and edema. These agents should not be used in patients with New York Heart Association Class 3 or 4 heart failure due to the risk of fluid retention leading to an acute exacerbation of congestive heart failure.<sup>4</sup> These agents are relatively expensive due to brand name availability only.

**Meglitinides:** Repaglinide (Prandin®) and nateglinide (Starlix®) are third line agents in therapy that work by stimulating the release of endogenous insulin from the pancreas.<sup>5</sup> The expected reduction in HbA1c is approximately 1.5% with repaglinide and approximately 1% with nateglinide.<sup>4</sup> Side effects of this class include weight gain and hypoglycemia. Meglitinides are usually dosed three times daily 30 minutes before or at meals. Repaglinide and nateglinide are only available by brand name, making these two agents more expensive when compared to other available oral hypoglycemics.

**Alpha-glucosidase inhibitors:** Acarbose (Precose®) and miglitol (Glyset®) are third line agents in therapy that work by slowing the absorption of carbohydrates in the intestine. These agents are dosed three times daily with carbohydrate-containing meals and have an expected reduction in HbA1c of approximately 0.5%. Advantages of this class of medication include no weight gain or risk for hypoglycemia. Contraindications include: hepatic impairment, renal impairment, intestinal obstructions, and intestinal or bowel disease.<sup>5</sup> Adverse effects, specifically gas and bloating lead to discontinuation of this class of medication in up to 45% of patients.<sup>4</sup> A gradual dosage titration (over 6-12 weeks) is preferred to minimize gastrointestinal side effects.<sup>5</sup> These agents are also relatively expensive when compared to other available oral hypoglycemic agents.

**DPP-4 inhibitors:** Sitagliptin (Januvia®) is considered a third line agent in therapy that works by enhancing the incretin system within the body. The incretin system is one of the mechanisms in the body which lowers blood glucose. When the body senses hyperglycemia in response to a glucose load (a meal), incretins are released from the intestine and stimulate the alpha and beta cells in the pancreas to release insulin and signal the liver to cease glucose production. The DPP-4 enzyme breaks down endogenous incretins. Sitagliptin blocks the DPP-4 enzyme, thereby increasing the active levels of incretin hormones in the body.<sup>5</sup> This medication is dosed once

daily, with or without food, and must be adjusted for patients with moderate or severe renal disease because the medication is eliminated by the kidney. The expected reduction in HbA1c is approximately 0.6% to 0.8%.<sup>4</sup> Sitagliptin has no significant side effects reported to date.<sup>5</sup> This medication is also relatively expensive when compared to other available hypoglycemic agents due to brand name availability only.

Type 2 diabetes is a major public health concern due to its increasing prevalence and associated morbidities. Aggressive therapy is required to rapidly achieve and maintain glycemic levels as close to normal as possible. Improved glycemic control with oral hypoglycemics is important to improve the quality of life for patients with type 2 diabetes.

Table 1 details the frequency of oral hypoglycemic agents prescribed in the fiscal year of 2006-2007 for the Wyoming Medicaid population. Metformin was the most commonly prescribed oral hypoglycemic agent in the past year.

### References

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**Table 1: Frequency of oral hypoglycemic agents prescribed in the fiscal year 2006-2007**

Metformin HCL	68.69%
Glipizide	16.13%
Glyburide	8.54%
Glimepiride	4.17%
Glyburide/Metformin HCL	1.50%
Micronized Glyburide	0.51%
Acarbose	0.33%
Repaglinide	0.13%

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