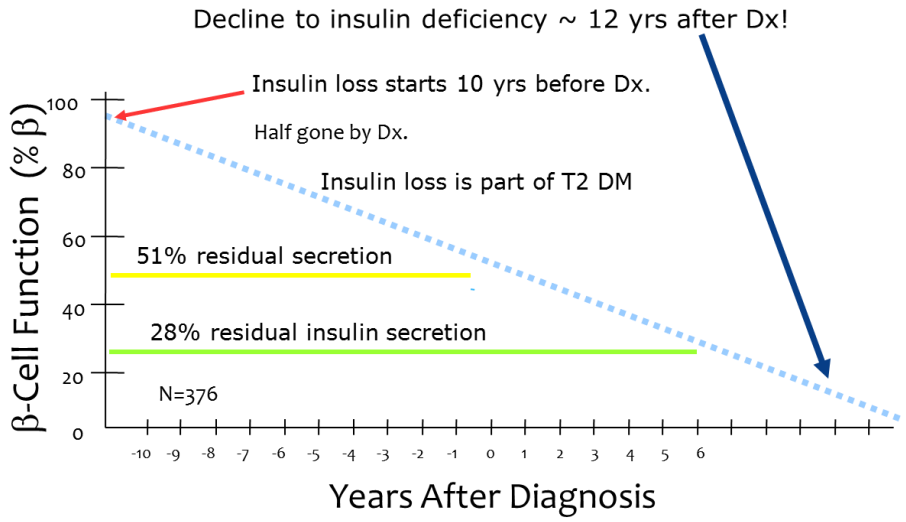
# Indian Health Service
# National Pharmacy and Therapeutics Committee
# Formulary Brief: Sulfonylureas
# - May 2015-

**Background:**
The IHS National Pharmacy and Therapeutics Committee (NPTC) performed a class review of sulfonylureas (SU) at the May 2015 meeting, including clinical, utilization and procurement data. Based on the results of the discussion, the NPTC voted to **remove glyburide** from the National Core Formulary (NCF). Additionally, it was felt that a Formulary Brief would benefit IHS providers with regard to the place in therapy of SUs in the management of type 2 diabetes mellitus (T2DM).

**Discussion:**
Sulfonylureas have been the mainstay for controlling blood glucose in T2DM patients since the mid-1950s. Use of SUs has steadily declined from 61% in 1997 to 22% in 2012.[1] This transition occurred with the development of new antidiabetic agents and from guideline changes from the American Diabetes Association (ADA) and American Association of Clinical Endocrinologist and American College of Endocrinology (AACE/ACE). The NTPC's review of the SU class, recent guidelines and systematic reviews is intended to provide pertinent information and clinical guidance for the IHS.

Diabetes is characterized by insulin deficiency, insulin resistance and numerous other metabolic abnormalities including glucagon, amylin, glucagon-like peptide, gastric inhibitory polypeptide, peptide-YY, leptin and ghrelin. The United Kingdom Prospective Diabetes Study (UKPDS) showed that at diagnosis, only half of the pancreas is able to produce insulin.[2] Of interest, progressive beta cell function decline has been observed at a greater rate with SU treatment when compared to metformin, eventually requiring management with insulin. To date, no treatment has been shown to alter this progressive decline in beta cell function. The graph below illustrates this decline. Understanding this concept allows for better utilization of SU in the treatment of T2DM.




**Current Guidelines:** Metformin continues to be the first-line choice for T2DM for both the ADA and AACE/ACE guidelines. Additionally, patients with the following characteristics are considered better candidates for oral (only) therapy and are likely to respond better to SU therapy:

1. Newly diagnosed T2DM
2. Obesity (body mass index < 30 kg/m2)
3. Absence of symptomatic diabetes mellitus (i.e., rapid weight loss, severe polyuria, severe polydipsia)
4. Hemoglobin A1c (HbA1c) less than 10%
5. Fasting serum glucose less than 250 mg/dL
6. Absence of non-fasting ketonuria[3]

**HbA1c Lowering Effects:** When considering medication options for T2DM patients, it is important to recognize the HbA1c lowering effects of different therapies and agents. The cornerstone of T2DM treatment centers around lifestyle modifications. Medical Nutrition Therapy (MNT) lowers HbA1c approximately 1-2% (short term: 3 to 6 months; 0.25-2.9%) when provided in concert with a registered dietitian.[4] A general rule is that oral antidiabetic medications lower HbA1c 1-2%, whereas insulin has been demonstrated to lower HbA1c by much as 3.5% without dose limitations in clinical trials. The following chart summarizes the different classes of antidiabetic medications and their potential HbA1c reduction.[5]

| Agent | Mean drop in HbA1C |
|---|---|
| Alpha-glucosidase inhibitors, Bile acid Sequestrants, Dopamine Agonists | 0.5-1% |
| Amylin Analogs | 0.5-1% |
| Biguanides, Sulfonylureas, Thiazolidinediones | 1-1.5% |
| Dipeptidyl peptidase 4 (DPP-4) inhibitors | 0.5-1% |
| Glucagon-like peptide-1 (GLP-1) receptor agonists | 1-1.5% |
| Insulin | 1.5-3.5% |
| Meglitinides | 0.5-1% |
| Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors | 0.7-1% |

In general, SUs have been shown to lower HbA1c between 0.4-1.2%, depending on its use as monotherapy or add-on therapy. The expected HbA1c reduction in treatment-naive individuals following initiation of SU monotherapy is 1% to 2%.[6] The efficacy of SUs as add-on therapy to metformin has been shown to lower HbA1c between 0.47% and 1.3%.[7] There are a limited number of studies that show comparable efficacy between newer antidiabetic agents and SUs. The LEAD-2 trial demonstrated equal efficacy of glimepiride vs. liraglutide as add-on therapy with metformin over a 26-week period.[8]

**Adverse Side Effects:** The most common adverse effects associated with SU therapy are weight gain, hypoglycemia, and concerns for cardiovascular (CV) morbidity and mortality. In a 6-year period during the UKPDS study, patients randomized to treatment with chlorpropamide and glyburide gained a mean body weight of 5.3 kg.[9] Hypoglycemia remains one of the most significant adverse effects leading to hospitalizations and non-adherence to pharmacotherapy and are classified as mild or severe episodes. With regard to mild hypoglycemia, the yearly rate of episodes is 10%, 1% and 0.05% for insulin, SUs and metformin, respectively.[10] However, varying rates of hypoglycemia among SUs differ as reflected in both the UKPDS and ADOPT studies. The rates of hypoglycemia (1 or more/year) for chlorpropamide vs. glyburide was 11% and 17.7%, respectively. In a meta-analysis glyburide was associated with a 1.44 times relative increased risk in overall hypoglycemic events and a 4.69 times increased risk for severe hypoglycemic events when compared with other SUs.[11] With regard to increasing CV disease, SUs received a black box warning after the 1970s University Group Diabetes Program (UGDP) study showed increase rates of CV events. However, UGDP subjects randomized to tolbutamide experienced more cardiac events at the time the study was initiated. Furthermore, numerous studies including the UKPDS, ADOPT and BARI 2D failed to show SUs causing increased risk of CV events.[12] The differences in CV rates among SUs may be due to different binding affinities to receptors SUR2A (Cardio) and SUR2B (Vascular). Glyburide binds stronger to these receptors than glipizide and glimepiride.

**Secondary Failure:** Secondary treatment failure is seen in T2DM as progressive beta cell decline occurs over time. The ADOPT study compared failure rates of glyburide, metformin and rosiglitazone over a 5 year period. The failure rates were higher among glyburide patients (34%). Metformin had 21% failure rates, whereas rosiglitazone was 15%.[13] Currently there is a prospective study evaluating add-on therapy to metformin with SUs, DPP-4 inhibitors, GLP-1 receptor agonists and basal insulin and will compare 7 year control and failure rates. The results of this study will help guide the best therapeutic options for long term glycemic control.

**Use in Pregnancy:** A 2010 meta-analysis (6 studies, 1388 patients) was conducted regarding the use of metformin, SUs and insulin in pregnancy. This retrospective cohort study evaluated fasting glycemic control, postprandial glycemic control, neonatal hypoglycemia, birth weight, large-for-gestational-age and cesarean rates. Results from the meta-analysis support that metformin and glyburide are non-inferior to insulin therapy in gestational diabetes, with no evidence of adverse fetal or maternal outcomes.[14]

**Findings:**

The current cost of health care is both substantial and rising with the annual cost of medications for diabetes reaching $18 trillion dollars. Sulfonylureas remain as one of the most cost-effective, add-on therapy to metformin available on the market. Additionally, this class of medications has a history of global experience in effectively controlling blood sugars with relatively low incidence of adverse effects and drug interactions. Their HbA1c lowering ability appears ideal for those patient recently diagnosed with diabetes as pharmacologic failure rates increase with beta cell dysfunction over time. It may be best to avoid use of glyburide in patients who have had a past history of CV disease or MI and are at risk for hypoglycemia. Additionally, several studies have shown that glyburide causes more mild and severe episodes of hypoglycemia then glimepiride and glipizide. Glyburide has been shown to be effective at controlling glucose during pregnancy with minimal adverse effects to the patient or the fetus.

Therefore, SUs still play a role as add-on therapy for patients failing to achieve treatment goals on regimens of 1 or 2 drugs that include metformin, however, their use is limited by increased failure rates as time progresses. The optimal time to use a SU based on UKPDS and ADOPT study results may be during the first one to five years from the date of diagnosis when there is adequate beta cell function.

*If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.*

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