Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: _GLP-1 Receptor Agonists_
- August 2017 -

Background:
The National Pharmacy & Therapeutics Committee (NPTC) reviewed the class of glucagon-like peptide-1 receptor agonists (GLP-1 RA) at the August 2017 Summer meeting. As a result of the NPTC's clinical and pharmacoeconomic evaluation, **no GLP-1 RA agents were added** to the National Core Formulary (NCF).

Discussion:
The GLP-1 RA class includes exenatide (Byetta®), exenatide extended-release (ER) (Bydureon®), dulaglutide (Trulicity®), liraglutide (Victoza® and Saxenda®), lixisenatide (Adlyxin®) and albiglutide (Tanzeum®). In 2016, two combination products were also approved, insulin glargine/lixisenatide (Soliqua®) and insulin degludec/liraglutide (Xultophy®). The GLP-1 RA are FDA approved for the treatment of type 2 diabetes.[1] Endogenous GLP-1 is glucose dependent and stimulates the secretion of insulin, inhibits glucagon secretion, delays gastric emptying, promotes satiety, and increases β-cell growth and replication. Endogenous GLP-1 is rapidly inactivated by dipeptidyl peptidase 4 (DPP-4), however synthetic GLP-1 RA are resistant to degradation by DPP-4 which prolongs the duration (and effect) of the GLP-1 RA. The GLP-1 RA have been shown to reduce A1c by 1.0-1.5%. Benefits of GLP-1 RA include limited hypoglycemia, weight loss, potential cardiac benefit, and limited renal impairment issues.[2]

The Agency for Healthcare Research and Quality (AHRQ) conducted a meta-analysis of 219 studies and determined that GLP-1 RA lowered risk of hypoglycemia compared to sulfonylureas (Odds Ratio [OR] 3.1-5.3).[3] Metformin + GLP-1 RA also lowered the risk of hypoglycemia (OR 0.23-0.89) compared to metformin + insulin and reduced systolic blood pressure by 3mm Hg vs. metformin alone. This study also found that metformin + GLP-1 RA reduced A1c by 0.65% more than metformin + DPP-4 inhibitors. When compared to thiazolidinediones, GLP-1 RA decreased weight by an additional 2.3-3.5 kilograms. Another meta-analysis of 21 randomized controlled trials (RCT) showed that patients with a BMI of $\geq$25 had a mean weight loss of -2.9 kilograms (-3.6 kg to -2.2 kg) vs. controls (placebo, insulin, and oral antidiabetic medications).[4]

The most common adverse effects observed within this class of medications are gastrointestinal (GI) related including nausea, vomiting, and diarrhea.[1] The AHRQ meta-analysis concluded that GLP-1 RA had greater GI side effects compared to sulfonylureas (OR 1.4-2.4).[3] In the same study, metformin + GLP-1 RA had more GI effects compared to metformin + DDP-4 inhibitor (OR 1.0-7.7). The GLP-1 RA do carry a boxed warning for the risk of thyroid C-cell tumors.[1] Caution should also be used in patients with pancreatitis, gastroparesis, or severe GERD. However, an additional meta-analysis of RCTs observed the overall risk of pancreatitis to be small.[5] Of the trials examining pancreatitis risk, 32 reported no events and the remaining 9 trials reported 10 events in the GLP-1 RA group and 6 in the control group. No heterogeneity was detected in the reported cases (I^2 = 0.0, p=0.53; Begg's tau 0.06) and the risk of pancreatitis was not different between groups (OR 1.01 [0.37 – 2.76]; p=0.99).

Head-to-head studies of GLP-1 RA demonstrated liraglutide and dulaglutide have the largest reduction in A1c.[2] In terms of weight loss, liraglutide has shown the greatest reduction. Exenatide ER and lixisenatide have less GI adverse effects, but lixisenatide has less effect on weight loss compared to other agents. In a meta-analysis examining 17 RCTs, exenatide ER and liraglutide decreased A1c by 0.2% and 0.24% more than insulin glargine, respectively.[6] Furthermore, exenatide ER decreased A1c more than exenatide BID (Byetta®), sitagliptin and pioglitazone. It was also noted that β-cell function improved during treatment but did not persist after cessation.[6]

The most recent American Diabetes Association (ADA) guidelines recommend considering the addition of liraglutide in patients with established cardiovascular disease (CVD) and suboptimal controlled type 2 diabetes.[7] This recommendation was largely based off findings from _The Liraglutide Effect and Action in_

Diabetes: Evaluation of Cardiovascular Outcome Results: A Long Term Evaluation (LEADER) trial, a FDA-mandated cardiovascular (CV) outcomes trial.[8] In the LEADER study, Type 2 diabetes patients with established CVD (~80% of patients) or at high risk who received liraglutide showed a statistically significant 13% reduction (HR 0.87; CI 95%, 0.78-0.97; *p*=0.01 for superiority) in the primary endpoint of CV death, nonfatal myocardial infarction or nonfatal stroke. The number needed to treat was 53, over 3.8 years. When the primary endpoints were evaluated separately however, only CV death remained significant. Interestingly, results from other GLP1 RA cardiovascular outcomes trials have been inconsistent and call into question whether a class effect of CV benefit truly exists.[9,10]

In a 2017 meta-analysis of 113 RCTs, patients with GLP-1 RA treatment had significantly lower all-cause mortality (0.88, CI: 0.79-0.97, *p*=0.015), CV mortality (0.84, CI: 0.74-0.96, *p*=0.009), and overall MI (0.90, CI: 0.80-1.00, *p*=0.050) compared to placebo.[11] No benefit was found for stroke (0.90, CI: 0.81-1.06, *p*=0.059) or heart failure (0.92, CI: 0.81-1.06, *p*=0.25). Several studies are underway to assess the cardiovascular effects of additional GLP-1 RA with results expected in the coming year.[1,11]

In addition, current guidelines by the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) recommend GLP-1 RA therapy can be considered as first-line monotherapy (if metformin is contraindicated or not tolerated) when the A1c <7.5% or with dual or triple therapy when the A1c >7.5%.[12] Treatment with GLP-1 RA is not recommended in combination with DPP-4 inhibitors or sodium-glucose co-transporter 2 (SGLT-2) inhibitors. According to the 2017 update of the National Institute for Health and Care Excellence (NICE) Guidelines on Type 2 Diabetes in Adults, if triple therapy (metformin and two other oral medications) is not effective, tolerated, or is contraindicated, GLP-1 RA may be considered.[13] Metformin with a sulfonylurea and a GLP-1 RA can be considered if the patient's BMI is >35 with specific psychological or medical issues associated with obesity. It can also be considered if the patient's BMI is <35 and insulin therapy would have negative occupational implications or the patient would benefit from weight loss. The ADA's 2017 Standards of Medical Care in Diabetes recommends that GLP-1 RA may be used in dual or triple therapy when a patient's A1c is >9%.[7]

Findings:
Many studies and current guidelines establish GLP-1 RA as a viable second-line treatment option in the management of type 2 diabetes. The GLP-1 RA have demonstrated significant reductions in A1c and decreased fluctuation in fasting and post-prandial glucose levels. Certain GLP-1 RA agents have shown additional benefits including reduction in mortality, reduction in cardiovascular events, improved glucose control when used in combination with basal insulin, improved blood pressure control, and weight loss. GLP-1 RA have a moderate side-effect profile including low risk of hypoglycemia, weight loss, GI issues, and low risk of pancreatitis and thyroid cancer. Pending the results of ongoing cardiovascular outcomes studies, GLP-1 RA may be considered for addition to the NCF in the future.

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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