Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: *GLP-1 Receptor Agonists*

-November 2019-

Background:

The IHS National Pharmacy & Therapeutics Committee (NPTC) reviewed the glucagon-like peptide-1 receptor agonists (GLP-1 RA) at the November 2019 meeting. After three prior reviews of this class of drugs, no agents were selected for formulary inclusion. Medical literature was evaluated including findings from each of the associated cardiovascular outcomes trials, various published meta-analyses, and practical guidance from both national and international professional guidelines. Following the analysis, the NPTC voted to **add either subcutaneous (1) dulaglutide, (2) liraglutide or (3) semaglutide to the National Core Formulary** (listed alphabetically only, no preference).

Discussion:

The GLP-1 RA class of available medications include dulaglutide (Trulicity®), exenatide (Byetta®, Bydureon®, and Bydureon BCise®), liraglutide (Victoza® and Saxenda®), lixisenatide (Adlyxin®), and semaglutide (Ozempic® and Rybelsus®)[1]. In 2016, two combination products were also approved, insulin glargine/lixisenatide (Soliqua®) and insulin degludec/liraglutide (Xultophy®). All GLP-1 RAs are FDA approved for the treatment of type 2 diabetes. Liraglutide is the only GLP-1 RA with indications in type 2 diabetes for both cardiovascular (CV) risk reduction and obesity management. 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. Agents in the GLP-1 RA class have been shown to reduce hemoglobin A1c by 1.0-1.5% and offer additional benefits including low risk of hypoglycemia, weight loss, potential cardiovascular benefits for certain high-risk patients, and potential reduction in nephropathy outcomes[1].

In 2016, the Agency for Healthcare Research and Quality (AHRQ) conducted a meta-analysis of 219 studies and determined that GLP-1 RAs posed lower risk of hypoglycemia compared to sulfonylureas (OR: 3.1-5.3)[2]. Metformin plus a GLP-1 RA also had a lower risk of hypoglycemia compared to metformin plus insulin (OR: 0.23-0.89) and reduced systolic blood pressure by 3mm Hg versus metformin alone. This study found that metformin plus a GLP-1 RA reduced hemoglobin A1c by 0.65% more than metformin and DPP-4 inhibitors. When compared to thiazolidinediones, GLP-1 RA decreased weight by an additional 2.3-3.5 kilograms (kg). Another meta-analysis of 21 randomized controlled trials (RCTs) showed that patients with a BMI of $\geq$25 had a greater mean weight loss of 2.9 kg (-3.6 to -2.2 kg) versus the control groups, which included placebo, insulin, and oral antidiabetic medications[3].

The GLP-1 RAs are administered subcutaneously either daily (exenatide, liraglutide, and lixisenatide) or weekly (dulaglutide, exenatide ER, and semaglutide) with the exception of the newly approved oral semaglutide agent[1]. The most common adverse effects observed within this class of medications are gastrointestinal (GI) in nature including nausea, vomiting, and diarrhea[1].

The AHRQ meta-analysis also concluded that GLP-1 RAs had greater GI side effects compared to sulfonylureas (OR: 1.4-2.4) [2]. In the same study, metformin plus a GLP-1 RA had more GI side effects compared to metformin plus a DDP-4 inhibitor (OR: 1.0-7.7). The GLP-1 RAs do carry a black box warning for the risk of thyroid C-cell tumors[1]. Caution should also be used in patients with pancreatitis, gastroparesis, or severe GERD although a supplemental meta-analysis of RCTs observed the overall risk of pancreatitis to be small[4]. Of the trials examining pancreatitis risk, 32 reported no events and the remaining 9 trials reported a total of 10 events in the GLP-1 RA group and 6 events in the control group. No heterogeneity was detected in the reported cases (I^2=0%, p=0.53; Begg's tau 0.06) and the risk of pancreatitis was not different between groups (OR 1.01, 95% CI: 0.37-2.76, p=0.99).

Clinical trials have shown an increase in retinal complications with semaglutide use (oral and injection) in those with CV disease and CV risk factors[1]. Highlighting this issue was the CV outcomes study for subcutaneous semaglutide, the SUSTAIN-6 trial, involving patients with type 2 diabetes and high CV risk. The study reported that more events of retinopathy-related complications occurred in patients treated with semaglutide (3.0%) compared to placebo (1.8%), HR=1.76; 95% CI: 1.11-2.78; p=0.02. The absolute risk increase for diabetic retinopathy was larger among patients with a history of diabetic retinopathy at baseline (semaglutide 8.2%, placebo 5.2%) than among those with no known history of diabetic

retinopathy (semaglutide 0.7%, placebo 0.4%)[5]. This finding was not however identified in the other SUSTAIN trials (SUSTAIN studies 1 through 5 and Japanese trials). The manufacturer advises that patients with a history of diabetic retinopathy receiving either semaglutide product should be monitored.

Cardiovascular outcomes trials (CVOTs) comparing the effects of DPP4i, SGLT2i and GLP-1 RA showed that GLP-1 RAs resulted in neutral effects on MI, although there was a statistically significant 12% reduction in CV death (p=0.01), a 13% reduction in stroke (p=0.02) and an 11% reduction in the combined endpoints of MI and stroke (p=0.001)[6]. The impact of GLP-1 RAs on HF admission was neutral. A second meta-analysis comparing the same antidiabetic drug classes showed that the GLP-1 RAs demonstrated significant reductions in major adverse cardiovascular events, or MACE (RR=0.92; 95% CI: 0.87–0.97), death from CV causes (RR=0.88; 95% CI: 0.80–0.97) and death from any cause (RR=0.89; 95% CI: 0.82–0.96)[7].

The largest meta-analysis, published in 2019, comparing these drug classes reported that both the SGLT2i's and GLP-1 RAs significantly reduced MACE (OR=0.88, 95% CI: 0.82–0.95 and OR=0.87, 95% CI: 0.82–0.93 respectively), hospitalization for HF (OR=0.68, 95% CI: 0.61–0.77 and OR 0.87, 95% CI 0.82–0.93 respectively), and renal composite outcomes (OR=0.59, 95% CI: 0.52–0.67 and OR=0.86, 95% CI: 0.78–0.94 respectively) compared with placebo[8]. Lastly, a 2019 meta-analysis examining the CV, mortality and renal outcomes of GLP-1 RAs reported that, collectively, these agents reduced MACE by 12% (95% CI: 0.82–0.94, p<0.0001)[9]. The analysis also showed significant reduction in each of the individual MACE endpoints including a 12% reduction in cardiovascular death (95% CI: 0.81–0.96, p=0.003), a 9% reduction in MI (95% CI: 0.84–1.00, p=0.043), and a 16% reduction in stroke (95% CI: 0.76–0.93, p<0.0001).

A recent placebo-controlled study evaluating oral semaglutide and liraglutide compared the change in HbA1c at 26 and 52 weeks and overall adverse effects[10]. Results showed the mean change in HbA1c from baseline at week 26 was similar between oral semaglutide (-1.2%) and liraglutide (-1.1%) when compared to placebo (p<0.0001). At week 52, oral semaglutide sustained HbA1c lowering (-1.2%) compared to liraglutide (-0.9%) and placebo (p<0.0001). Oral semaglutide resulted in superior weight loss (–4.4 kg) compared with liraglutide (–3.1 kg) and placebo at week 26 (p<0.0001). Adverse events were more frequent with oral semaglutide (n=229 [80%]) and subcutaneous liraglutide (n=211 [74%]) than with placebo (n=95 [67%]).[9] Despite the obvious potential of an oral GLP-1 RA, the role of oral semaglutide remains presently unclear due to a number of concerns including limited drug exposure in clinical trials, pharmacokinetic challenges and non-inferiority (versus placebo) of primary endpoints in CVOTs[11].

A pediatric study aimed to determine if liraglutide added to metformin (with or without basal insulin) was safe and effective[12]. At 26 weeks, the mean HbA1c decreased by 0.64% with liraglutide and increased by 0.42% with placebo, for an estimated treatment difference of −1.06% (p<0.001). The difference increased to −1.30% points by 52 weeks. The fasting plasma glucose level decreased at both time points in the liraglutide group but increased in the placebo group. The number of patients who reported adverse events was similar in the two groups (56 [84.8%] with liraglutide and 55 [80.9%] with placebo), but the overall rates of adverse events and GI adverse events were higher with liraglutide.

Most guidelines and cardiology consensus statements recommend GLP-1 RAs as a second line therapy, in addition to metformin, especially for those with established CVD or CV risk factors. The American Diabetes Association (ADA) guidelines recommend metformin as the preferred initial pharmacologic agent and, for those who need the greater efficacy of an injectable medication, a GLP-1 RA is the next choice ahead of insulin[13]. Among patients with CVD, a GLP-1 RA or SGLT2i with demonstrated CV benefit is recommended. For patients with CVD and high risk of HF or established HF, a SGLT2i is preferred. For patients with CKD, a SGLT2i or GLP-1 RA with demonstrated benefit in reducing CKD progression, CV events, or both is recommended. The American Association of Clinical Endocrinologists and American College of Endocrinology (ACCE/ACE) guidelines parallel the ADA in their recommendation to initiate a GLP-1 RA in advance of insulin[14]. These guidelines also focus on GLP-1 RAs with CV benefits and highlight their low risk of hypoglycemia and reduced fluctuations in both fasting and postprandial glucose levels. The European Cardiology (ESC/EASD) guidelines align with both the ADA and ACCE/ACE guidelines on the issue of GLP-1 RAs being considered early in therapy, especially in patients with CVD or CV risk factors[15]. Additionally, the ESC/EASD guidelines highlight GLP-1 RA use in the management of hypertension, HF, and CKD. The American College of Cardiology released a position statement in 2018 regarding novel therapies for patients with diabetes and CV risk. This position statement references the use of GLP-1 RAs for their potential renal and weight-loss benefits[16].

Findings:

Current studies and clinical practice guidelines show that GLP-1 RAs remain a viable second-line treatment option following metformin in the management of type 2 diabetes. The GLP-1 RAs have a favorable side-effect profile including low risk of hypoglycemia and GI symptoms, along with a low risk of pancreatitis and thyroid cancer. Notably, the GLP-1 RAs have shown substantial reductions in A1c levels and decreased fluctuation in fasting and post-prandial glucose levels. Additional benefits including reductions in cardiovascular events and mortality, improved blood pressure control, and weight loss favor the long-acting agents in the class. As a result, subcutaneous dulaglutide, liraglutide and semaglutide were added to the IHS National Core Formulary for the treatment of diabetes.

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.

References:

1. Dungan K. Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus. UpToDate. Oct 2019.
2. Bolen S, Tseng E, Hutfless S, et al. Diabetes medications for adults with type 2 diabetes: an update. Comparative Effectiveness Review 173. Agency for Healthcare Research and Quality (AHRQ). April 2016.
3. Bilsboll T, Christensen M, Junker AE, et al. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analysis of randomized controlled trials. BMJ. 2012; 344:d7771.
4. Monami M, Dicembrini I, Nardini C, et al. Glucagon-like peptide-1 receptor agonists and pancreatitis: a meta-analysis of randomized clinical trials. Diabetes Res Clin Pract. 2014;103(2):269-75.
5. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. NEJM, 2016; 375:1834-44.
6. Sinha B, Ghosal S. Meta-analyses of the effects of DPP-4 inhibitors, SGLT2 inhibitors and GLP1 receptor analogues on cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure. Diabetes Research and Clinical Practice. 2019. 150:8-16.
7. Alfayez OM, Al Yami MS, Alshibani M, et al. Network meta-analysis of nine large cardiovascular outcome trials of new antidiabetic drugs. Primary Care Diabetes. 2019 (13); 204-211.
8. Fei Y, Tsoi M, Cheung B. Cardiovascular outcomes in trials of new antidiabetic drug classes: a network meta-analysis. Cardiovasc Diabetol. 2019; 18:112.
9. Kristensen SL, Rorth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocr. 2019: 1-10.
10. Pratley R, Amod A, Tetens S, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet. S0140-6736(19)31271-1.
11. Husain M, Birkenfelf AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with Type 2 Diabetes. NEJM 2019; 381:841-51.
12. Tamborlane W, et al. Liraglutide in Children and Adolescents with Type 2 Diabetes. NEJM 2019; 381:637-46.
13. American Diabetes Association. ADA Standards of Medical Care in Diabetes—2019. Diabet Care 2018; 42(1):S1–S194.
14. AACE/ACE. Consensus Statement by the AACE/ACCE on the Comprehensive Type 2 Diabetes Management Algorithm – 2019 Executive Summary. Endocr Pract. 2019; 25(No. 1).
15. ESC/EASD. The ESC/EASD 2019 Guidelines on Diabetes, Pre-Diabetes, and Cardiovascular Diseases. *Euro Heart J.* 2019; 1-69.
16. The American College of Cardiology. ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes and Atherosclerotic Cardiovascular Disease. 2018; 1–24.