Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: *Dipeptidyl peptidase-4 (DPP-4) inhibitors*
-August 2017-

Background:

The IHS National Pharmacy & Therapeutics Committee (NPTC) discussed the class of DPP-4 inhibitors at the August 2017 meeting. Currently, there are four approved DPP-4 inhibitors available in the U.S.; alogliptin (Nesina®), linagliptin (Tradjenta®), saxagliptin (Onglyza®) and sitagliptin (Januvia®). Prior to the review, the National Core Formulary (NCF) did not include any of the DPP-4 inhibitors. Based on the findings and following discussion of cost benefit analysis, the NPTC **added saxagliptin to the NCF**.

Dipeptidyl peptidase-4 inhibitors are a class of oral medications used to improve glycemic control in type 2 diabetes mellitus (T2DM). DDP-4 inhibitors act by preventing breakdown of incretins such as GLP-1 and GIP which promote endogenous insulin production and prevent secretion of glucose from the liver (suppression of glucagon) resulting in lower serum glucose and ultimately improved glycemic control.[1,2] FDA indications for DPP-4 inhibitors are as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (non-insulin dependent) as mono- or combo-therapy.[3] Notable warnings for this class include a recent FAERS database report indicating the increased incidence of severe and disabling joint pain. Other notable adverse events include bullous pemphigus, hypersensitivity reactions, exacerbation or development of CHF, and risk of renal impairment. Alogliptin alone carries a warning for risk of hepatic failure. All DPP-4 inhibitors are renally cleared (alogliptin both renal and hepatic) and are considered safe for use in renal patients at reduced doses. Notable drug-drug interactions include all CYP3A4 metabolized medications, use with other hypoglycemic agents, decreased efficacy of thiazide drugs with concurrent use, and enhanced renal toxicity of ACE-inhibitors. Renal function should be checked before starting these medications, and for alogliptin, liver function studies should be checked prior to initiation.[3]

Discussion:

Efficacy in hemoglobin A1C reduction are similar across the four approved medications when used as monotherapy for glycemic control, ranging from 0.5% to 1.5% reduction.[4,5,6,7,8,9] In particular, sitagliptin showed a greater reduction (-1.52%) in A1C in patient's whose initial value was greater than 9%.[5] A 2008 Cochrane review of all DPP-4 inhibitors found no improved metabolic control over other hypoglycemic medications, no increased weight gain, and no statistically significant increase of all cause infections.[10] Theoretical benefits of DPP-4 inhibitors over other oral hypoglycemic medications include a lower incidence of hypoglycemia, associated weight loss, and pancreatic beta-cell protection.[11,12]. Multiple meta-analyses have attempted to compare DPP-4 inhibitors in combination with other hypoglycemic agents. Craddy et al. compared DPP-4 inhibitors in combination with metformin, sulfonylureas, metformin plus sulfonylureas, pioglitazone and insulin. They concluded that there were equivalent effects across the class in efficacy and safety and that the only therapy comparison reaching statistically significant difference was alogliptin plus metformin where patients achieved A1C <7% more frequently than those with saxagliptin plus metformin.[13] In 2017, Lin et al. compared DPP-4 inhibitors to placebo and to SGLT2 inhibitors in combination with insulin and found no difference in A1C reduction between SGLT2 inhibitors and DDP-4 inhibitors (0.18% vs. 0.16%). Both were better than placebo but with covariate analysis, SGLT2 inhibitors reduced A1c significantly more in combination with insulin with hypoglycemic events being equal.[14] A 2016 Cochrane review looking at insulin monotherapy versus oral agents plus insulin found that insulin plus DPP-4 inhibitors showed a mean decrease in A1c of 0.4% (95% CI: -0.5 to -0.4; p<0.01) and less weight gain (-0.7kg to 1.3kg) versus insulin alone (0.6kg-1.1kg).[15]

With respect to prevention of secondary cardiovascular (CV) outcomes, several large studies looking at major adverse cardiovascular events (MACE) have been conducted. The SAVOR-TIMI 53 trial was an RCT with 16,492 patients using saxagliptin with A1C ranging from 6.5-12% and median duration of exposure of 2.1 years. The primary CV endpoint as a composite of CV death, non-fatal MI, and non-fatal stroke occurred in 7.3% of saxagliptin patients and 7.2% with placebo. Ultimately saxagliptin proved non-inferior (p<0.001) to placebo in the primary outcome (but not superior) however there were more hospitalizations for heart failure (3.5% vs. 2.8%, p=0.007) with the intervention.[16] In the TECOS trial over 14,000 patients were randomized to placebo or sitagliptin for the same composite primary endpoint as the SAVOR-TIMI trial. There were no differences in the primary or secondary composite outcomes, CV death

from any cause was unchanged, and while the incidence of pancreatitis was higher it was not statistically significant.[17] Meta-analysis of CV outcomes with DPP-4 inhibitors included the aforementioned large RCTs. Monami et al.'s meta-analysis of DPP-4 inhibitors vs. placebo or any oral or injectable hypoglycemic therapy (including insulin) showed an overall reduction in MACE (OR 0.71, p<0.001, 63 trials). Other statistically significant differences favoring DDP-4 inhibitors included reduced MI (OR 0.64, 95% CI: 0.44-0.94; 41 trials) and all-cause mortality (OR 0.60, 95% CI: 0.41-0.88; 30 trials).[18]

Concerns about significant adverse events with DPP-4 inhibitors have been studied. Toh et al. conducted a retrospective cohort study comparing rates of hospitalization for heart failure (HF) in patients using saxagliptin and sitagliptin. Overall risk of HF was not increased with DDP-4 inhibitors and when patients were stratified according to prior CVD or high HF risk, no increases in hazard ratios were found.[19] A 2014 meta-analysis showed that overall risk of HF hospitalization was higher for DPP-4 inhibitors, however, if the analysis excluded the SAVOR-TIMI trial, there was no increase in risk.[20] Sitagliptin, saxagliptin and linagliptin have been studied for their impact on renal impairment. In a trial of sitagliptin, serum creatinine increased 1.6% vs. 7.7% in the sitagliptin vs. placebo/glipizide groups, respectively. Similarly, in the saxagliptin study, 13.3% of sitagliptin patients (vs. 23.8% of placebo patients) increased from moderate to severe renal impairment.[21] Lastly, several meta-analyses failed to show any increased rate in pancreatitis with DPP-4 inhibitor treatment.[22]

Current guidelines from the American Diabetes Association and the European Association for the Study of Diabetes recommend tailored therapy for second line treatment (after metformin) and include DPP-4 inhibitors in these therapies. The American College of Endocrinology and the American Association of Clinical Endocrinologists recommend DPP-4 inhibitors as second or third line or as a monotherapy in metformin-intolerant patients with an A1c <7.5%.

Conclusions:

DPP-4 inhibitors are safe and effective at lowering blood glucose in patients with T2DM both alone and in combination with other oral and injectable hypoglycemic agents. The risk of hypoglycemia is not increased with DPP-4 inhibitors. DPP-4 inhibitors may reduce CVD risk in long-term studies. Studies have shown increased risk of HF with DPP-4 inhibitors, however the data is skewed by a single large trial, thus clinically, saxagliptin should likely not be used in patients with high risk of HF. DPP-4 inhibitors do not increase risk of pancreatitis. DPP-4 inhibitors are safe in patients with all stages of renal failure.

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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