



**Indian Health Service**  
**National Pharmacy and Therapeutics Committee**  
**Formulary Brief: Dipeptidyl Peptidase-IV Inhibitors**  
**-February 2019-**



**Background:**

The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the class, Dipeptidyl Peptidase-IV Inhibitors (DPP-IV inhibitors), for the treatment of Type 2 Diabetes Mellitus at the February 2019 Winter meeting. This drug class was reviewed in August 2017 at which time saxagliptin was named to the National Core Formulary (NCF). Currently, there are four approved DPP-IV inhibitors available in the U.S.; alogliptin (Nesina<sup>®</sup>), linagliptin (Tradjenta<sup>®</sup>), saxagliptin (Onglyza<sup>®</sup>) and sitagliptin (Januvia<sup>®</sup>). Based on the clinical findings and cost benefit analysis, the NPTC **added alogliptin to the NCF and removed saxagliptin.**

**Discussion:**

Dipeptidyl peptidase-IV inhibitors are a class of oral medications used to improve glycemic control in Type 2 Diabetes Mellitus (T2DM). DPP-IV 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.<sup>1,2</sup> DPP-IV inhibitors are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (non-insulin dependent) as mono- or combination therapy.<sup>3</sup>

**Guidelines**

In October 2018, the [American Association of Clinical Endocrinologists / American College of Endocrinology \(AAACE/ACE\)](#) released updated guidelines for the management of T2DM. The A1c goal for patients without concurrent serious conditions or risk for hypoglycemia remains  $\leq 6.5\%$ . For patients at higher risk for hypoglycemia with concurrent conditions, an A1c goal  $>6.5\%$  is acceptable. The AAACE/ACE guidelines recommend DPP-IV inhibitors as fourth-line monotherapy in patients with A1c  $<7.5\%$ , third-line for dual therapy in those with A1c  $>7.5\%$ , and fifth-line in triple therapy.<sup>4</sup> The [2019 America Diabetes Association guidelines](#) were consistent with their previous recommendations regarding DPP-IV inhibitors. The A1c goals remain the same ( $\leq 7\%$ ), with emphasis placed on individualizing glycemic targets based on factors such as risk of hypoglycemia, disease duration, life expectancy, comorbidities, established vascular complications, patient resources and support. Finally, incorporating patient preference favors the successful management of T2DM.<sup>5</sup>

**Clinical Studies**

The NPTC review focused on randomized, controlled studies that included alogliptin. One 2013 landmark study (the EXAMINE study) compared alogliptin to placebo with respect to major cardiovascular (CV) events in patients with T2DM at very high risk for such events (i.e., recent acute coronary syndrome). The study was an international, multicenter, randomized, double-blinded, non-inferiority trial that enrolled 5,380 patients in 49 countries. The primary endpoint was the composite of CV death, nonfatal MI, or nonfatal stroke as determined by a pre-specified non-inferiority margin hazard ratio of 1.3. Additional safety end points included angioedema, hypoglycemia, pancreatitis, cancer, and various laboratory tests. Study duration was 40 months with median follow up of 18 months. No significant differences were noted in primary endpoints in the two study groups. The endpoint data showed adverse CV events in 11.3% of patients receiving alogliptin compared with 11.8% in the placebo group (HR, 0.96 [95% CI,  $\leq 1.16$ ];  $p=0.32$  for superiority;  $p<0.001$  for non-inferiority). For glycemic control, the results favored alogliptin. The baseline A1c change was  $-0.33\%$  in the alogliptin group versus  $0.03\%$  in the placebo group, and was statistically significant (95% CI:  $-0.43$  to  $-0.28$ ;  $p<0.001$ ). There was no significant change in body weight between groups. Results were similar for serious adverse effects, 33.6% in the alogliptin arm and 35.5% for placebo. There were also similar rates for hypoglycemia, acute and chronic pancreatitis (no fatal cases), eGFR, and dialysis initiation in both groups. Finally, there were no differences in elevated serum aminotransferase values or cancer rates between groups.<sup>6</sup>

A 2015 post-hoc analysis of the EXAMINE trial was performed to determine the relationship between alogliptin and heart failure (HF)-related hospital admissions. This analysis demonstrated that risk for

major adverse CV events or hospital admission for HF did not increase with use of alogliptin (16% vs. 16.5% placebo, HR 0.98, 95% CI: 0.86-1.12). CV death and hospital admissions for HF were similar (HR 1.00, 95% CI: 0.82-1.21). Recurrent hospital admission for HF was also similar between groups (HR 1.05, 95% CI: 0.82-1.34,  $p=0.71$ ). **Hospital admissions for HF were higher in patients with no history of HF and receiving alogliptin, 2.2% vs. 1.3%, HR 1.76 (95% CI: 1.07-2.90,  $p=0.026$ ).** Researchers concluded that the use of alogliptin in patients with T2DM and recent acute coronary syndrome did not increase risk of adverse HF outcomes, except for the subgroup of patients with no history of HF. This latter data was used to support the [FDA label warning](#) that alogliptin, in addition to saxagliptin, may increase the risk of HF.<sup>7</sup>

Finally, in 2018, another subgroup analysis of EXAMINE study evaluated the addition of alogliptin to traditional antidiabetic combination therapy with a particular focus on antihyperglycemic efficacy and safety.<sup>8</sup> The study arms included alogliptin plus metformin/sulfonylurea combination therapy vs. placebo plus metformin/sulfonylurea combination therapy. Endpoints included change in A1c, adverse events, CV outcomes, laboratory data, and various safety parameters. There were 693 patients randomized to receive alogliptin compared to 705 patients in the placebo arm. Improvement in A1c statistically favored the alogliptin group. There was no statistical difference in the rate of hypoglycemia. Cardiovascular death and all-cause mortality rates were lower in those receiving alogliptin (HR, 0.49; 95% CI: 0.28-0.84 and HR, 0.61; 95% CI: 0.38-0.96, respectively). HF hospitalizations were no different between groups with HF rates for alogliptin reported at 3.7% vs 2.7% for placebo (HR 1.15, 95% CI: 0.59-2.26,  $p=0.67$ ). The authors concluded that, in this EXAMINE subgroup of ~1400 patients, the addition of alogliptin to metformin/sulfonylurea combination therapy significantly reduced HbA1c as well as adverse CV outcomes and it was also well tolerated.

#### Findings:

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. More recently, DPP-4 inhibitors have been shown to be CV neutral in cardiovascular outcomes trials. Studies have shown an increased risk of HF hospitalization with saxagliptin and alogliptin (subgroup only with no HF history in EXAMINE). DPP-4 inhibitors do not appear to increase risk of pancreatic cancer but may slightly increase risk of acute pancreatitis. Finally, DPP-4 inhibitors are safe in patients with all stages of renal failure.

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*If you have any questions regarding this document, please contact the NPTC at [IHSNPTC1@ihs.gov](mailto:IHSNPTC1@ihs.gov). For more information about the NPTC, please visit the [NPTC website](#).*

#### References:

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