

Dipeptidyl-peptidase-4 (DPP-4) Inhibitors: Saxagliptin, Sitagliptin, Linagliptin, Alogliptin Criteria for Use

VA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

Saxagliptin is on the VA National Formulary (the other DPP-4-inhibitors remain non-formulary)

Exclusion Criteria

- History of a serious hypersensitivity reaction to DPP-4 inhibitors such as anaphylaxis or angioedema
- Patients with a history of acute pancreatitis, chronic or recurring pancreatitis and those with a history of pancreatitis secondary to exenatide or another DPP-4 inhibitor or has pancreatic cancer **

***It is unknown whether use of these medications in patients with other risk factors for pancreatitis such as elevated triglycerides (e.g., >1000mg/dL), gallstones, alcohol abuse increases rates of adverse events, but their presence should be considered in the decision to use these agents.*

Inclusion Criteria

- Type 2 diabetes
- A1C not at goal on metformin or other agent if unable to tolerate metformin
- Expected change in A1C is < 1% in order to reach patient specific goal*

*Refer to the VA/DoD Diabetes Guidelines <http://www.healthquality.va.gov/index.asp> for recommendations on individualizing A1C targets

Insulin may be considered any time prior to using a DPP-4 inhibitor; however, it should be considered if patient is symptomatic or a greater reduction beyond what is achievable by a DPP-4 inhibitor is desired

Dosage

Refer to product labeling for dosing information

Please note the following:

- Sitagliptin, saxagliptin, and alogliptin require dosage adjustment for patients with renal impairment
- The dose of saxagliptin requires adjustment if taken concurrently with a strong CYP3A4/5 inhibitor
- Linagliptin should not be used if patient is receiving a P-glycoprotein or CYP3A4 inducer
- When used with a sulfonylurea, a lower dose of the sulfonylurea may be required as hypoglycemia was reported more often in those treated with this combination.

Issues for Consideration

- The long-term cardiovascular safety trial for saxagliptin (SAVOR), alogliptin (EXAMINE), and sitagliptin (TECOS) showed that there was no increase or decrease in the primary endpoint (composite of CV death, nonfatal MI, or nonfatal ischemic stroke). Sensitivity analysis performed by the FDA of the on-treatment population revealed an increased incidence of death in the patients receiving saxagliptin; the significance of this finding is unknown

A secondary endpoint from the SAVOR trial found a higher risk of hospitalization for heart failure in patients receiving saxagliptin relative to placebo HR=1.27 [95%CI 1.07, 1.51; p=0.007]. Post-hoc analyses of SAVOR found that patients with Class 3 or 4 heart failure, or eGFR <60mL/min were at a greater risk for hospitalization for heart failure. Several observational studies, including a risk evaluation conducted in VA patients, found the risk for hospitalization for heart failure was not greater with saxagliptin compared to sitagliptin.

Hospitalization due to heart failure was not a predefined endpoint in the EXAMINE trial for alogliptin. However, a post hoc analysis found a numerically higher risk of hospitalization for heart failure in patients receiving alogliptin relative to placebo HR=1.19 [95%CI 0.90, 1.58; p=0.220]. A secondary endpoint in the TECOS trial found that the rate of hospitalization for heart failure did not differ between sitagliptin and placebo HR=1.0 [95%CI 0.83, 1.20; p=0.98]

Consider the risks and benefits of saxagliptin or alogliptin prior to initiating treatment in patients at a higher risk for heart failure. Observe patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage

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according to current standards of care and consider discontinuation of saxagliptin/alogliptin.

- Pancreatitis has been reported with the DPP-4 inhibitors. Monitor patients for the development of pancreatitis after initiation or dose increases of agent. Discontinue agent if pancreatitis is suspected while using these products.
- Some infections have been reported more often with DPP-4 inhibitors than placebo: upper respiratory tract infection, urinary tract infection, nasopharyngitis
- Serious allergic and hypersensitivity reactions (e.g. anaphylaxis, angioedema, exfoliative skin conditions including Stevens-Johnson syndrome) have been reported with the DPP-4 inhibitors. If these reactions occur, discontinue agent and initiate alternative treatment for diabetes.
- Consider discontinuing the DPP4 inhibitor if insulin is initiated.

Discontinuation criteria

Discontinue if little to no improvement in glycemic (e.g., A1C, postprandial glucose) goals are seen after 3-6 months of therapy

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