

GLP-1 Agonists (Exenatide, Liraglutide, Albiglutide, Dulaglutide) 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.**

These Criteria for Use apply to the GLP-1 agonists for the management of diabetes mellitus. Please consult the liraglutide (SAXENDA) documents for information on its use as a weight loss drug.

Exclusion Criteria

- Type 1 diabetes
- History of hypersensitivity to GLP-agonist or excipients¹
- End-stage renal disease or CrCl < 30ml/min (for exenatide)²
- Personal or family history of medullary thyroid carcinoma or with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
- Severe gastrointestinal disease (e.g., gastroparesis)
- History of pancreatitis³

¹It is unknown at this time if patients who experienced a hypersensitivity reaction to one GLP-1 agonist can safely use another.

²Exenatide should be used with caution in patients with renal transplantation or when initiating or escalating the dose in patients with moderate renal failure. There is limited experience using liraglutide or dulaglutide in patients with mild, moderate, and severe renal impairment or albiglutide in patients with moderate-severe renal impairment. Use with caution in these patients.

³Relative exclusions to use include triglyceride level > 1000mg/dL, known gallstones with intact gallbladder, and alcohol abuse.

Inclusion Criteria - Combination with Oral Agents

- Type 2 diabetes
- Inadequate glycemic control on two oral medications, one of which should be metformin, unless contraindicated or not tolerated. Patients experiencing GI side effects with metformin should be offered a trial of metformin XR *[§]

*GLP-1 agonists should not be used in combination with DPP-4 inhibitors, alpha-glucosidase inhibitors, or meglitinides. There have been no prospective randomized controlled trials evaluating GLP-1 agonists in combination with SGLT2 inhibitors. Potential concerns include increased risk of dehydration due to GI side effects (nausea, vomiting, and diarrhea) of the GLP-1 agonists and diuresis from the SGLT2 inhibitors.

§ Insulin may be considered at any time prior to using a GLP-1 agonist; however, it is preferred if patient is symptomatic or the desired A1C reduction is beyond what is achievable by a GLP-1 agonist. In clinical trials the **mean** reduction in A1C when used alone or added to oral hypoglycemic agents is approximately 1.0% (**means** ranging from 0.7% to 1.9% across studies)

Inclusion Criteria-Combination with Insulin

- Type 2 diabetes
- Inadequate glycemic control on basal insulin + metformin (or another agent if unable to use metformin/ metformin XR)[†]

[†]Consider addition of mealtime insulin instead of using a GLP-1 agonist; however, mealtime insulin should be used if patient is symptomatic or the desired A1C reduction is beyond what is achievable by a GLP-1 agonist. In clinical trials the **mean** reduction in A1C when used with insulin is approximately 1.2% (**means** ranging from 0.7% to 1.9% across studies).

[†]Exenatide extended-release has not been studied in combination with any insulin at this time; the manufacturer recommends that it not be used with insulin. The data for GLP-1 agonists in combination with both basal and prandial insulin are very limited at this time. **Concomitant use of GLP-1 agonists with regimens containing basal insulin AND prandial insulin (including premixed formulations) may be done on a case-by-case basis in consultation with an endocrinologist or diabetologist.**

Dosing

Refer to product package insert for detailed dosing information

Note: When a GLP-1 agonist is used in combination with an insulin secretagogue (e.g., a sulfonylurea) or insulin, consider lowering the dose of the secretagogue or insulin to reduce the risk of hypoglycemia.

Issues for Consideration

- As part of the Risk Evaluation and Mitigation Strategies (REMS) Program, a medication guide is required to be dispensed with each prescription

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- Patients should be instructed to report any unexplained persistent severe abdominal pain which may or may not be accompanied by vomiting to their provider immediately. Discontinue agent if pancreatitis is suspected while using these products. Do not restart if pancreatitis is confirmed.
 - Use with caution in patients taking oral medications that require rapid gastric absorption or have a narrow therapeutic index
 - There have been post-marketing reports of increased INR with concomitant use of exenatide and warfarin. Monitor INR more frequently after initiation or dosage change of exenatide. Once a stable INR has been achieved, INR can be monitored at the usually recommended interval for warfarin.
 - Avoid initiating in individuals whom the potential for dehydration poses a considerable risk (e.g., frail elderly, multiple co-morbid conditions, etc.)
 - Use cautiously in patients who have undergone bariatric surgery due to the potential interaction the GLP-1 agonists may have on the gastrointestinal motor complications and gastric hormone changes associated with bariatric interventions. With bariatric surgery, there is increased GLP-1, changes in GI motility, and potential for hypoglycemia if a GLP-1 agonist is given.
 - In pregnant animals exposed to GLP-1 agonists, fetal abnormalities or abnormalities in offspring have been noted. There are no adequate and well-controlled studies using GLP-1 agonists in pregnant women. GLP-1 agonist should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether GLP-1 agonists are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for clinical adverse reactions from the GLP-1 agonist in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Follow-up

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

PBM Contact: Deb Khachikian, PharmD