Reference number(s)
2750-A

STANDARD MEDICARE PART B MANAGEMENT

SOMATULINE DEPOT (lanreotide acetate injection)
LANREOTIDE INJECTION (lanreotide acetate injection)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Somatuline Depot
      a. Long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.
      b. Treatment of adult patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.
      c. Treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analog rescue therapy.

   2. Lanreotide Injection
      a. Long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.
      b. Treatment of adult patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

B. Compendial Uses
   1. Neuroendocrine tumors (NETs):
      a. NETs of the gastrointestinal (GI) tract, lung, and thymus (carcinoid tumors)
      b. NETs of the pancreas (islet cell tumors)
      c. Well-differentiated grade 3 NETs with favorable biology
   2. Pheochromocytoma/paraganglioma
   3. Hepatocellular carcinoma
   4. Thyroid carcinoma
   5. Thyroid stimulating hormone (TSH)-secreting pituitary adenoma
   6. Uterine leiomyoma
   7. Zollinger-Ellison syndrome

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions for acromegaly:

A. For initial approval: Laboratory report indicating high pretreatment insulin-like growth factor-1 (IGF-1) level and chart notes indicating an inadequate or partial response to surgery or radiotherapy or a clinical reason for not having surgery or radiotherapy.
B. For continuation: Laboratory report indicating normal current IGF-1 levels or chart notes indicating that the member's IGF-1 level has decreased or normalized since initiation of therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Acromegaly

Authorization of 12 months may be granted for the treatment of acromegaly when all of the following criteria are met:

1. Member has a high pretreatment insulin-like growth factor-1 (IGF-1) level for age and/or gender based on the laboratory reference range.
2. Member had an inadequate or partial response to surgery or radiotherapy OR there is a clinical reason why the member has not had surgery or radiotherapy.

B. Carcinoid syndrome

Authorization of 12 months may be granted for treatment of carcinoid syndrome.

C. Neuroendocrine tumors (NETs)

1. Authorization of 12 months may be granted for treatment of NETs of the gastrointestinal (GI) tract, lung, and thymus (carcinoid tumors).
2. Authorization of 12 months may be granted for treatment of NETs of the pancreas (islet cell tumors) including gastrinomas, glucagonomas, insulinomas, and VIPomas.
3. Authorization of 12 months may be granted for treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs).
4. Authorization of 12 months may be granted for treatment of well-differentiated grade 3 NETs (not of gastroenteropancreatic origin) with favorable biology (e.g., relatively low Ki-67 [less than 55%], somatostatin receptor [SSR] positive imaging).

D. Pheochromocytoma and paraganglioma

Authorization of 12 months may be granted for treatment of pheochromocytoma/paraganglioma.

E. Hepatocellular carcinoma

Authorization of 12 months may be granted for treatment of hepatocellular carcinoma.

F. Thyroid carcinoma

Authorization of 12 months may be granted for treatment of thyroid carcinoma.

G. Thyroid stimulating hormone (TSH)-secreting pituitary adenoma

Authorization of 12 months may be granted for treatment of TSH-secreting pituitary adenoma.

H. Uterine leiomyoma

Authorization of 12 months may be granted for treatment of uterine leiomyoma.

I. Zollinger-Ellison syndrome

Authorization of 12 months may be granted for treatment of Zollinger-Ellison syndrome.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefits are defined as:
    1. Acromegaly: decreased or normalized IGF-1 level since initiation of therapy.
    2. All other indications: improvement or stabilization of clinical signs and symptoms since initiation of therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The package insert for Somatuline Depot.
2. The package insert for lanreotide injection.
3. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
4. The following professional guidelines:
    a. Medical guidelines for the clinical practice for the diagnosis and treatment of acromegaly from the American Association of Clinical Endocrinologists
    b. Acromegaly: an endocrine society clinical practice guideline from the Endocrine Society Clinical Guidelines Subcommittee
    c. NCCN Guideline: Neuroendocrine and adrenal tumors

After reviewing the information in the above resources, the FDA-approved indications listed in the package insert for Somatuline Depot (lanreotide) and the package insert for lanreotide injection are covered in addition to the following:
1. Neuroendocrine tumors (NETs)
    a. NETs of the gastrointestinal (GI) tract, lung and thymus
    b. NETs of the pancreas (islet cell tumors)
    c. Well-differentiated grade 3 NETs (not of gastroenteropancreatic origin) with favorable biology
2. Pheochromocytoma and paraganglioma
3. Hepatocellular carcinoma
4. Thyroid carcinoma
5. Thyroid stimulating homone (TSH)-secreting pituitary adenoma
6. Uterine leiomyoma
7. Zollinger-Ellison syndrome

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer’s prescribing information.

Support for using Somatuline Depot and lanreotide to treat neuroendocrine tumors (not of gastroenteropancreatic origin), pheochromocytoma, and paraganglioma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Somatuline Depot and lanreotide to treat hepatocellular carcinoma and thyroid carcinoma can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Somatuline Depot and lanreotide to treat thyroid stimulating hormone (TSH)-secreting pituitary adenomas can be found in a study by Gancel and colleagues (1994). In a small study (n=4), single injections of lanreotide 500 micrograms subcutaneously or 30 mg (slow-release formulation) intramuscularly resulted in significant decreases in plasma levels of thyroid-stimulating hormone (TSH) in patients with TSH-secreting pituitary adenomas and related hyperthyroidism. Plasma free thyroxine (fT4) and free triiodothyronine (fT3) were measured after slow-release lanreotide and also showed substantial reductions. Subsequent treatment with slow-release lanreotide 30 mg every 10 to 14 days in these patients was associated with progressive reductions in TSH, fT3, and fT4 for up to 6 months and a corresponding decrease in clinical symptoms. However, there was no change in pituitary adenoma volume during 3 to 6 months of therapy with these doses, which is in contrast to experience with octreotide (decrease in adenoma size in 30% of patients).

Support for using Somatuline Depot and lanreotide to reduce uterine and myoma volume can be found in a small study by DeLeo and colleagues (2001). Administration of lanreotide reduced uterine and myoma volume in 7 fertile women with uterine leiomyomata. Lanreotide 30 mg was administered as a depot formulation on the second day of the menstrual cycle and every 14 days for 3 months. After 3 months of therapy, mean basal uterine volume declined by 24% (p less than 0.05) while mean myoma volume declined by 42% (p less than 0.05) after therapy and 29% (p less than 0.5) 3 months after the end of treatment. During therapy, plasma levels of estradiol and follicle-stimulating hormone did not change. However, mean growth hormone and insulin-like growth factor-I concentrations were significantly reduced (p less than 0.05).

Support for using Somatuline Depot and lanreotide to treat Zollinger-Ellison syndrome can be found in the National Comprehensive Cancer Network's guideline for neuroendocrine and adrenal tumors. The NCCN Guideline supports the use of lanreotide and octreotide long-acting release (LAR) for symptom and tumor control.

Support for utilizing a high pretreatment insulin-like growth factor-1 (IGF-1) as a diagnostic requirement and targeting IGF-1 in patients with acromegaly is supported by two professional guidelines.
According to Katznelson et al the biochemical target goal is an age-normalized IGF-1. An age-normalized IGF-1 signifies control of acromegaly.
According to the Endocrine Society, IGF-1 should be measured and patients with elevated or equivocal serum IGF-1 levels should have the diagnosis confirmed by finding lack of suppression of growth hormone to less than 1 microgram/L following documented hyperglycemia during an oral glucose load. The Endocrine Society also supports the normalization of IGF-1 as the biochemical target goal of therapy with Somatuline Depot.
Finally, the studies cited in the package insert for Somatuline Depot required patients to have an IGF-1 concentraion 1.3 times or greater than the upper limit of the normal age-adjusted range.

VII. REFERENCES

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5. The NCCN Clinical Practice Guidelines in Oncology® Neuroendocrine and Adrenal Tumors (Version 1.2023). © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed August 3, 2023.
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8. Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med.* 2014;371:224-233.
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10. DeLeo V, laMarca A, Morgante G, et al: Administration of somatostatin analogue reduces uterine and myoma volume in women with uterine leiomyomata. Fertil Steril 2001; 75(3):632-633.