Reference number(s)
2748-A

STANDARD MEDICARE PART B MANAGEMENT

SANDOSTATIN LAR (octreotide acetate for injectable suspension)

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
Sandostatin LAR Depot is indicated in patients who have responded to and tolerated Sandostatin subcutaneous injection for:
1. Long-term maintenance therapy in acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option.
2. Long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.
3. Long-term treatment of the profuse watery diarrhea associated with vasoactive intestinal peptide (VIP)-secreting tumors.

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. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)
2. Pheochromocytoma/paraganglioma
3. Meningiomas
4. Thymomas and thymic carcinomas
5. Bowel obstruction due to peritoneal carcinomatosis
6. Postgastrectomy dumping syndrome
7. Hepatocellular carcinoma
8. Zollinger-Ellison syndrome
9. Merkel cell carcinoma

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. Vasoactive intestinal peptide tumors (VIPomas)
Authorization of 12 months may be granted for management of symptoms related to hormone hypersecretion of VIPomas.

D. 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, and insulinomas.
3. Authorization of 12 months may be granted for treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

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

F. Meningiomas
Authorization of 12 months may be granted for treatment of unresectable meningioma.

G. Thymomas and thymic carcinomas
Authorization of 12 months may be granted for treatment of thymoma and thymic carcinoma.

H. Bowel obstruction due to peritoneal carcinomatosis
Authorization of 12 months may be granted for treatment of bowel obstruction due to peritoneal carcinomatosis.

I. Postgastrectomy dumping syndrome
Authorization of 12 months may be granted for treatment of postgastrectomy dumping syndrome.

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

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

L. Merkel cell carcinoma

Authorization of 12 months may be granted as a single agent for treatment of metastatic Merkel cell carcinoma when one of the following criteria is met:
1. The member has contraindication to anti-PD-L1 or anti-PD-1 therapy.
2. The member has disease progression while on anti-PD-L1 or anti-PD-1 therapy.

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:
   3. Acromegaly: decreased or normalized IGF-1 level since initiation of therapy.
   4. All other indications: improvement or stabilization in 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 prescribing information for Sandostatin LAR.
2. 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
3. NCCN Guideline: Thymomas and thymic carcinomas
4. NCCN Guideline: Neuroendocrine and adrenal tumors
5. NCCN Guideline: Central nervous system cancers
6. NCCN Guideline: Merkel cell carcinoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Sandostatin LAR are covered in addition to the following:
A. Neuroendocrine tumors of the gastrointestinal tract, lungs and thymus
B. Neuroendocrine tumors of the pancreas (islet cell tumors)
C. Gastroenteropancreatic neuroendocrine tumors
D. Pheochromocytoma/paraganglioma
E. Meningiomas
F. Thymomas and thymic carcinomas
G. Bowel obstruction due to peritoneal carcinomatosis
H. Postgastrectomy dumping syndrome
I. Hepatocellular carcinoma
J. Zollinger-Ellison syndrome
K. Merkel cell carcinoma

VI. EXPLANATION OF RATIONALE

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

Support for using Sandostatin LAR to treat neuroendocrine tumors not discussed in the prescribing information can be found in the NCCN Drugs and Biologics Compendium and the Lexi-Drugs database. Use of information in the NCCN Drugs and Biologics Compendium and the Lexi-Drugs 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 Sandostatin LAR to treat meningiomas 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 Sandostatin LAR to treat pheochromocytomas and paragangliomas 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 Sandostatin LAR to treat thymomas and thymic carcinomas 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 Sandostatin LAR to treat hepatocellular 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 Sandostatin LAR to treat bowel obstruction due to peritoneal carcinomatosis can be found in a randomized, double-blind, non-comparative, pilot study in adults with inoperable symptomatic bowel obstruction due to peritoneal carcinomatosis (n=64), an intention-to-treat analysis showed that IM long-acting repeatable (LAR) octreotide administered with immediate-release (IR) octreotide for the first 6 days of therapy yielded success in 38% (12/32) of patients compared with 28% (9/32) of patients randomized to placebo. In addition to corticosteroids (methylprednisolone 3 to 4 mg/kg/day IV days 1 through 6) and best supportive care, eligible patients were randomized to receive either IM octreotide LAR 30 mg every 28 days and octreotide IR 600 mcg/day (given subQ in 2 to 3 divided doses or by continuous infusion) on days 1 through 6 (n=32), or matching placebo (n=32). The primary endpoint, determined at day 14, was a composite of the absence of a nasogastric tube, vomiting less than twice per day, and no requirement for anticholinergic agents. Because only 64 of the planned 102 patients were enrolled in this study, the primary endpoint could not be attained in the overall population, and the analysis was strictly exploratory. Notably, at baseline, a higher proportion of patients in the octreotide group had a Karnofsky score of less than 50 (46.4%) compared with the placebo group (21.9%). In a subgroup analysis of patients with Karnofsky scores of 50 or greater, a higher response rate was observed in the octreotide group compared with the placebo group (60% (9/15) vs 28% (7/25)). Octreotide was well tolerated, with only 3 drug-related events (severe hyperglycemia, mild injection erythema, and mild local inflammation) attributed to octreotide LAR. However, 28 patients withdrew after randomization (11 in the octreotide group and 17 in the placebo group); insufficient clinical response was the most common reason for discontinuation in the placebo group and death was the most common reason in the octreotide group, most likely due to the poor condition of these patients.

Support for using Sandostatin LAR to treat postgastrectomy dumping syndrome is supported by a prospective study. Didden et al conducted a small, prospective, observational study (n=34) and found both subcutaneous (SUBQ) and long-acting release (LAR) octreotide improved symptoms associated with severe dumping syndrome (early and/or late) after gastric surgery. It should be noted the dropout rate was 59% at the end of a mean of seven and a half years. The mean age was 54 years (range, 27 to 73 years), and the vast majority (71%) of patient underwent partial gastrectomy. Subcutaneous octreotide dose was initiated at 25 to 50 mcg one to three times daily before meals, and intramuscular LAR octreotide was started at 10 mg per month. Dosing regimens were adjusted according to patient response and satisfaction; resulting in a mean SUBQ dose of 183 mcg per day (mcg/d) (range, 50 to 600 mcg), and a mean LAR dose of 475 mcg/d (14 mg per month) (range, 333 to 666 mcg/d). Sixteen (47%) patients discontinued octreotide therapy due to lack of effectiveness (n=7; 21%) or intolerable adverse reactions (n=9; 26%), particularly diarrhea. Among 14 remaining evaluable patients during a mean follow-up of 93 months (range, 7 to 204 months), persistent and frequent early systemic symptom scores were reduced by 50% after initiation of octreotide therapy (p less than 0.05). On the other hand, abdominal symptoms and late dumping symptoms were reduced by 31% and 35%, respectively (all p less than 0.05). The proportion of patients experiencing more than 4 symptoms significantly reduced to 43% during octreotide treatment (p less than 0.05). The 24-hour fecal fat output was 24 grams (normal, less than 7 grams) for patients treated with SUBQ octreotide (n=7) compared with 16 grams for individuals receiving LAR therapy (n=7) (p less than 0.05). Patient ratings on quality of life (80 vs 74) and composite symptom diary score (38 vs 42) were slightly better for SUBQ than LAR formulation.
Additional support for using Sandostatin LAR to treat dumping syndrome can be found in a study by Arts et al. The study included 30 consecutive patients with postoperative dumping, evidenced by oral glucose tolerance test (OGTT) results and insufficient response to dietary measures. OGTT, dumping severity score (summary of scores 0-3 for 8 early and 6 late dumping symptoms), and quality-of-life data were evaluated at baseline, after 3 days of subcutaneous administration of octreotide (0.5 mg), and then after 3 monthly intramuscular injections of octreotide LAR (20 mg). Both formulations of octreotide significantly reduced total dumping severity scores (21.7 +/- 1.6 at baseline, 11.2 +/- 1.2 for subcutaneous and 14.0 +/- 1.8 for LAR formulations; $P < .05$). This reduction was associated with significant improvements in the increase in pulse rate (13.8 +/- 5.8 at baseline vs -0.3 +/- 2.2 and 1.9 +/- 1.7; $P < .05$) as well as the increase in hematocrit level (4.0 +/- 1.4 at baseline vs 0.3 +/- 0.9. and 0.4 +/- 1.0; $P < .05$), and the lowest glycemia level in the OGTT (54.1 +/- 6.7 at baseline vs 98.9 +/- 7.1 and 67.8 +/- 5.9; $P < .05$). LAR octreotide administration significantly improved patients' quality of life. Patients' evaluations of their overall treatment efficacy was higher on LAR compared with the subcutaneous formulation (83% vs 52%; $P = .01$).

Support for using Sandostatin LAR 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 using Sandostatin LAR to treat Merkel cell carcinoma can be found in the National Comprehensive Cancer Network's guideline for Merkel cell carcinoma. The NCCN Guideline supports the use of Sandostatin long-acting release (LAR) if anti-PD-L1 therapy is contraindicated or disease has progressed on anti-PD-L1 or anti-PD-1 therapy.

VII. REFERENCES

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