Clinical Policy Bulletin: Somatostatin Analogs

Number: 0693

Policy

I. Aetna considers octreotide (Sandostatin) medically necessary for members with any of the following indications:
A. Treatment of acromegaly for any of the following conditions:

1. For adjunctive therapy with irradiation to help relieve symptoms of acromegaly and possibly slow the rate of tumor growth; or
2. For inability to tolerate bromocriptine; or
3. For inadequate response to surgery or when surgical resection is not an option; or
4. For inadequate therapeutic response to radiation.

Note: The goal is to reduce growth hormone and insulin-like growth factor-1 (IGF-1, somatomedin C) levels to normal.

B. Prophylactic treatment prior to hepatic artery embolization for non-resectable multiple and hormone-secreting neuroendocrine tumors.

C. Prophylactic treatment prior to pancreatic resection for malignancy.

D. Prophylactic treatment prior to surgery for gastrinoma.

E. Prophylactic treatment to prevent carcinoid crises prior to surgery of carcinoid tumor.

F. Treatment of profuse watery diarrhea associated with vasoactive intestinal polypeptide (VIP)-secreting tumors.

G. Stabilization of blood glucose levels in persons with functioning islet cell tumors (insulinomas or glucagonomas).

H. Treatment of functioning gastrinomas (Zollinger Ellison syndrome).

I. Treatment of chemotherapy and/or radiation therapy-induced diarrhea when oral anti-diarrheal medications such as loperamide have become ineffective.

J. Treatment of severe secretory diarrhea associated with acquired immunodeficiency syndrome (AIDS) when anti-microbial or anti-motility agents have become ineffective.

K. Treatment of acute bleeding of gastro-esophageal varices associated with cirrhosis when used in conjunction with endoscopic band ligation or sclerotherapy, or alone if ligation/sclerotherapy is not immediately available.

L. Management of gastro-intestinal (GI) symptoms (e.g., nausea, pain, and vomiting) of in-operable bowel obstruction in persons with terminal cancer.

M. Management of persons with short bowel syndrome if daily intravenous fluid requirements are greater than 3 liters.

N. Treatment for surgically inaccessible recurrent or progressive meningiomas when further radiation is not possible.

O. Thymomas and thymic carcinomas - Second-line therapy with or without prednisone following radiation therapy for locally advanced unresectable disease.

P. Amelioration of volume depletion from enterocutaneous fistulae.

Q. Treatment of pituitary adenomas (including growth hormone-secreting and thyroid stimulating hormone-secreting adenomas).

R. Neuroendocrine tumors of the adrenal gland, for symptom control if somatostatin scintigraphy positive in patients with non-adrenocorticotropic hormone-dependent Cushing’s syndrome with tumors less than 4 cm, benign imaging characteristics, and abnormal contralateral gland and symmetric cortisol production.

S. Neuroendocrine tumors of the GI tract, lung and thymus, for management of unresectable locoregional disease and/or distant metastases for tumor control, or for symptom control in persons with carcinoid syndrome, or supplemental treatment with short-acting
octreotide for breakthrough symptoms in patients taking long-acting octreotide.

T. Lung neuroendocrine tumors, for stage IIIb (T4 due to multiple lung nodules)-IV if octreotide scan positive or for symptoms of carcinoid syndrome.

U. Neuroendocrine tumors of the pancreas, for treatment of symptoms related to hormone hypersecretion, or for tumor control in persons with unresectable locoregional disease and/or metastatic disease and clinically significant tumor burden or clinically significant progression.

Y. Poorly differentiated (high-grade)/large or small cell neuroendocrine tumors, for symptom control of somatostatin scintigraphy positive.

II. Aetna considers octreotide experimental and investigational for all other indications, including any of the following, because its effectiveness for these indications has not been established:

A. Management of diabetes mellitus (e.g., control of an excess of pro-angiogenic factors in diabetes-associated retinal complications); or
B. Management of hormone refractory prostate cancer; or
C. Management of individuals undergoing pancreaticoduodenectomy (Whipple's procedure); or
D. Management of obesity (e.g., control of hyperinsulinemia); or
E. Salvage therapy for small cell lung cancer; or
F. Treatment of acute non-variceal upper GI bleeding; or
G. Treatment of acute pancreatitis; or
H. Treatment of advanced breast carcinoma; or
I. Treatment of chylothorax in neonates; or
J. Treatment of gastric paresis; or
K. Treatment of GI bleeding; or
L. Treatment of hepatocellular carcinoma (HCC); or
M. Treatment of polycystic kidney disease; or
N. Treatment of protein-losing enteropathy following the Fontan operation; or
O. Treatment of thyroid cancer; or
P. Treatment of thyroid eye disease; or
Q. Treatment of vascular (arterio-venous) malformations of the gastrointestinal tract.

III. Aetna considers lanreotide depot injection (Somatuline Depot) medically necessary for the treatment of any of the following indications:

A. Treatment of acromegaly in persons who have had an inadequate response to or can not be treated with surgery and/or radiotherapy.

B. Use in persons undergoing pancreatic resection for malignancy.

C. Neuroendocrine tumors of the adrenal gland, for symptom control if somatostatin scintigraphy positive in patients with non-adrenocorticotropic hormone-dependent Cushing's syndrome with tumors less than 4 cm, benign imaging characteristics, and abnormal contralateral gland and symmetric cortisol production.


E. Neuroendocrine tumors of the GI tract, lung and thymus, for management of unresectable locoregional disease and/or distant
metastases for tumor control, or for symptom control in persons with carcinoid syndrome.

F. Neuroendocrine tumors of the pancreas, for treatment of symptoms related to hormone hypersecretion, or for tumor control in persons with unresectable locoregional disease and/or metastatic disease and clinically significant tumor burden or clinically significant progression.

G. Poorly differentiated (high-grade)/large or small cell neuroendocrine tumors, for symptom control of somatostatin scintigraphy positive.

IV. Aetna considers lanreotide depot injection experimental and investigational for all other indications because its effectiveness for these indications has not been established, including:

A. Treatment of castration-resistant prostate cancer.

B. Treatment of GI bleeding,

C. Treatment of hepatocellular carcinoma (HCC)

D. Treatment of polycystic kidney disease.

V. Aetna considers pasireotide (Signifor LAR) medically necessary for the treatment of persons with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option.

VI. Aetna considers pasireotide experimental and investigational for all other indications.

Note: Octreotide, pasireotide and lanreotide are not covered for constitutional (idiopathic) tall stature because such use is not considered treatment of disease.

For Aetna’s CPB on OctreoScan, please see CPB 0168 - Tumor Scintigraphy.

See also CPB 0170 - Growth Hormone (GH) and Growth Hormone Antagonists.

Background

Somatostatin, a hypothalamic peptide, regulates the functions of several endocrine and exocrine glands. It acts on the anterior pituitary to inhibit the release of growth hormone and thyroid-stimulating hormone. It is also secreted by cells in the pancreas and in the intestine where it inhibits the secretion of a variety of other hormones. Its regulatory actions are mediated via 5 different receptors, which are expressed in a tissue-specific manner. Somatostatin receptors are also present in neuroendocrine gastro-entero-pancreatic tumors. Two long-acting somatostatin analogs, octreotide (Sandostatin) and lanreotide, are recognized by the receptor subtypes 2 and 5. Gastrointestinal endocrine tumors include carcinoid tumors as well as vasoactive intestinal polypeptide (VIP)-secreting tumors.
Neuroendocrine tumors are rare, occurring in less than 1% of the general population. Clinically, these tumors are divided into 2 groups: (i) functionally active, and (ii) functionally non-active. The former produces a variety of substances (e.g., peptides or serotonin) that are responsible for symptoms and sometimes can lead to the death of the patient independently from tumor proliferation. The most effective compounds that can control symptoms in these patients are somatostatin analogs since native somatostatin is unsuitable for long-term clinical application because of its short half-life. Octreotide is one of these synthetic agents with improved pharmacokinetic characteristics compared to native somatostatin. It has been reported to alleviate symptoms in 30 to 70% of the patients, mainly through a direct inhibitory effect on hormone production from the tumors. There is little or no effect on tumor growth during octreotide therapy; clinical responses were recorded in only 10 to 30% of the patients. Recently, significant improvement in the management of the disease has been demonstrated with long-acting repeatable (LAR) octreotide. This new formulation requires only once-monthly intramuscular injection, and has been reported to demonstrate better acceptability and patient compliance to therapy. Available evidence show super-imposable results of both standard octreotide and LAR octreotide in controlling symptoms, lowering hormone and tumor marker levels, and in reducing tumor growth.

Carcinoid tumors are extremely rare and originate primarily from the gastrointestinal (GI) tract. The tumor histology is ambiguous and malignancy is determined by metastases. Many carcinoid tumors are found incidentally or from symptoms related to the hormones that the tumor secretes. Carcinoid syndrome occurs when an abundance of hormones are produced from GI carcinoid metastases or a non-GI primary tumor. The hallmark carcinoid symptoms include flushing, diarrhea, and cardiac involvement. Treatment consists of a wide resection for local primaries and usually palliative, medical support for patients with metastases. The tumors are very slow-growing and patients have lived for up to 30 years after metastasis is diagnosed. Administration of somatostatin analogs (e.g., octreotide) controls many of the carcinoid symptoms.

Guidelines from the UK Network on Neuroendocrine Tumours stated that, when a carcinoid tumor is found before surgery, a potential carcinoid crisis should be prevented by prophylactic administration of octreotide, given by constant intravenous infusion for 12 hours prior to and at least 48 hours after surgery (Ramage et al., 2004). The guidelines state that similar prophylactic measures may be required for gastrinoma surgery and for hepatic artery embolization of non-resectable multiple and hormone secreting neuroendocrine tumors.

These guidelines stated that persons with VIPomas (watery diarrhea hypokalemia achlorhydria (WDHA) syndrome or Werner-Morrison syndrome) frequently respond dramatically to small doses of somatostatin analogs with cessation of diarrhea (Ramage et al., 2004). The guidelines stated that improvements with somatostatin analogs have been reported in patients with glucagonomas, although there is no indication for somatostatin analogs if the patient has no syndrome.

UK Network on Neuroendocrine Tumour guidelines stated that gastrinomas are adequately controlled with high-dose proton pump inhibitors, and there is no definite added benefit in the control of symptoms by addition of somatostatin
analogs. The guidelines noted, however, that some groups advise the addition of somatostatin analogues in this situation (see, e.g., NCCN, 2005). The guidelines stated that administration of somatostatin analogues has variable effects on blood glucose levels in insulinomas. The guidelines explained that about 50% of insulinomas have somatostatin receptors, and that somatostatin analogues may also possibly act by suppressing counter-regulatory hormones such as glucagons.

Currently, somatostatin analogs are the most effective medical therapy available for the treatment of acromegaly. Octreotide is the first somatostatin analog used for this indication. Initially, it was administered subcutaneously at doses of 100 to 500 ug thrice-daily. The advent of new depot formulations, such as LAR octreotide, slow-release lanreotide and lanreotide autogel (Somatuline Autogel), improved patients' compliance with long-term therapy, overcoming the inconvenience of multiple daily doses. It has been reported that somatostatin analogs induce biochemical control and tumor shrinkage in about 50 to 70% and 30 to 60% of patients with acromegaly, respectively.

Octreotide is approved by the FDA for use in the management of patients with acromegaly, carcinoid tumors, and VIP-secreting tumors. A consensus development panel on diarrhea management (Harris et al, 1995) established guidelines for octreotide dose titration in patients with secretory diarrhea. In general, the panel recommended an aggressive approach in selecting the initial octreotide dose and in making subsequent dose escalations in patients with secretory diarrhea associated with various conditions including carcinoids, VIPomas, AIDS, short bowel syndrome (SBS), radiation therapy, and chemotherapy. The American Gastroenterological Association (2003) stated that octreotide is rarely needed for SBS. It should only be used if daily intravenous fluid requirements are greater than 3 liters.

Several meta-analyses indicated that octreotide is useful in the management of patients with acute bleeding of gastroesophageal varices. Imperiale and co-workers (1995) reported that somatostatin is more effective in controlling acute hemorrhage from esophageal varices and has a lower risk of adverse effects than vasopressin. Corley and colleagues (2001) stated that their findings favor octreotide over vasopressin/terlipressin in the control of esophageal variceal bleeding and suggest it is a safe and effective adjunctive therapy after variceal obliteration techniques. Moreover, trials are needed to determine the optimal dose, route, and duration of octreotide treatment. Gross et al (2001) concluded that ligation is the most effective treatment option for ongoing variceal bleeding. Additionally, no significant difference was found between the effectiveness of sclerotherapy and treatment with somatostatin or octreotide. The authors recommended that administration of somatostatin or octreotide may be recommended as 1st-line therapy if ligation is not immediately available.

Erstad (2001) noted that "while additional investigations are needed ... there is substantial evidence that octreotide is an effective therapy with relatively few adverse effects when used in the management of acute variceal bleeding". Rossle (2003) stated that the recommended standard treatment for acute variceal bleeding consists of immediate drug treatment with terlipressin or octreotide together with early endoscopic band ligation or sclerotherapy. Furthermore, the
United Kingdom guidelines on the management of variceal hemorrhage in cirrhotic patients (Jalan and Hayes, 2000) stated that variceal band ligation is the method of choice to control bleeding. If banding is difficult because of continued bleeding or this technique is unavailable, endoscopic variceal sclerotherapy should be performed. If endoscopy is unavailable, vasoconstrictors such as octreotide or glypressin may be used while more definitive therapy is arranged.

While there is adequate evidence that octreotide is beneficial in the management of patients with acute bleeding of gastroesophageal varices, there is insufficient evidence that it is effective in the treatment of acute non-variceal gastrointestinal bleeding. In this regard, a multidisciplinary consensus group representing 11 national societies does not recommend the use of somatostatin and octreotide in the management of patients with acute non-variceal upper gastrointestinal bleeding (Barkun et al, 2003).

Results from several randomized controlled studies also indicated that octreotide is useful in the management of patients with in-operative malignant bowel obstruction. Ripamonti et al (2000) stated that such patients should undergo treatment with anti-secretory drugs so as to evaluate the possibility of removing the nasogastric tube. When a more rapid reduction in gastrointestinal secretions is desired, octreotide should be considered as the drug of choice. Mercadante and colleagues (2000) reported that octreotide induced a significantly rapid reduction in the number of daily episodes of vomiting and intensity of nausea compared with hyoscine butylbromide at the different time intervals examined. Octreotide was more effective than hyoscine butylbromide (at the doses used in this study) in controlling gastrointestinal symptoms of bowel obstruction (e.g., nausea, vomiting, and pain). Furthermore, Mystakidou and associates (2002) concluded that the administration of octreotide, in combination with traditional pharmacological treatment, can be very effective in managing symptoms of in-operative bowel obstruction in terminal cancer patients.

There is ongoing research to expand the therapeutic role of octreotide -- for use in the management of patients with acute pancreatitis, advanced breast cancer, diabetes mellitus, gastric paresis, hepatocellular carcinoma, hormone refractory prostate cancer, obesity, protein-losing enteropathy following the Fontan operation, thyroid cancer, and thyroid eye disease. However, the effectiveness of octreotide for these indications has not been established.

Hejna et al (2002) stated that there appears to be evidence that somatostatin analogs are able to enhance the therapeutic effects of hormonal intervention in patients with breast cancer, prostate cancer and probably pancreatic cancer. However, interpretation of these findings is confounded by the fact that patients were heavily pre-treated in some studies and response criteria have not been uniformly applied. Furthermore, most studies have not been designed to distinguish between receptor-mediated (direct) and indirect effects of somatostatin analogs in tumor patients. The authors concluded that there can be no doubt about the wide therapeutic index and the high efficacy of somatostatin analogs in the symptomatic management of neuroendocrine tumors. Apart from these indications, the data do not justify recommendation of these agents as anti-neoplastic drugs outside of clinical trials, as the optimal dose and schedule of application for anti-neoplastic activity has not been defined for currently used
agents. Well-designed clinical studies including investigation of the status of somatostatin receptors before treatment, evaluation of an indirect mechanism of somatostatin analogs, as well as assessment of optimal combination of hormone therapy and chemotherapy with somatostatin analogs are needed.

In a randomized, multi-center prospective trial assessing LAR octreotide plus tamoxifen as a first line therapy for advanced breast carcinoma (n = 203), Bajetta et al (2002) concluded that there is no indication for adding somatostatin analogs to tamoxifen in the treatment of patients with advanced breast carcinoma.

Octreotide has also been used to treat advanced malignant thymoma that is refractory to conventional chemotherapeutic agents. In a review, Kurup and Loehrer (2004) stated that thymomas and thymic carcinomas, which are rare epithelial tumors arising from the thymus gland, are the most common tumors of the anterior mediastinum. Thymomas are generally encapsulated, slow-growing tumors that have a “bland” histologic appearance. Thymic carcinomas possess more overtly malignant histologic features than thymomas and are more likely to present as invasive or disseminated disease. Surgery is the treatment of choice for localized thymic tumors, with complete resection being the most important prognostic factor. Complete resection also improves survival in locally invasive thymic tumors. Adjuvant post-operative radiation therapy may improve the outcome in patients with invasive disease, although the data are conflicting. Multi-modal regimens, including neoadjuvant combination chemotherapy, surgery, and/or post-operative radiation therapy, are recommended for patients with advanced thymomas and thymic carcinomas. The authors stated that use of octreotide plus prednisone has produced responses in thymomas, but the dosing and schedule have not been clearly defined. The authors concluded that prospective studies have been limited, and, as such, enrollment in clinical trials is encouraged.

In a phase II study (Palmieri et al, 2002), 16 patients with advanced thymic tumors, unresponsive to conventional chemotherapeutic regimens, were enrolled in the study. The schedule included administration of somatostatin analog octreotide (1.5 mg/day subcutaneously) associated with prednisone (0.6 mg/kg/day orally for 3 months, 0.2 mg/kg/day orally during follow-up). In 8 cases, octreotide was replaced by the long-acting analog lanreotide (30 mg/every 14 days intramuscularly). Treatment was prolonged until progression of disease was documented. The overall response rate among 16 evaluable patients was 37 %. One patient (6 %) had a complete response, 5 (31 %) had a partial response, 6 obtained a stabilization of disease, and 4 progressed during the treatment. After a median follow-up of 43 months, the median survival was 15 months, and median time to progression was 14 months. The investigators reported that treatment was generally well-tolerated with acceptable toxicity: cholelithiasis (1 patient), grade 2 cushingoid appearance (3 patients), grade 1 diarrhea (5 patients), grade 2 hyperglycemia (3 patients). The authors concluded that treatment with somatostatin analogs and prednisone has shown efficacy in patients with recurrent and metastatic malignant thymic tumors refractory to standard therapeutic options. The results obtained are very satisfactory given the lack of effective alternative treatments. Such therapy is not burdened by the same toxicity of chemotherapy; thus, it can be administered to heavily pretreated patients.
Somatostatin analogs and prednisone are well-tolerated, and the long-acting analog lanreotide, which requires fewer injections, improves patients’ compliance.

In a phase II clinical trial, Loehrer et al (2004) determined the objective response rate, duration of remission and toxicity of octreotide alone or with the later addition of prednisone in patients with unresectable, advanced thymic malignancies in whom the pre-treatment octreotide scan was positive. A total of 42 patients with advanced thymoma or thymic carcinoma were entered into the trial, of whom 38 were fully assessable (1 patient had inconclusive histology; 3 patients had negative octreotide scan). Patients received octreotide 0.5 mg subcutaneously three times a day. At 2 months, patients were evaluated. Responding patients continued to receive octreotide alone; patients with progressive disease were removed from the study. All others received prednisone 0.6 mg/kg orally qid for a maximum of 1 year. Two complete (5.3 %) and 10 partial responses (25 %) were observed (4 partial responses with octreotide alone; the remainder with octreotide plus prednisone). None of the 6 patients without pure thymoma responded. The 1 - and 2-year survival rates were 86.6 % and 75.7 %, respectively. Patients with an Eastern Cooperative Oncology Group performance status of 0 lived significantly longer than did those with a performance status of 1 (p = 0.031). The authors found that octreotide alone has modest activity in patients with octreotide scan-positive thymoma. The authors noted that prednisone improves the overall response rate but is associated with increased toxicity. The authors concluded that additional studies with the agent are warranted.

Octreotide has also been evaluated as a treatment for constitutional tall stature. Noordam et al (2006) stated that an optimal treatment for tall stature in boys in terms of safety and effectiveness is not available. Treatment with somatostatin analogue 201-995 (SMS) has been tried with positive short-term results. These investigators assessed the effect of SMS treatment on reducing adult height. Over 2 years, 16 boys presenting to the authors’ university hospital with tall stature (constitutional tall stature (n = 13), Marfan syndrome (n = 2) and tethered spinal cord (n = 1)) with a predicted final height above 197 cm were included in the study and prospectively followed until final height was reached. As 1 boy was lost to follow-up, these researchers reported on 15 boys. Treatment with SMS as a single subcutaneous dose was started and continued until final height was reached. In 8 boys androgens were given to induce puberty after the start of SMS and 5 boys were on treatment with androgens prior to SMS treatment. Effect on reduction of final height prediction, calculated with the index of potential height based on the bone age of Greulich and Pyle, was the main outcome measure. Standard anthropometric assessments were performed a year before and every 3 months during treatment. Bone age was assessed by the method of Greulich and Pyle at the start and after 6 and 12 months. Mean reduction in final height prediction (predicted adult height minus achieved adult height) was -0.1 cm (range of -6.4 to +5.7). In 3 boys, asymptomatic microlithiasis of the gall bladder was diagnosed. The authors concluded that, in spite of encouraging short-term results, long-term treatment with SMS does not reduce final height in a manner sufficient to justify SMS treatment in tall stature.

The efficacy of octreotide in the treatment of angiodysplasias has been limited to case reports and small series, in which a response has been observed in some patients. Sziliagy and Ghali (2006) stated that vascular malformation (AVM) in the
gastrointestinal tract is an uncommon, but not rare, cause of bleeding and iron
deficiency anemia, especially in an aging population. While endoscopic
coagulative therapy is the method of choice for controlling bleeding, a substantial
number of cases require additional therapy. Adjunctive or even primary
pharmacotherapy may be indicated in recurrent bleeding. However, there is little
evidence-based proof of effectiveness for any agent. The bulk of support is
derived from anecdotal reports or case series. These researchers compared the
outcome of AVM after no intervention, coagulative therapy or focus on
pharmacological agents. Most of the literature encompassed 2 common AVMs,
angiodysplasia and hereditary hemorrhagic telangiectasia. Similarly, the bulk of
information evaluated 2 therapies, hormones (estrogen and progesterone) and the
somatostatin analogue octreotide. Of these, the former is the only therapy
evaluated in randomized trials, and the results are conflicting without clear
guidelines. The latter therapy has been reported only as case reports and case
series without prospective trials.

Octreotide has been investigated as a treatment for small cell lung
cancer. Charpidou and colleagues (2006) evaluated the effectiveness of pegylated
liposomal doxorubicin (Caelyx) combined with Sandostatin LAR as salvage
treatment of small cell lung cancer (SCLC) in platinum-pretreated patients. A total
of 9 pretreated patients (median age of 53.5 years, performance status [PS]: 0 to
1) with histologically confirmed SCLC were treated intravenously with Caelyx 40
mg/m2 on day 1 and Sandostatin LAR 30 mg (intramuscular) on day 1 every 28
days. Four (44 %) out of the 9 patients had received 2 prior regimens and 5 (55
%) were refractory to front-line chemotherapy. No complete or partial responses
were observed. Disease stabilization was obtained in 2 (22 %) patients. The
median overall survival was 18.7 months and the median time to progression was
9.1 months. The authors concluded that the combination of Caelyx and
Sandostatin LAR was inactive as salvage treatment in this poor prognosis group of
patients with relapsed SCLC. However, the combination would merit further
investigation in patients pretreated with one prior regimen.

There is evidence to support the use of octreotide for ameliorating volume
depletion in enterocutaneous fistulae. According to Sabiston Textbook of Surgery
(Townsend et al, 2007): "The volume depletion that occurs from a proximal small
bowel fistula may present a formidable problem. Agents that inhibit gut motility,
such as codeine or diphenoxylate, are generally not helpful. The long-acting
somatostatin analogue octreotide has been used in patients with enterocutaneous
fistulas, with a successful decrease in the volume of output. Some series have
reported that octreotide significantly improved the rate of fistula closure, whereas
other studies have failed to document this increased closure rate. However, there
is no doubt that octreotide greatly ameliorates the problems associated with a
massive volume loss and allows better control of the fistula tract."

A randomized controlled trial of the use of somatostatin in enterocutaneous
have shown some beneficial effects with regard to fistula closure rate and hospital
stay, but the effects are statistically insignificant....Thus the role of somatostatin is
not established in the closure of enterocutaneous fistula".
Leandros et al (2004) evaluated and compared the potential clinical benefit and cost effectiveness of pharmacotherapy (somatostatin versus octreotide) versus conventional therapy. A total of 51 patients with gastrointestinal or pancreatic fistulas were randomized to 3 treatment groups: (i) 19 received 6000 IU/day of somatostatin intravenously, (ii) 17 received 100 ug of octreotide thrice-daily subcutaneously, and (iii) 15 received only standard medical treatment. The fistula closure rate was 84 % in the somatostatin group, 65 % in the octreotide group, and 27 % in the control group. These differences were of statistical significance (p = 0.007). Overall mortality rate was less than 5 % and statistically significant differences in mortality among the 3 groups could not be established. Overall, treatment with somatostatin and octreotide was more cost effective than conventional therapy (control group), and somatostatin was more cost effective than octreotide. The average hospital stay was 21.6 days, 27.0 and 31.5 days for the somatostatin, octreotide and control groups, respectively. The authors concluded that these findings suggested that pharmacotherapy reduces the costs involved in fistula management by reducing hospitalization and also offered increased spontaneous closure rate.

In a Cochrane review, Jia and colleagues (2010) evaluated the effect of octreotide therapy on the survival of patients with advanced hepatocellular carcinoma (HCC). The secondary endpoints were to assess tumor response, quality of life and adverse effects. PUBMED, MEDLINE, OVID and SPRINGER databases were searched through January 2009. Randomized controlled trials that compared octreotide treatment with placebo or no treatment were selected. Finally, 4 randomized controlled trials (3 of which were high quality trials) published in 1998 or later with a total of 373 patients were included in this review. Because a significant clinical heterogeneity existed between the included trials, making meta-analysis inappropriate; only a narrative systematic review was performed. Of the 3 high-quality trials, only 1 (n = 126) reported octreotide could improve survival and quality of life of HCC patients, whereas the other 2 (n = 189) suggested octreotide did not have survival benefit in HCC; moreover, none of the 3 trials indicated that octreotide has significant beneficial effect on tumor regression or decrease of tumor mass. Nonetheless, serious adverse effects were not reported in these included trials. In this review, results from included randomized controlled trials demonstrated no clear benefit of octreotide therapy in Advanced HCC patients. In order to detect a realistic treatment advantage, further larger well-designed multi-center randomized trials will have to be conducted.

In a Cochrane review, Das and Shah (2010) evaluated the safety and effectiveness of octreotide in the treatment of chylothorax in neonates. These investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library), MEDLINE and EMBASE (to March 7, 2010). They assessed the reference lists of identified trials and abstracts from the annual meetings of the Pediatric Academic Societies published in Pediatric Research (2002 to 2009) without language restrictions. They planned to include randomized or quasi-randomized controlled trials of octreotide in the treatment of congenital or acquired chylothorax in term or preterm neonates, with any dose, duration or route of administration. Data on primary (amount of fluid drainage, respiratory support, mortality) and secondary outcomes (side effects) were planned to be collected and analysed using mean difference, relative risk and risk difference with 95 % confidence intervals. No randomized controlled trials were identified. A total of 19 case reports of 20 neonates with chylothorax in whom octreotide was used either subcutaneously or intravenously were identified.
Fourteen case reports described successful use (resolution of chylothorax), 4 reported failure (no resolution) and 1 reported equivocal results following use of octreotide. The timing of initiation, dose, duration and frequency of doses varied markedly. Gastrointestinal intolerance and clinical presentations suggestive of necrotizing enterocolitis and transient hypothyroidism were reported as side effects. The authors concluded that no practice recommendation can be made based on the evidence identified in this review. A prospective registry of chylothorax patients and a subsequent multi-center randomized controlled trial are needed to assess the safety and effectiveness of octreotide in the treatment of chylothorax in neonates.

In August 2007, the FDA approved lanreotide injection (Somatuline Depot) for the long-term treatment of patients with acromegaly who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy. The most common side effects (incidence greater than 5 %) associated with lanreotide injection are diarrhea, cholelithiasis, abdominal pain, nausea, injection site reaction, flatulence, arthralgia, and loose stools.

Samonakis et al (2008) noted that somatostatin (SST) acts as an inhibitory peptide of various secretory and proliferative processes. Apart from neuroendocrine tumors, where SST analogs have an established role, they have been tested in other tumors such as hepatocellular carcinoma (HCC). Several positive reports have been published. Approximately 40 % of patients respond with improved survival and an impressive quality of life. A usual misunderstanding in trial designs is that, although SST is not a rescue drug, selection of patients is inappropriate, with mostly moribund patients being recruited. Somatostatin analogs do not seem to work in 60 % of HCCs and this has been linked to the presence of SST receptors (SSTR) in the tumor, while several resistance mechanisms might be involved. Future management should engage more specific SST analogs targeted to a tumor with a known SSTR map. The use of SST analogs as an adjunct therapy in combination with other treatment modalities should also be investigated.
Mitsogiannis and colleagues (2009) stated that despite initial sensitivity to hormone treatment, prostate cancer eventually progresses to a castration-resistant stage (CRPC), which carries an ominous prognosis. Lanreotide has been shown to be highly effective in treating various hyper-secretory disorders and tumors. It has been given to patients with CRPC within a novel treatment concept, with the aim of targeting not only cancer cells but also various factors secreted in the tumor cell milieu that confer protection from apoptosis. Within this concept, lanreotide has been administered as part of the "anti-survival factor therapy" in combination with dexamethasone and a gonadotropin releasing hormone (GnRH) analog. It has also been given combined with estrogens in patients with CRPC. The so far published series have documented a clinical response in many patients treated along with significant improvement in parameters related to quality of life. The authors concluded that in view of these promising results, large-scale, randomized, controlled trials are needed to clearly define the exact role of lanreotide and other SST analogs in the treatment of patients with CRPC.

In a randomized, cross-over, placebo-controlled trial, Ruggenenti and colleagues (2005) compared the risk/benefit profile of 6-month treatment with octreotide LAR depot (40 mg intramuscularly every 28 days) or placebo in autosomal-dominant polycystic kidney disease (ADPKD) patients with mild-to-moderate renal insufficiency and no evidence of other kidney disease. Volumes of kidney structures were evaluated by a 2-slice computed tomography (CT) scanner; while glomerular filtration rate (GFR) was estimated by iohexol plasma clearance. One patient on octreotide and 1 on placebo were prematurely withdrawn because of non-symptomatic, reversible calciolithiasis and asthenia, respectively. In the remaining 12 patients octreotide was well-tolerated. Kidney volume increased by 71 +/- 107 ml (p < 0.05) on octreotide and by 162 +/- 114 ml (p < 0.01) on placebo. The percent increase was significantly lower on octreotide (2.2 +/- 3.7 % versus 5.9 +/- 5.4 %) (p < 0.05). Cystic volume tended to increase less on octreotide than on placebo (3.0 +/- 6.5 % versus 5.6 +/- 5.8 %). The "parenchymal" volume non-significantly increased by 2.5 +/- 8.4 % on placebo and slightly decreased by 4.4 +/- 8.9 % on octreotide. The GFR did not change significantly during both treatment periods. The authors concluded that in ADPKD patients, 6-month octreotide therapy is safe and may slow renal volume expansion. This may reflect an inhibited growth in particular of smallest cysts beyond the detection threshold of CT scan evaluation. Whether this effect may prove reno-protective in the long-term should be tested in additional trials of longer duration.

Edelstein (2008) noted that ADPKD is the most common life-threatening hereditary disease in the United States and causes end-stage renal failure requiring dialysis and renal transplantation. There is no effective treatment for ADPKD in humans. However, there are now multiple clinical trials testing a host of therapeutic interventions in children and adults with ADPKD. The major therapeutic interventions being tested in patients with ADPKD include everolimus, octreotide, sirolimus, statins, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers.

Hogan et al (2010) enrolled 42 patients with severe polycystic liver disease (PLD) resulting from ADPKD or autosomal dominant PLD (ADPLD) in a randomized,
double-blind, placebo-controlled trial of octreotide. These researchers randomly assigned 42 patients in a 2:1 ratio to octreotide LAR depot (up to 40 mg every 28 +/- 5 days) or placebo for 1 year. The primary end point was percent change in liver volume from baseline to 1 year, measured by MRI. Secondary end points were changes in total kidney volume, GFR, quality of life, safety, vital signs, and clinical laboratory tests. Thirty-four patients had ADPKD, and 8 had ADPLD. Liver volume decreased by 4.95 % +/- 6.77 % in the octreotide group but remained practically unchanged (+0.92 % +/- 8.33 %) in the placebo group (p = 0.048). Among patients with ADPKD, total kidney volume remained practically unchanged (+0.25 % +/- 7.53 %) in the octreotide group but increased by 8.61 % +/- 10.07 % in the placebo group (p = 0.045). Changes in GFR were similar in both groups. Octreotide was well-tolerated; treated individuals reported an improved perception of bodily pain and physical activity. The authors concluded that octreotide slowed the progressive increase in liver volume and total kidney volume, improved health perception among patients with PLD, and had an acceptable side effect profile.

Hutchinson et al (2010) described a case of obscure gastrointestinal bleeding in a male with non-cirrhotic portal hypertension who required multiple admissions and repeated blood transfusions over a 5-month period. Upper and lower gastrointestinal endoscopy failed to establish a cause for bleeding, which was eventually ascribed to universal portal hypertensive stigmata in stomach, small bowel and colon, which were not amenable to endoscopic therapy. On account of extensive venous thrombosis, neither surgical shunting nor interventional radiology was an option. Initial management with prothrombotic agents failed. This patient was successfully stabilized on long-acting somatostatin (SMS) analog therapy using lanreotide, resulting in avoidance of further admissions and blood transfusion and restoration of his independence and quality of life. The use of short-acting SMS analogs is recognized in acute variceal hemorrhage secondary to portal hypertension in cirrhosis, and long-acting SMS analog therapy has been described in obscure gastrointestinal bleeding though secondary to angiodysplasia. However, the potential role of long-term SMS analogs in non-cirrhotic portal hypertensive bleeding of this type has not been reported earlier. This case supports its use in this scenario in the absence of surgical options and when only palliative approaches are available.

Brown et al (2010) reviewed pooled clinical response rates from prospective studies using somatostatin analogs for prevention of recurrent bleeding from gastrointestinal angiodyplasia and quantified the effects that therapy has on the use of blood transfusions. These investigators searched several electronic databases including PubMed for full journal articles published after 1966 reporting on the use of somatostatin analogs in the treatment of gastrointestinal angiodyplasia. They hand searched the reference lists of all retrieved articles. Prospective studies involving 10 or more patients were included in the analysis. They calculated the pooled proportion of patients who had a clinical response to therapy in the selected studies and the weighted mean difference (MD) in transfusion requirements before and after therapy. Heterogeneity between the studies was assessed using the I2 statistic. A total of 3 studies involving 62 patients met the inclusion criteria. The proportional meta-analysis showed a clinical response to treatment of 0.76 (95 % confidence intervals [CI]: 0.64 to 0.85). The weighted MD in transfusion requirements before starting therapy (control group) and after treatment initiation (treatment group) was -2.2 (95
Somatostatin Analogs

% CI: -3.9 to -0.5). No significant heterogeneity was seen between the studies. The authors concluded that a significant number of patients with bleeding gastrointestinal angiodysplasia respond to treatment with octreotide by reducing the need for blood products. They stated that, however, as all the included studies had small sample sizes, multi-center randomized trials are needed to confirm these findings.

In a Cochrane review, Gurusamy et al (2010) examined if prophylactic somatostatin analogs should be used routinely in pancreatic surgery. These investigators searched the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 4), MEDLINE, EMBASE and Science Citation Index Expanded to November 2009. They included randomized controlled trials comparing prophylactic somatostatin or one of its analogs versus no drug or placebo during pancreatic surgery (irrespective of language or publication status). Two authors independently assessed trials for inclusion and independently extracted data. They analyzed data with both the fixed-effect and the random-effects models using Review Manager (RevMan). They calculated the risk ratio (RR), MD or standardized mean difference (SMD) with 95 % CI based on an intention-to-treat or available case analysis. When it was not possible to perform either of the above, these researchers performed per protocol analysis. A total of 17 trials (of high risk of bias) involving 2,143 patients were identified. The overall number of patients with post-operative complications was lower in the somatostatin analog group (RR 0.71; 95 % CI: 0.62 to 0.82) but there was no difference in the peri-operative mortality, re-operation rate or hospital stay between the groups. The incidence of pancreatic fistula was lower in the somatostatin analog group (RR 0.64; 95 % CI: 0.53 to 0.78). The proportion of these fistulas that were clinically significant was not mentioned in most trials. On inclusion of trials that clearly distinguished clinically significant fistulas, there was no difference between the two groups (RR 0.69; 95 % CI: 0.34 to 1.41). Subgroup analysis revealed a shorter hospital stay in the somatostatin analog group than the controls for patients with malignant etiology (MD -7.57; 95 % CI: -11.29 to -3.84). The authors concluded that somatostatin analogs reduce peri-operative complications but do not reduce peri-operative mortality. In those undergoing pancreatic surgery for malignancy, they shorten hospital stay. Further adequately powered trials with low risk of bias are necessary. Based on the current available evidence, the authors recommended somatostatin and its analogs for routine use in patients undergoing pancreatic resection for malignancy. There is currently no evidence to support their routine use in pancreatic surgeries performed for other indications.

O'Toole and colleagues (2000) stated that the somatostatin analogs lanreotide and octreotide have previously been shown to be effective in controlling flushing and diarrhea in patients with carcinoid syndrome. As lanreotide requires injection only every 10 days, compared with twice-daily injections of octreotide, a direct comparison between these 2 treatments in terms of patient acceptability, patient preference, and efficacy in controlling symptoms was performed in patients with carcinoid syndrome. A total of 33 patients with carcinoid syndrome were included in an open, multi-center, cross-over study. Half of the patients received octreotide 200 microg subcutaneously twice- or thrice-daily for 1 month followed by lanreotide 30 mg intramuscularly every 10 days for 1 month, while the other 50 % commenced with lanreotide followed by octreotide in a similar fashion. Quality-of-
life assessments were performed at each visit and patient preference for one of the
two treatments evaluated. The number and intensity of flushing episodes and
bowel movements, urinary 5-hydroxy indole acetic acid (5-HIAA) levels, and
plasma serotonin levels were recorded. No significant differences were found
between lanreotide and octreotide in terms of quality-of-life. The majority of
patients (68%) preferred lanreotide (p = 0.03), largely due to its simplified mode of
administration. Disappearance or improvement in flushes occurred in 53.8% of
patients (14 of 26) while on lanreotide and in 68% (17 of 25) on octreotide. A
disappearance or improvement of diarrhea in 45.4% (10 of 22) on lanreotide,
compared with 50% (11 of 22) on octreotide, was also observed. Lanreotide and
octreotide were equally effective in reducing urinary 5-HIAA levels and plasma
serotonin levels. Both treatments were well-tolerated, with mild symptoms of
abdominal pain and nausea observed in 29% and 14% receiving octreotide and
lanreotide, respectively. The authors concluded that lanreotide and octreotide are
equally efficacious in terms of symptom control and reduction in tumor cell
markers for patients with carcinoid syndrome. Due to its simplified mode of
administration, most patients prefer treatment with lanreotide.

In a 6-month, open, non-controlled, multi-center, dose-titration study, Ruszniewski
et al (2004) evaluated the efficacy and safety of 28-day prolonged-release (PR)
lanreotide in the treatment of carcinoid syndrome. Eligible patients had a carcinoid
tumor with greater than or equal to 3 stools/day and/or greater than or equal to 1
moderate/severe flushing episodes/day. Six treatments of 28-day PR lanreotide
were administered by deep subcutaneous injection. The dose for the first 2
injections was 90 mg. Subsequent doses could be titrated (60, 90, 120 mg)
according to symptom response. A total of 71 patients were treated. Flushing
decreased from a mean of 3.0 at baseline to 2.3 on day 1, and 2.0 on day 2, with a
daily mean of 2.1 for the first week post-treatment (p < 0.05). Diarrhea decreased
from a mean of 5.0 at baseline to 4.3 on day 1 (p < 0.05), and 4.5 on day 2, with a
daily mean of 4.4 for the first week post-treatment (p < 0.001). Symptom
frequency decreased further after the second and third injections, and reached a
plateau after the 4th injection. By month 6, flushing and diarrhea had significantly
decreased from baseline by a mean of 1.3 and 1.1 episodes/day, respectively
(both p < or = 0.001); 65% of patients with flushing as the target symptom and 18
% of diarrhea-target patients achieved greater than or equal to 50% reduction
from baseline. Median urinary 5-HIAA and chromogranin A levels decreased by
24 and 38%, respectively. Treatment was well-tolerated; 28-day PR lanreotide
was effective in reducing the symptoms and biochemical markers associated with
carcinoid syndrome.

Khan et al (2011) presented long-term results of prolonged release lanreotide in a
large cohort of patients with malignant carcinoid syndrome, assessing clinical and
objective response and tolerance. A total of 76 patients with metastatic midgut
neuroendocrine tumors and carcinoid syndrome were included in this 9-year
retrospective study. Clinical response was based on symptom score with
radiological assessment based on RECIST (Response Evaluation Criteria In Solid
Tumours). Data were available in 69 patients; 94% achieved symptomatic
response at first follow-up visit; 46% had loss of symptomatic response, but 44%
of these achieved control with an increase in dose of prolonged release
lanreotide. Overall, symptoms were well-controlled throughout the study period
with prolonged release lanreotide alone in 74% of patients; 26% required
additional treatment despite good initial response. Only 30% demonstrated radiological progression. Eleven patients who were switched from octreotide LAR had return of symptomatic control. No significant adverse effects were experienced. The authors concluded that prolonged release lanreotide provides good symptomatic control of diarrhea and flushing as well as tumor stability in patients with malignant carcinoid syndrome.

Also, an UpToDate review on "Treatment of the carcinoid syndrome" (Goldfinger and Strosberg, 2012) states that "we usually begin therapy with octreotide LAR 20 to 30 mg every four weeks. Depot lanreotide is another alternative to octreotide LAR".

Guidelines from the National Comprehensive Cancer Network (NCCN, 2014) recommend octreotide acetate and long-acting octreotide acetate (LAR) for the following indications:

- Meningiomas - Treatment for surgically inaccessible recurrent or progressive meningiomas when further radiation is not possible.
- Lung neuroendocrine tumors - Consider for stage IIIb (T4 due to multiple lung nodules)-IV if octreotide scan positive or for symptoms of carcinoid syndrome.
- Neuroendocrine tumors of the adrenal gland - Consider for symptom control if somatostatin scintigraphy positive in patients with non-adrenocorticotropic hormone-dependent Cushing's syndrome with tumors less than 4 cm, benign imaging characteristics, and abnormal contralateral gland and symmetric cortisol production.
- Neuroendocrine tumors of the gastrointestinal tract, lung, and thymus - Treatment of underlying Zollinger-Ellison syndrome.
  - Management of unresectable locoregional disease and/or distant metastases as tumor control
  - symptom control in patients with carcinoid syndrome
  - supplemental treatment for breakthrough symptoms in patients taking long-acting octreotide (short-acting octreotide only).
- Neuroendocrine tumors of the pancreas - Treatment of symptoms related to hormone hypersecretion.
  - Consider for tumor control in patients with unresectable locoregional disease and/or metastatic disease and clinically significant tumor burden or clinically significant progression if not already given (long-acting octreotide only).
  - Poorly differentiated (high-grade)/large or small cell neuroendocrine tumors - Consider for symptom control if somatostatin scintigraphy positive.
  - Thymomas and thymic carcinomas - Second-line therapy with or without prednisone following radiation therapy for locally advanced unresectable disease (short-acting octreotide only).

Guidelines from the National Comprehensive Cancer Network on neuroendocrine tumors (2013) recommend lanreotide as an alternative to octreotide for symptomatic relief from neuroendocrine tumors (carcinoid tumors, neuroendocrine tumors of the pancreas (islet cell tumors), pheochromocytoma/paraganglioma, and
poorly differentiated neuroendocrine tumors). The NCCN guidelines state that lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an intramuscular (IM) versus subcutaneous (SC) injection.

NCCN guidelines (2014) recommend lanreotide for the following indications:

- **Neuroendocrine tumors of the adrenal gland** - Consider for symptom control if somatostatin scintigraphy positive in patients with non-adrenocorticotropic hormone-dependent Cushing's syndrome with tumors less than 4 cm, benign imaging characteristics, and abnormal contralateral gland and symmetric cortisol production.

- **Neuroendocrine tumors of the gastrointestinal tract, lung, and thymus**
  - Treatment of underlying Zollinger-Ellison syndrome.
  - Management of unresectable locoregional disease and/or distant metastases as tumor control.
  - Symptom control in patients with carcinoid syndrome.

- **Neuroendocrine tumors of the pancreas**
  - Treatment of symptoms related to hormone hypersecretion.
  - Consider for tumor control in patients with unresectable locoregional disease and/or metastatic disease and clinically significant tumor burden or clinically significant progression if not already given.

- **Poorly differentiated (high-grade)/large or small cell neuroendocrine tumors** - Consider for symptom control if somatostatin scintigraphy positive.

The Alberta Provincial CNS Tumour Team's clinical practice guideline on “Pituitary adenomas” (2012) stated that standard treatment options [for growth hormone- and thyroid stimulating hormone-secreting adenomas] include surgery (usually a trans-sphenoidal approach), bromocriptine, somatostatin analog (e.g., octreotide), growth-hormone antagonist, or surgery plus post-operative radiotherapy. Maximal reductions in growth-hormone levels may not be seen for years after institution of radiotherapy, during which time medical therapy may continue to be required.

Also, an UpToDate review on “Thyrotropin (TSH)-secreting pituitary adenomas” (Weiss and Refetoff, 2013) states that “The somatostatin analogue octreotide is effective in nearly all patients. One series evaluated 73 patients treated with octreotide (50 to 750 micrograms given subcutaneously two or three times daily), most of whom had already undergone surgery. The most appropriate therapy for patients with TSH-secreting pituitary adenomas is transsphenoidal resection of the tumor. Transsphenoidal resection results in cure in about one-third of patients, improvement in one-third, and no change in one-third. Because of the relatively poor results of surgery, many patients need additional therapy (e.g., dopamine agonists, octreotide).”

Drymousis et al (2013) examined if the prophylactic administration of somatostatin or somatostatin analogs in patients undergoing pancreaticoduodenectomy (Whipple's procedure) is beneficial in terms of improved surgical outcomes, reduced morbidity or reduced mortality. A total of 118 papers were found using the reported searches of which 5 represented the best evidence (1 meta-analysis, 1 systematic review and 3 randomized control trials). The authors, date, journal, study type, population, main outcome measures and results were tabulated.
There is evidence that the peri-operative administration of somatostatin or somatostatin analogs reduces biochemical incidence of pancreatic fistula but, it is still unclear if there is a beneficial effect in the incidence of clinically significant pancreatic fistula. The authors concluded that further adequately powered trials with low-risk of bias are necessary. From the available data, somatostatin or somatostatin analogs have no effect on mortality post-pancreatectoduodenectomy.

Furthermore, an UpToDate review on “Pancreatectoduodenectomy (Whipple procedure): Techniques” (Reber, 2013) does not mention the prophylactic use of octreotide or somatostatin analogs.

In a meta-analysis, Xu and colleagues (2013) evaluated the safety and effectiveness of octreotide on primary moderate-to-severe acute pancreatitis. The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, PubMed, EMBASE, Science Citation Index Expanded (SCI-E), and Chinese Biomedicine Database (CBM) were searched in September 2011. Major outcomes contained mortality, incidence rate of complications, rate of surgical intervention, and length of hospital stay. A total of 11 randomized clinical trials (RCTs) with 720 participants were included and evaluated, only 2 of which had a high study quality and were combined in meta-analysis. The pool estimate of RR of mortality was 0.88 (95 % CI: 0.53 to 1.45) and that of incidence rate of complication was 1.08 (95 % CI: 0.94 to 1.26); both of which had no significant difference. The other 2 outcomes could not be combined for lack of enough data. The authors concluded that present evidence does not approve octreotide's benefit in the major health outcomes of moderate-to-severe acute pancreatitis and further RCTs with high quality and large sample size are needed.

In a multi-center, randomized, single-blind, placebo-controlled, parallel-group trial, Caroli et al (2013) examined the effect of 3 years of octreotide-LAR treatment on kidney and cyst growth and renal function decline in participants with polycystic kidney disease. Adult (greater than 18 years) patients with estimated GFR of 40 ml/min per 1.73 m(2) or higher were randomly assigned (central allocation by phone with a computerized list, 1:1 ratio, stratified by center, block size 4 and 8) to 3 year treatment with two 20-mg IM injections of octreotide-LAR (n = 40) or 0.9 % sodium chloride solution (n = 39) every 28 days. Study physicians and nurses were aware of the allocated group; participants and outcome assessors were masked to allocation. The primary end-point was change in total kidney volume (TKV), measured by MRI, at 1 year and 3 year follow-up. Analyses were by modified intention-to-treat. Recruitment was between April 27, 2006, and May 12, 2008. A total of 38 patients in the octreotide-LAR group and 37 patients in the placebo group had evaluable MRI scans at 1 year follow-up, at this time-point, mean TKV increased significantly less in the octreotide-LAR group (46.2 ml, SE 18.2) compared with the placebo group (143.7 ml, 26.0; p = 0.032). A total of 35 patients in each group had evaluable MRI scans at 3 year follow-up, at this time-point, mean TKV increase in the octreotide-LAR group (220.1 ml, 49.1) was numerically smaller than in the placebo group (454.3 ml, 80.8), but the difference was not significant (p = 0.25); 37 (92.5 %) participants in the octreotide-LAR group and 32 (82.1 %) in the placebo group had at least 1 adverse event (p = 0·16). Participants with serious adverse events were similarly distributed in the 2 treatment groups. However, 4 cases of cholelithiasis or acute cholecystitis occurred in the octreotide-LAR group and were probably treatment-related. The
authors concluded that these findings provided the background for large RCTs to test the protective effect of somatostatin analogs against renal function loss and progression to end-stage kidney disease.

Sideris et al (2012) noted that for decades, somatostatin analogs ([SAs]; including octreotide and lanreotide) have been indicated for relief of the symptoms of flushing, diarrhea, and wheezing associated with secretory neuroendocrine tumors (NETs). Recently, it has been suggested that SAs may provide direct and indirect anti-tumor effects in secretory and non-secretory NETs in addition to symptom control in secretory NETs. These investigators performed a systematic review of Medline to identify studies that examined the anti-tumor effects of octreotide or lanreotide for patients with NETs. Additional studies not published in the peer-reviewed literature were identified by searching online abstracts. In all, 17 octreotide trials and 11 lanreotide trials that included anti-tumor effects were identified. Partial response rates were between 0 % and 31 %, and stable disease rates were between 15 % and 89 %. Octreotide was the only SA for which results of a phase III, randomized, placebo-controlled clinical trial (PROMID) that investigated anti-tumor effects were published. After 6 months of treatment in this randomized phase III trial, stable disease was observed in 67 % of patients (hazard ratio [HR] for time to disease progression: 0.34; 95 % CI: 0.20 to 0.59; p = 0.000072). The authors concluded that in addition to symptom control for NETs, the data supported an anti-tumor effect of SAs and suggested that they may slow tumor growth. Long-acting repeatable octreotide has been shown to have an anti-tumor effect in a randomized phase III trial in mid-gut NETs, whereas results are pending in a corresponding controlled trial (CLARINET) with lanreotide for patients with intestinal and pancreatic primary NETs.

Toumpanakis and Caplin (2013) stated that SAs are the standard of care for controlling symptoms of patients with functional gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Somatostatin analogs control symptoms in more than 70 % of patients with carcinoid syndrome. Similar results are obtained in patients with functional, hormone-secreting, pancreatic NETs. The use of SAs as anti-proliferative agents has been established only recently. Retrospective studies have shown stabilization of tumor growth in greater than 50 % of patients with progressive disease. The results of a recent randomized phase III trial (PROMID [Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors]) demonstrated that the median time to progression in patients with mid-gut carcinoid tumors treated with octreotide LAR was more than twice as long compared to that of patients treated with placebo. The results of a phase III study (CLARINET) of lanreotide versus placebo in non-functional NETs are not yet available. More studies are needed to determine whether combining SAs with novel targeted treatments will result in enhanced anti-proliferative activity compared to treatment with a SA alone. Studies are ongoing using pan-receptor agonists (e.g., pasireotide) and chimeric dimers, which possess features of somatostatin and dopamine agonists (dopastatins) and are thought to enhance symptom control by binding multiple receptors (somatostatin and dopamine receptors). Somatostatin receptor antagonists are also currently being developed for clinical use. Peptide receptor radionuclide therapy, consisting of yttrium-90 and lutetium-177 isotopes conjugated with SAs, appeared to be effective in advanced NETs. The authors concluded that randomized studies are
needed to definitively establish the safety and effectiveness of this strategy compared to other available treatments, and to determine which radiolabeled isotopes or combinations are most effective.

Caplin and colleagues (2014) noted that SAs are commonly used to treat symptoms associated with hormone hyper-secretion in neuroendocrine tumors; however, data on their anti-tumor effects are limited. In a randomized, double-blind, placebo-controlled, multi-national study, these investigators examined the effects of lanreotide in patients with advanced, well-differentiated or moderately differentiated, non-functioning, somatostatin receptor-positive neuroendocrine tumors of grade 1 or 2 (a tumor proliferation index [on staining for the Ki-67 antigen] of less than 10 %) and documented disease-progression status. The tumors originated in the pancreas, mid-gut, or hind-gut or were of unknown origin. Patients were randomly assigned to receive an extended-release aqueous-gel formulation of lanreotide (Autogel [known in the United States as Depot], Ipsen) at a dose of 120 mg (101 patients) or placebo (103 patients) once every 28 days for 96 weeks. The primary end-point was progression-free survival (PFS), defined as the time to disease progression (according to the RECIST, version 1.0) or death. Secondary end-points included overall survival (OS), quality of life (assessed with the European Organization for Research and Treatment of Cancer questionnaires QLQ-C30 and QLQ-GI.NET21), and safety. Most patients (96 %) had no tumor progression in the 3 to 6 months before randomization, and 33 % had hepatic tumor volumes greater than 25 %. Lanreotide, as compared with placebo, was associated with significantly prolonged PFS (median not reached versus median of 18.0 months, p < 0.001 by the stratified log-rank test; HR for progression or death, 0.47; 95 % CI: 0.30 to 0.73). The estimated rates of PFS at 24 months were 65.1 % (95 % CI: 54.0 to 74.1) in the lanreotide group and 33.0 % (95 % CI: 23.0 to 43.3) in the placebo group. The therapeutic effect in pre-defined subgroups was generally consistent with that in the overall population, with the exception of small subgroups in which confidence intervals were wide. There were no significant between-group differences in quality of life or OS. The most common treatment-related adverse event was diarrhea (in 26 % of the patients in the lanreotide group and 9 % of those in the placebo group). The authors concluded that lanreotide was associated with significantly prolonged PFS among patients with metastatic enteropancreatic neuroendocrine tumors of grade 1 or 2 (Ki-67 less than 10 %).

This study had several drawbacks: (i) 96 % of the patients had stable disease at baseline. Such patients are likely to have fewer tumor-related events (disease progression or death) than those with progressive disease. Data are lacking from controlled trials involving patients with documented progressive disease, (ii) no significant between-group difference in OS was apparent at 2 years, probably because of the long life expectancy for patients with slow-growing tumors and cross-over from placebo to active treatment with disease progression. Other studies involving patients with neuroendocrine tumors have reported similar outcomes, and (iii) this study included only patients with non-functioning tumors, whereas PROMID did include some patients with mildly functioning tumors and showed similar treatment effects on time to tumor progression in patients with non-functioning tumors.

An UpToDate review on “Metastatic pancreatic neuroendocrine tumors and poorly differentiated gastroenteropancreatic neuroendocrine carcinomas: Systemic
therapy options to control tumor growth and symptoms of hormone hypersecretion” (Chan et al, 2014) states that “Lanreotide, another long-acting somatostatin analog, can be self-administered once monthly using a deep subcutaneous injection and appears to have similar efficacy to octreotide. While available internationally, it is currently approved only for the treatment of acromegaly in the United States”.

The FDA has approved pasireotide (Signifor LAR) for injectable suspension, for intramuscular use, as an orphan drug for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option (Novartis, 2014). Pasireotide is a somatostatin analogue that has the potential to stimulate both SSTR2 and SSTR5 subtype somatostatin receptors, which are relevant for inhibition of GH and IGF-1 secretion.

The FDA approval was based on two multicenter phase III studies, C2305 and C2402, which respectively examined medically naïve patients who have had prior surgery or for whom surgery was not an option and patients with acromegaly inadequately controlled on first generation somatostatin analogues. In both studies, higher rates of full biochemical control (defined as mean GH level < 2.5mcg/L and normal IGF-1 levels) were achieved with pasireotide compared to a first generation somatostatin analog.

The C2305 study was a multicenter, randomized, double-blind study in patients with active acromegaly who were not previously treated with medication (medically naïve), and had persistent disease despite prior surgery or were ineligible for surgery. Patients were randomized to receive either pasireotide (starting dose of 40 mg with possibility to up-titrate to 60 mg) or the active comparator. The efficacy endpoint of proportion of patients achieving full GH and IGF-1 biochemical control at month 12 was met. Specifically, the percentage of patients achieving biochemical control was 31.3% for pasireotide and 19.2% for the active comparator (p < .01 for treatment difference). Biochemical control was achieved early in the study (i.e., month 3) by 30.1% of patients in the pasireotide arm. Ninety-eight percent of patients treated with pasireotide had either a reduction or no change in tumor volume from baseline as assessed by MRI at month 12. Additionally, ring size and acromegaly symptoms score (i.e., headache, fatigue, perspiration, paresthesia or tingling sensation in limbs, and osteoarthralgia or joint pain) were followed. At month 12, reductions in ring size and in symptom severity scores in both treatment groups compared to baseline were noted.

The most common adverse events with pasireotide versus the active comparator in this study were diarrhea (39% vs. 45%), cholelithiasis (26% vs. 36%), hyperglycemia (29% vs. 8%) and diabetes mellitus (26% vs. 4%).

The C2402 study was a randomized study evaluating the efficacy and safety of double-blind pasireotide (40 mg and 60 mg) versus continued open-label pre-trial somatostatin analog therapies at maximal or near maximal doses in 198 patients with inadequately controlled acromegaly. Inadequate control was defined as mean GH level > 2.5 mcg/L and IGF-1 > 1.3 times the sex- and age-adjusted upper normal limit.
The efficacy endpoint of the proportion of patients achieving biochemical control, as defined by GH and IGF-1 levels, at 6 months with pasireotide 40 mg or 60 mg versus continued pre-trial somatostatin analog therapy, was met for both pasireotide doses. Specifically, 15.4% and 20.0% of patients treated with pasireotide 40 mg and 60 mg, respectively, achieved full GH and IGF-1 biochemical control at 6 months compared with 0% in the pre-trial therapy somatostatin analog control arm. Biochemical control was achieved by month 3 in 15.4% and 18.5% of patients in the pasireotide 40 mg and 60 mg arms, respectively. Eighty-one percent and 70% of patients treated with pasireotide 40 mg and 60 mg, respectively, had either a reduction or no change in tumor volume from baseline as assessed by MRI at month 6.

The most common adverse events associated with pasireotide 40 mg, 60 mg and pre-trial somatostatin analog therapies in this study were hyperglycemia (33%, 30%, 14%) and diabetes mellitus (21%, 31%, 9%).

The initial dose of pasireotide (Signifor LAR) is 40 mg by intramuscular injection once every 4 weeks (every 28 days). The product labeling recommends that dosing be adjusted based upon biochemical response and tolerability.

Adverse drug reactions associated with pasireotide and occurring in ≥ 20% of patients were diarrhea, cholelithiasis, hyperglycemia and diabetes mellitus. Warnings include hyperglycemia and diabetes, sometimes severe. The labeling recommends monitoring of glucose levels periodically during therapy. Other warnings include bradycardia and QT Prolongation. The labeling recommends use with caution in at-risk patients. ECG and electrolytes should be evaluated prior to dosing and periodically while on treatment. The labeling states that patients should also be monitored for elevated liver enzymes, cholelithiasis and pituitary hormone deficiencies.

CPT Codes / HCPCS Codes / ICD-9 Codes

**Octreotide (Sandostatin):**

**Other CPT codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>33615</td>
<td>Repair of complex cardiac anomalies (e.g., tricuspid atresia) by closure of atrial septal defect and anastomosis of atria or vena cava to pulmonary artery (simple Fontan procedure)</td>
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<tr>
<td>33617</td>
<td>Repair of complex cardiac anomalies (e.g., single ventricle) by modified Fontan procedure</td>
</tr>
<tr>
<td>43204</td>
<td>Esophagoscopy, flexible, transoral; with injection sclerosis of esophageal varices</td>
</tr>
<tr>
<td>43400</td>
<td>Ligation, direct, esophageal varices</td>
</tr>
<tr>
<td>43405</td>
<td>Ligation or stapling at gastroesophageal junction for pre-existing esophageal perforation</td>
</tr>
</tbody>
</table>
48150  Pancreatectomy, proximal subtotal with total duodenectomy, partial gastrectomy, choledochoenterostomy and gastrojejunostomy (Whipple-type procedure); with pancreatojejunostomy

48152  without pancreatojejunostomy

48153  Pancreatectomy, proximal subtotal with near-total duodenectomy, choledochoenterostomy and duodenoojejunostomy (pylorus-sparing, Whipple-type procedure); with pancreatojejunostomy

48154  without pancreatojejunostomy

96365 - 96379  IV therapy, subcutaneous infusion, therapeutic injection, and home infusion/specialty drug administration

99601 - 99602

**HCPCS codes covered if selection criteria are met:**

J2353  Injection, octreotide, depot form for intramuscular injection, 1 mg

J2354  Injection, octreotide, nondepot form for subcutaneous or intravenous injection, 25 mcg

**Other HCPCS codes related to the CPB:**

S9338  Home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem

**ICD-9 codes covered if selection criteria are met:**

150.0 - 150.9  Malignant neoplasm of esophagus

151.0 - 151.9  Malignant neoplasm of stomach

152.0 - 154.0  Malignant neoplasm of small intestine including duodenum, colon, and rectosigmoid junction

157.0 - 157.9  Malignant neoplasm of pancreas

162.0 - 162.9  Malignant neoplasm of trachea, bronchus and lung [non-small cell]

164.0  Malignant neoplasm of thymus

194.0  Malignant neoplasm of adrenal gland

194.3  Malignant neoplasm of pituitary gland and craniopharyngeal duct [pituitary adenomas]
209.00 - 209.69
   Neuroendocrine tumors

211.7    Benign neoplasm of the Islets of Langerhans

227.3    Benign neoplasm of pituitary gland and craniopharyngeal duct (pouch)

237.0    Neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct

251.5    Abnormality of secretion of gastrin

253.0    Acromegaly and gigantism

259.2    Carcinoid syndrome

456.0    Esophageal varices with bleeding

456.20   Esophageal varices in diseases classified elsewhere, with bleeding

569.81   Fistula of intestine, excluding rectum and anus [enterocutaneous fistulae of small intestine with volume depletion]

579.3    Other and unspecified postsurgical nonabsorption

787.91   Diarrhea

990      Effects of radiation, unspecified

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

174.0 - 175.9 Malignant neoplasm of breast

185      Malignant neoplasm of prostate [hormone refractory prostate cancer]

193      Malignant neoplasm of thyroid gland

249.00 - 249.91 Secondary diabetes mellitus

250.00 - 250.93 Diabetes mellitus

278.00 - 278.01 Obesity

457.8    Other noninfectious disorders of lymphatic channels [chylothorax in neonates]
530.82  Esophageal hemorrhage [acute non-variceal upper gastrointestinal bleeding]
536.3  Gastroparesis
577.0  Acute pancreatitis
578.0 - 578.9  Gastrointestinal hemorrhage
579.8  Other specified intestinal malabsorption [protein-losing enteropathy following the Fontan operation]
751.69  Other anomalies of gallbladder, bile ducts, and liver [vascular (arterio-venous) malformations of the gastrointestinal tract]
753.12 - 753.14  Polycystic kidney
783.9  Other symptoms concerning nutrition, metabolism, and development hypometabolism [constitutional (idiopathic) tall stature]

Other ICD-9 codes related to the CPB:
042  Human immunodeficiency virus [HIV] disease
251.0 - 251.2  Hypoglycemia
276.50 - 276.52  Volume depletion
560.0 - 560.9  Intestinal obstruction without mention of hernia
571.2  Alcoholic cirrhosis of liver
571.5  Cirrhosis of liver without mention of alcohol
576.4  Fistula of bile duct
577.8  Other specified diseases of pancreas [pancreatic fistula]
787.01  Nausea with vomiting
787.02  Nausea alone
787.03  Vomiting alone
789.00 - 789.9  Abdominal pain
998.6  Persistent postoperative fistula
E933.1  Adverse effect of antineoplastic and immunosuppressive drugs
V58.0  Encounter for radiotherapy
Lanreotide depot injection (Somatuline Depot):

Other CPT codes related to the CPB:

96372 Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular

HCPCS codes covered if selection criteria are met:

J1930 Injection, lanreotide, 1 mg

ICD-9 codes covered if selection criteria are met:

157.0 - 157.9 Malignant neoplasm of pancreas
209.00 - 209.79 Neuroendocrine tumors
253.0 Acromegaly and gigantism [with inadequate response to or can not be treated with surgery and/or radiotherapy]
259.2 Carcinoid syndrome

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

155.0 - 155.2 Malignant neoplasm of liver and intrahepatic bile ducts
185 Malignant neoplasm of prostate [castration resistant]
578.0 - 578.9 Gastrointestinal hemorrhage
753.12 - 753.14 Polycystic kidney
783.9 Other symptoms concerning nutrition, metabolism, and development hypometabolism [constitutional (idiopathic) tall stature]

Other ICD-9 codes related to the CPB:

251.0 - 251.2 Hypoglycemia
401.0 - 401.9 Hypertension
784.0 Headache
787.01 - 787.03 Nausea and vomiting
790.29 Hyperglycemia

The above policy is based on the following references:


73. Goldfinger SE, Strosberg JR. Treatment of the carcinoid syndrome. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed June 2012.


77. Weiss RE, Refetoff S. Thyrotropin (TSH)-secreting pituitary adenomas. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed June 2013.

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