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Somatostatin Analogs [Medicare]

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

Number: 0693m

Commercial CPB (0693.html) | Medicare CPB

Medicare Part B Step Therapy Criteria

Signifor LAR and **Somavert**, for the indication listed below:

- Treatment of acromegaly in members who have inadequate response to surgery or radiation therapy or for whom these therapies are not appropriate

  Are not covered for new starts, unless the member meets ANY of the following:

  1. Inadequate response to a trial of Sandostatin LAR or Somatuline Depot
  2. Intolerable adverse event to Sandostatin LAR or Somatuline Depot
  3. Sandostatin LAR or Somatuline Depot is contraindicated for the member.

Policy

Policy History

Effective: 01/01/2022

Next Review: 01/27/2022

Definitions

Additional Information

Clinical Policy Bulletin Notes

Note: Requires Precertification:

Precertification of octreotide acetate (Bynfezia Pen, Sandostatin, Sandostatin LAR), lanreotide (Somatuline), pasireotide diaspartate (Signifor), and pasireotide pamoate (Signifor LAR) is required of all Aetna participating providers and members in applicable plan designs. For precertification of these products, call (866) 752-7021 (Commercial), (866) 503-0857 (Medicare), or fax (866) 267-3277.

Octreotide (Bynfezia Pen, Sandostatin, Sandostatin LAR Depot)

I. *Criteria for Initial Approval*

Aetna considers octreotide (Bynfezia Pen, Sandostatin, Sandostatin LAR Depot) medically necessary for members with *any* of the following indications:

A. Acromegaly - considered medically necessary 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; *and*
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. Acquired immune deficiency syndrome (AIDS)-associated diarrhea - treatment of AIDS-associated severe secretory diarrhea when anti-microbial (eg. ciprofloxacin or metronidazole) or anti-motility agents (eg. loperamide or diphenoxylate and atropine) have become ineffective;

C. Bowel obstruction in terminal cancer - management of gastrointestinal (GI) symptoms (e.g., nausea, pain, vomiting) of inoperable bowel obstruction in members with terminal cancer;

D. Carcinoid syndrome - for treatment when used in *any* of the following clinical settings:

1. As a single agent; *or*
2. In combination with telotristat for persistent diarrhea due to poorly controlled carcinoid syndrome; *or*
3. In combination with other systemic therapy options for persistent symptoms such as flushing or diarrhea, or for progressive disease;

E. Chemotherapy- or radiation-induced diarrhea - for treatment when *all* of the following criteria are met:

1. Member is receiving treatment with chemotherapy or radiation; *and*
2. Member has Grade 3 or greater diarrhea according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE);*;

F. Congenital hyperinsulinism (CHI)/persistent hyperinsulinemic hypoglycemia of infancy (octreotide and Sandostatin only) - treatment of CHI and persistent hyperinsulinemic hypoglycemia in an infant;

G. Enterocutaneous fistulae - management of volume depletion from enterocutaneous fistulae;

H. Gastroesophageal varices - treatment of acute bleeding of gastroesophageal varices associated with cirrhosis;

I. Islet cell tumors - for stabilization of blood glucose levels in members with functioning islet cell tumors (e.g., insulinomas or glucagonomas);

J. Neuroendocrine tumors (NETs) - considered medically necessary for *any* of the following:

1. Tumors of the gastrointestinal (GI) tract (carcinoid tumor) - treatment of locoregional advanced or metastatic NETs of the GI tract or unresected primary gastrinoma; *or*
2. Tumors of the thymus (carcinoid tumor) - treatment of unresectable or metastatic NETs of the thymus; *or*
3. Tumors of the lung (carcinoid tumor) - treatment of unresectable or metastatic NETs of the lung; *or*

4. Tumors of the pancreas - treatment of NETs of the pancreas;

K. Pancreatic fistulas - prevention and treatment of pancreatic fistulas following pancreatic surgery;
L. Pheochromocytoma and paraganglioma - for treatment of locally unresectable or metastatic pheochromocytoma and paraganglioma;
M. Pituitary adenomas;
N. Short-bowel syndrome - treatment of short bowel syndrome when the daily intravenous fluid requirement is greater than 3 liters;
O. Thymomas and thymic carcinomas - for treatment when the requested drug is used as a second-line therapy with or without prednisone in *any* of the following clinical settings:

1. Unresectable disease following first-line chemotherapy for potentially resectable locally advanced disease, solitary metastasis, or ipsilateral pleural metastasis; *or*
2. Extrathoracic metastatic disease;

P. Vasoactive intestinal peptide tumors (VIPomas) - for management of symptoms related to hormone hypersecretion of VIPomas;
Q. Zollinger-Ellison syndrome.

Aetna considers octreotide experimental and investigational for all other indications (for additional information, see Experimental and Investigational and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of octreotide therapy medically necessary for the following:

A. Acromegaly - when the member's IGF-1 level has decreased or normalized since initiation of therapy; *or*
B. Carcinoid syndrome, VIPomas, AIDS-associated diarrhea, bowel obstruction, chemotherapy/radiation-induced diarrhea, islet

cell tumors, and Zollinger-Ellison syndrome - when the member is experiencing clinical benefit as evidenced by improvement or stabilization in clinical signs and symptoms since initiation of therapy; *or*

C. All other indications - member must meet all initial authorization criteria.

Lanreotide Depot Injection (Somatuline Depot)

I. *Criteria for Initial Approval*

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

A. Acromegaly - considered medically necessary 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; *and*
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 - treatment of carcinoid syndrome when used in *any* of the following clinical settings:

1. As a single agent; *or*
2. In combination with telotristat for persistent diarrhea due to poorly controlled carcinoid syndrome; *or*
3. In combination with other systemic therapy options for persistent symtpoms such as flushing or diarrhea, or for progressive disease;

C. Neuroendocrine tumors (NETs) - considered medically necessary for *any* of the following:

1. Tumors of the gastrointestinal (GI) tract (carcinoid tumor) - treatment of locoregional advanced or metastatic NETs of the GI tract or unresected primary gastrinoma; *or*
2. Tumors of the thymus (carcinoid tumor) - treatment of unresectable or metastatic NETs of the thymus; *or*
3. Tumors of the lung (carcinoid tumor) - treatment of unresectable or metastatic NETs of the lung; *or*
4. Tumors of the pancreas - treatment of NETs of the pancreas; *or*
5. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) - for treatment of unresectable, well- or moderately-differentiated, locally advanced or metastatic GEP-NETs;

D. Pheochromocytoma and paraganglioma - for treatment of locally unresectable or metastatic pheochromocytoma and paraganglioma;
E. Zollinger-Ellison syndrome.

Aetna considers lanreotide depot injection experimental and investigational for all other indications (for additional information, see Experimental and Investigational and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of lanreotide depot (Somatuline Depot) therapy medically necessary for the following:

A. Acromegaly - continuation of therapy for acromegaly when the member's IGF-1 level has decreased or normalized since initiation of therapy;
B. Carcinoid syndrome and Zollinger-Ellison syndrome - when the member is experiencing clinical benefit as evidenced by improvement or stabilization in clinical signs and symptoms since starting therapy;
C. All other indications - members (including new members) must meet all initial authorization criteria.

Pasireotide Diaspartate (Signifor)

I. *Criteria for Initial Approval*

Aetna considers pasireotide diaspartate solution for subcutaneous injection (Signifor) medically necessary for Cushing's disease/syndrome for members who either have had surgery that was not curative or for members who are not candidates for surgery.

Aetna considers pasireotide diaspartate experimental and investigational for all other indications (for additional information, see Experimental and Investigational and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of pasireotide diaspartate (Signifor) therapy medically necessary for members with Cushing's disease/syndrome who meet one of the following criteria:

A. Lower urinary free cortisol levels since the start of therapy; *or*
B. Lower cortisol levels since the start of therapy per one of the following tests (if UFC is not an appropriate measure due to the member's condition):

    1. Late-night salivary cortisol; *or*
    2. 1 mg overnight dexamethasone suppression test (DST); *or*
    3. Low dose DST (2mg per day for 48 hours); *or*

C. Improvement in signs or symptoms of the disease.

Pasireotide Pamoate (Signifor LAR)

I. *Criteria for Initial Approval*

Aetna considers pasireotide pamoate for intramuscular injection (Signifor LAR) medically necessary for the following indications:

A. Acromegaly - treatment 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; *and*
2. Member had an inadequate or partial response to surgery or there is a clinical reason why the member has not had surgery;

B. Cushing's syndrome/disease - for treatment when the member has had surgery that was not curative or the member is not a candidate for surgery.

Aetna considers pasireotide pamoate experimental and investigational for all other indications (for additional information, see Experimental and Investigational and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of pasireotide pamoate for intramuscular injection (Signifor LAR) therapy medically necessary for the following:

A. Acromegaly - when the member's IGF-1 level has decreased or normalized since initiation of therapy;
B. Cushing syndrome/disease - when member meets all initial authorization criteria.

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

* The NCI definitions for diarrhea are, using a grading system: *Grade 1*: mild diarrhea, 2-3 stools above normal per day; *Grade 2:* mild to moderate: 4 to 6 stools above normal per day; *Grade 3*: moderate severe to severe: 7 or more stools above normal; and *Grade 4* is severe: life-threatening consequences; urgent intervention indicated.

Note: see Pharmacy Clinical Policy Bulletin (PCPB) for Mycapssa (octreotide delayed-release capsule)

For Aetna's CPB on OctreoScan, please see CPB 0168 - Tumor Scintigraphy (../100_199/0168.html).

For Somavert (pegvisomant), see also CPB 0170 - Growth Hormone (GH) and Growth Hormone Antagonists (../100_199/0170.html) or CPB 0170m - Growth Hormone (GH) and Growth Hormone Antagonists [Medicare] (../100_199/0170m.html).

Dosage and Administration

Bynfezia Pen

2,500 mcg/mL octreotide acetate injection is available as 2.8 mL single-use pen for subcutaneous use.

The FDA-approved labeling of Bynfezia Pen (octreotide acetate) has the following recommendations regarding dosing:

- Acromegaly: initiate dosage at 50 mcg three times daily. Typical dosage is 100 mcg three times a day.
- Carcinoid Tumors: 100-600 mcg daily in 2-4 divided doses for first 2 weeks. In clinical studies, the median daily maintenance dosage was approximately 450 mcg, but clinical and biochemical benefits were obtained in some individuals with as little as 50 mcg, while others required doses up to 1,500 mcg daily. Experience with doses above 750 mcg daily is limited.
- VIPomas: 200-300 mcg daily in 2-4 divided doses for first 2 weeks. Adjust the dosage to achieve a therapeutic response; daily dosage is 150 mcg to 750 mcg but usually doses above 450 mcg daily are not required.

Source: Sun Pharmaceuticals Industries, 2020

Sandostatin Dosing

Octreotide acetate injection is available in ampules and vials containing:

- 50 mcg/mL ampule
- 100 mcg/mL ampule
- 500 mcg/mL ampule

Octreotide acetate injection is available in multi dose vials containing:

- 200 mcg/mL vial
- 1000 mcg/mL vial

Octreotide acetate injection is available in a single dose syringe as follows:

- 50 mcg/mL
- 100 mcg/mL
- 500 mcg/mL

Octreotide acetate is available as Sandostatin LAR Depot in single dose vials:

- 10 mg
- 20 mg
- 30 mg

The FDA-approved labeling of Sandostatin (octreotide acetate) injection has the following recommendations regarding dosage and administration:

- Individuals not currently receiving Sandostatin Injection subcutaneously:
    - Acromegaly: 50 mcg three times daily Sandostatin Injection subcutaneously for 2 weeks followed by Sandostatin LAR Depot 20 mg intragluteally every 4 weeks for 3 months.
    - Carcinoid Tumors and VIPomas: Persons not currently receiving octreotide acetate should begin therapy with Sandostatin Injection given subcutaneously. The suggested daily dosage for carcinoid tumors during the first 2 weeks of therapy ranges from 100-600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg). Some individuals may require doses up to

1500 mcg/day. The suggested daily dosage for VIPomas is 200-300 mcg in 2-4 divided doses (range 150-750 mcg); dosage may be adjusted on an individual basis to control symptoms but usually doses above 450 mcg/day are not required.

Note: Sandostatin LAR Depot should never be administered intravenously or subcutaneously and should be administered by a trained healthcare provider.

- Individuals currently receiving Sandostatin Injection subcutaneously can be switched to Sandostatin LAR Depot per below:

  - Acromegaly: 20 mg intragluteally every 4 weeks for 3 months.
  - Carcinoid Tumors and VIPomas: 20 mg intragluteally every 4 weeks for 2 months.

- Renal Impairment, individuals on dialysis: 10 mg every 4 weeks
- Hepatic Impairment, individuals with cirrhosis: 10 mg every 4 weeks.

Source: Mylan, 2019; Novartis, 2020.

Somatuline Depot Dosing

Lanreotide is available as Somatuline Depot Injection as 60 mg, 90 mg, and 120 mg in a pre-filled syringe.

The FDA-approved labeling of Somatuline Depot (lanreotide) injection has the following recommendations regarding dosage and administration:

- Deep subcutaneous injection only. Intended for administration by a healthcare provider.
- Acromegaly: recommended starting dose is 90 mg every 4 weeks for 3 months. After 3 months, dosage may be adjusted based on GH and/or IGF-1 levels. Dose range is 60 mg to 120 mg.

  - Individuals who are controlled on Somatuline Depot 60 or 90 mg may be considered for an extended dosing interval of 120 mg every 6 or 8 weeks.
  - GH and IGF-1 levels should be obtained 6 weeks after this change in dosing regimen to evaluate persistence of individual's response.
  - Moderate and Severe Renal and Hepatic Impairment: Initial dose is 60 mg every 4 weeks for 3 months. Adjust thereafter based on GH and/or IGF-1 levels.

- GEP-NETs: 120 mg every 4 weeks. Somatuline Depot has not been studied in persons with hepatic impairment for this indication.
- Carcinoid Syndrome: 120 mg every 4 weeks. If individual is already being treated with Somatuline Depot for GEP-NET, do not administer an additional dose for treatment of carcinoid syndrome.

Source: Ipsen Biopharmaceuticals, 2019

Signifor Dosing

Pasireotide is available as Signifor for injection in 0.3 mg/mL, 0.6 mg/mL, and 0.9 mg/mL single-dose ampules.

Cushing's Disease:

- The recommended initial dosage of Signifor (pasireotide) is 0.6 mg or 0.9 mg given by subcutaneous injection twice-daily. The dosage range is 0.3 mg to 0. 9 mg twice-daily based on treatment response, tolerability, and hepatic impairment.

Source: Novartis, 2020

Signifor LAR Dosing

Pasireotide pamoate for injectable suspension is available as Signifor LAR in 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg, powder in a vial to be reconstituted with the provided 2 mL diluent. Intended to be administered via intramuscular injection by a trained healthcare provider.

Acromegaly:

- The recommended initial dose of Signifor LAR for the treatment of acromegaly is 40 mg administered by intramuscular injection once every 4 weeks (every 28 days).
- The dose may be increased to a maximum of 60 mg for persons who have not normalized growth hormone (GH) and/or age and sex adjusted insulin-like growth factor-1 (IGF-1) levels after 3 months of treatment with Signifor LAR at 40 mg and who tolerate this dose.
- Hepatic impairment

    - Child-Pugh B: Recommended initial dose is 20 mg once every 4 weeks and maximum dose is 40 mg once every 4 weeks.
    - Child-Pugh C: Avoid use in these individuals

Cushing's Disease:

- The recommended initial dose of Signifor LAR for the treatment of Cushing's disease is 10 mg administered by intramuscular injection once every 4 weeks (every 28 days).
- Following 4 months of treatment with the initial dose of 10 mg once every 28 days, the dose may be increased for persons who have not normalized 24-hour urinary free cortisol (UFC) and who tolerate this dose, up to a maximum dose of 40 mg once every 28 days.
- Hepatic impairment

    - Child-Pugh B: Recommended initial dose is 10 mg once every 4 weeks and maximum dose is 20 mg once every 4 weeks.
    - Child-Pugh C: Avoid use in these individuals.

Source: Novartis, 2020.

Experimental and Investigational

Octreotide

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 (not an all-inclusive list):

1. Acute pancreatitis, treatment; *or*
2. Breast cancer, treatment of advanced breast carcinoma; *or*
3. Chylothorax, treatment of chylothorax in neonates; *or*
4. Congenital lymphedema, treatment; *or*
5. Craniopharyngioma-related hypothalamic obesity; *or*
6. Crohn's disease-associated refractory diarrhea, *or*
7. Cirrhosis-associated hyponatremia; *or*
8. Diabetes mellitus management (e.g., control of an excess of pro-angiogenic factors in diabetes-associated retinal complications); *or*
9. Dumping syndrome; *or*
10. Gastric paresis, treatment; *or*
11. Gastro-intestinal (GI) bleeding in left ventricular assist device recipients; *or*
12. Hepatocellular carcinoma (HCC), treatment; *or*
13. Idiopathic intracranial hypertension; *or*
14. Lymphorrhea reduction in gynecological malignancies; *or*
15. Non-variceal upper GI bleeding, treatment of acute bleeding; *or*
16. Obesity, management (e.g., control of hyperinsulinemia); *or*
17. Pancreaticoduodenectomy, management of individuals undergoing pancreaticoduodenectomy (Whipple's procedure); or
18. Polycystic kidney disease, treatment; *or*
19. Prostate cancer, management of hormone refractory prostate cancer; *or*
20. Protein-losing enteropathy following the Fontan operation, treatment; *or*
21. Small cell lung cancer, salvage therapy; *or*
22. Thyroid cancer, treatment; *or*
23. Thyroid eye disease, treatment; *or*
24. Tumor-induced osteomalacia; *or*
25. Vascular (arterio-venous) malformations of the gastro-intestinal tract (e.g., cecal AV malformation), treatment.

Lanreotide Depot Injection

Aetna considers lanreotide depot injection experimental and investigational for all other indications because its effectiveness for these indications has not been established, including (not an all-inclusive list):

1. Focal forms of congenital hyperinsulinemia treatment;
2. GI bleeding treatment;
3. Hepatocellular carcinoma (HCC) treatment;
4. High-output stoma;
5. Polycystic kidney disease treatment;
6. Prevention and management of high-output ileostomy after colorectal cancer surgery;
7. Prostate cancer - treatment of castration-resistant prostate cancer.

Pasireotide

I. Aetna considers pasireotide diaspartate for subcutaneous injection (Signifor) experimental and investigational for uveal melanoma.

II. Aetna considers pasireotide pamoate for intramuscular injection (Signifor LAR) experimental and investigational for uveal melanoma.

III. Aetna considers pasireotide experimental and investigational for the following indications (not an all-inclusive list):

A. Reduction of the development of post-operative pancreatic fistula
B. Treatment of dopamine-resistant prolactinoma
C. Treatment of dumping syndrome after bariatric or upper GI cancer surgery
D. Treatment of GI angiodysplasias
E. Treatment of hepatic cysts
F. Treatment of hepatocellular carcinoma
G. Treatment of medullary thyroid cancer
H. Treatment of metastatic melanoma
I. Treatment of prostate cancer
J. Treatment of unresectable neuroendocrine tumors with hepatic metastases.

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.

Octreotide

U.S. Food and Drug Administration (FDA)-Approved Indications

- Octreotide acetate/Sandostatin/Bynfezia Pen:
  - Indicated to reduce blood levels of growth hormone and IGF-1 (somatomedin C) in acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses.
  - Indicated for the symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.
  - Indicated for the treatment of the profuse watery diarrhea associated with vasoactive intestinal peptide (VIP)-secreting tumors.

- Sandostatin LAR: Sandostatin LAR Depot is indicated in patients in whom initial treatment with Sandostatin injection has been shown to be effective and tolerated.
  - Indicated for 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.
- Indicated for long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.
- Indicated for long-term treatment of the profuse watery diarrhea associated with vasoactive intestinal peptide (VIP)-secreting tumors.

Compendial Uses

- Neuroendocrine tumors (NETs):
  - Tumors of the gastrointestinal (GI) tract, lung, and thymus (carcinoid tumors)
  - Tumors of the pancreas
- Pheochromocytoma and paraganglioma
- Thymomas and thymic carcinomas
- Congenital hyperinsulinism (CHI)/persistent hyperinsulinemic hypoglycemia of infancy (PHHI)5 (octreotide and Sandostatin only)
- Acquired immune deficiency syndrome (AIDS)-associated diarrhea
- Inoperable bowel obstruction
- Chemotherapy- and radiation-induced diarrhea
- Enterocutaneous fistula
- Gastroesophageal varices
- Islet cell tumors
- Pancreatic fistulas
- Pituitary adenoma
- Short bowel syndrome
- Zollinger-Ellison syndrome

Octreotide is the acetate salt of a cyclic octapeptide. It is a long-acting octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. Octreotide is a more potent inhibitor of growth hormone, glucagons, and insulin than somatostatin. It suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

Octreotide is indicated for long-term maintenance therapy in acromegalic patients, for long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors, and for long-term treatment of the profuse waterydiarrhea associated with VIP-secreting tumors. Other medical alternatives exist including, but not limited to: transphenoidal surgical resection; radiation therapy; dopamine agonists; serotonin antagonists; somatostatin analogues; GH receptor antagonists; and anti-diarrhea agents (e.g. loperamide, diphenoxylate-atropine).

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 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.

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-operable 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-operable 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. Szilagyi 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 fistulae by Jamil et al (2004) concluded that " [s]omatostatin and its analogues 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.

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.

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.

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.

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 angiodysplasia 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 % 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, 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.

Yin and colleagues (2017) noted that the influence of somatostatin/octreotide treatment on outcomes of neonates with congenital chylothorax remains controversial. In an observational study, these investigators retrospectively reviewed their experience with somatostatin/octreotide therapy in neonates with this very rare disease. A total of 14 neonates with congenital chylothorax who were treated with somatostatin (3.5 to 7 μg/kg/hour, before 2016) or octreotide (1 to 6 μg/kg/hour, after January 2016), along with traditional management between 2013 and 2016, were retrospectively reviewed. Their daily volumes of pleural drainage and parameters of respiratory support were recorded, and the potential side effects of somatostatin/octreotide were screened; 4 patients (28.6 %) had a unilateral presentation of pleural effusion, whereas 10 patients (71.4 %) had a bilateral presentation; 12 patients (85.7 %) survived until discharge without later recurrence or death, whereas 2 patients (14.3 %) died within the first 3 days after birth. Somatostatin/octreotide treatment was maintained for a median period of 6 days (range of 1 to 16 days). The chest tube was removed after a median duration of 14 days (range of 2 to 51 days), and no patient needed pleurodesis or thoracic duct ligation surgery. The average daily drain output within 3 days post-treatment (median of 62 ml, range of 10 to 651 ml) was significantly lower than that before treatment (median 133 ml, range of 70 to 620 ml) ($p = 0.002$). The need for ventilation support was reduced in most patients (85.7 %) after the initiation of somatostatin/octreotide therapy. No serious side effects were identified. The authors concluded that somatostatin/octreotide treatment reduced pleural drainage and respiratory support without significant side effects.

Moreover, these researchers stated that further RCTs with more patients are needed to determine the benefits of somatostatin/octreotide in neonates with congenital chylothorax.

The authors stated that this study had several drawbacks. First, it was a retrospective study and included only a small number of patients; however, it might be one of the largest available studies performed in neonates with congenital chylothorax. Due to the rarity of congenital chylothorax, patients with both somatostatin and octreotide treatment were included in this study, because these drugs share similar mechanisms. The majority of neonates (n=11) received somatostatin and only a few patients received octreotide (n=3); thus, these investigators were unable to identify the differences between somatostatin and octreotide effects due to the small number of cases. Second, the selection bias of the patient group could occur and the study lacked a control group. When these researchers screened the neonates, they found several patients with congenital chylothorax treated without somatostatin/octreotide; however, they did not use them as controls, because most patients only had small pleural effusions and responded relatively well to dietary control. Finally, the follow-up data need to be interpreted with caution, because 67 % of hospital survivors were unable to come to the authors' clinic, and only the results of chest X-ray and ultrasound (US) imaging performed at their local hospitals were obtained over the phone.

In January 2020, a new administration option became available for octreotide acetate. Bynfezia Pen is a somatostatin analogue injection for subcutaneous use that is available as disposable single-patient-use pen with a deliverable volume of 2.8 mL. The FDA-approved indications for Bynfezia Pen is the same as Sandostatin (octreotide acetate): acromegaly, carcinoid tumors and vasoactive intestinal peptide tumors (VIPomas). Limitations for use include:

- In acromegaly, the effect of Bynfezia Pen on improvement in clinical signs and symptoms, reduction in tumor size and rate of growth, has not been determined;
- In carcinoid syndrome and VIPomas, the effect of Bynfezia Pen on size, rate of growth and development of metastases, has not been determined (same as Sandostatin and Sandostatin LAR Depot).

Octreotide for the Treatment of Chyle Leak Following Oropharyngectomy

In a prospective study, Jain et al (2015) examined the effectiveness of octreotide in managing chyle fistula neck and its effect on duration of hospitalization. A total of 19 patients with chyle fistula following neck dissection over a period of 10 years were included in the study. All the patients first underwent conservative management of the chyle leak, including suction drainage, pressure dressings, bed rest, and nutritional modifications. In all of the cases, chyle leak persisted despite conservative management. Octreotide was started in a dose of 100 µg subcutaneously every 8 hours for 5 days in cases with low-output leaks and for 7 days in cases with high-output leaks. In all of the cases, the duration of chyle leak after starting treatment with octreotide and the duration of hospitalization was recorded. Chyle leak stopped in all the cases using octreotide. The mean duration of hospitalization was 13.8 days. The authors concluded that chyle leak stopped within 5 days of starting octreotide in the low-output cases and within 7 days in the high-output cases. This allowed early resumption of a regular oral diet and reduced morbidity associated with chyle fistula. The rapid response and minimal side effect profile made octreotide a promising addition to the medical management of a chyle fistula.

Swanson et al (2015) noted that chyle fistula is an uncommon complication of neck surgery. A variety of management strategies have been described, including diet restriction, parenteral nutrition, use of pressure dressings, and revision surgery. Octreotide has been used with success in patients with neck and thoracic chyle fistulas, but data regarding efficacy in neck chyle fistulas are lacking. In a retrospective study, these researchers evaluated the efficacy of octreotide for use in patients with post-operative chyle fistulas. They carried out a retrospective review of 12 patients who received octreotide for neck chylous fistula after neck dissection was performed during the period 2004 through 2014 at 2 tertiary care academic hospitals. Patients with post-operative neck chyle fistulas were given a restricted diet and subcutaneous octreotide. The main outcome was fistula closure rate, defined as fistula resolution without surgical intervention. Secondary outcomes of fistula duration (days from detection until resolution), length of hospital stay (surgery to discharge), and treatment complications were

also examined. All 12 patients had resolution of their neck chyle fistula with octreotide therapy without need for revision surgery. Mean (SD) hospital stay was 8.7 (4.76) days, with a range of 3 to 18 days. The chyle fistula resolved after a mean (range) 5.5 (2 to 11) days. Self-resolving nausea was encountered in 1 patient from octreotide use, and 1 patient developed a salivary fistula as a result of the chylous fistula. The authors concluded that in these patients, octreotide was safe and effective in resolving neck chylous fistulas. Octreotide therapy appeared superior to traditional conservative measures of diet restriction and pressure dressings when compared with literature rates.

Chan et al (2017) stated that post-operative chylous fistula after neck dissection is an uncommon complication associated with significant patient morbidity. Octreotide acetate is a somatostatin analog established in the treatment of chylothorax; however, its utility in the management of cervical chylous fistulae has not been fully evaluated. These investigators hypothesized that chylous fistula can be managed by a combination of octreotide and peripheral total parenteral nutrition (TPN). They carried out a retrospective review of cases compiled at their institution from 2009 to 2015. A total of 10 patients, all men, were identified as having a post-operative chylous fistula after a neck dissection. All patients were treated with peripheral TPN and intravenous (IV) octreotide. Mean age of the patients was 63.0 years (range of 49 to 82); 5 (50.0 %) had a neck dissection for the management of metastatic nasopharyngeal carcinoma and had previous neck irradiation. In 8 (80 %) patients, chylous fistula occurred in the left neck; 7 (70.0 %) of the leaks occurred within the first 2 post-operative days; 8 (80 %) leaks were controlled using TPN and octreotide, with 2 (20 %) patients requiring surgical intervention. No factors were significant in the successful conservative management of chylous fistulae; 1 patient with a chylous fistula of 1,800 ml/day was managed successfully without surgical intervention. The authors concluded that the findings of this case-series study suggested that chylous fistulae may be managed conservatively with octreotide and TPN.

Furthermore, an UpToDate review on "Management of chylothorax" (Heffner, 2019) states that "Postoperative chyle leaks are the most common form of chylothorax encountered. While most postoperative leaks are low volume (<1 L per day), some are high volume (>1 L per

day) with the former being treated conservatively and the latter typically treated aggressively with thoracic duct repair/ligation or embolization … In most cases, patients with high volume leaks are treated by complete bowel rest by the administration of parenteral nutrition and surgical repair of the thoracic duct (within hours to days). Some patients may benefit from somatostatin/octreotide while waiting for surgery. The rationale for this approach is that these patients are likely to have major thoracic duct injury which is unlikely to close spontaneously rather than leaks that originate from a smaller thoracic duct tributary which are more likely to undergo spontaneous closure. In addition, early surgical repair avoids severe metabolic or nutritional derangements that are more likely to occur in those with large amounts of chyle loss".

Octreotide for the Treatment of Craniopharyngioma-Related Hypothalamic Obesity

Ni and Shi (2018) noted that craniopharyngiomas (CPs) and their treatment are associated with hypothalamic damage that causes hypothalamic obesity (HO) in 30 to 70 % of cases. Therefore, there is ongoing research regarding solutions for HO, because these patients have unrelenting resistance to basic weight-loss interventions. In a systematic review, these investigators summarized the interventions that are used to treat CP-related HO (CP-HO), including pharmacotherapy and bariatric surgery. The Cochrane Library, Embase, and PubMed databases were searched up to June 2017 for relevant reports; 2 reviewers conducted independent evaluations of the studies identified. A total of 18 articles were included in the systematic review, with 3 reports describing pharmacotherapy in RCTs and 15 reports describing bariatric surgery. Although several studies described effective interventions for treating CP-HO, the evidence base was limited by its low quality and the inability to perform a meta-analysis, which was related to a lack of adequate or integrated data. The authors concluded that octreotide appeared to be a preferred treatment for patients with CP-HO, based on limited data. Gastric bypass surgery may also be suitable for select patients with CP-HO, based on a review of various procedures in this setting. Microsurgical preservation of the hypothalamic structures is mandatory to decrease CP-HO-related morbidity and mortality. Moreover,

these researchers stated that more well-designed studies with adequate analytical power and sufficient follow-up are needed to identify effective strategies for CP-HO treatment.

Octreotide for the Treatment of Gastro-Intestinal Bleeding in Left Ventricular Assist Device Recipients

Hayes et al (2010) noted that gastro-intestinal (GI) bleeding in ventricular assist devices (VADs) has been reported with rotary devices. The pathophysiological mechanisms and treatments are in evolution. These researchers performed a retrospective review of GI bleeding episodes for all VADs implanted at our institution; 5 male patients experienced GI bleeding-age 63.6 ± 3.64 years. VAD type VentrAssist n = 1, Jarvik 2000 n = 2, and HeartWare n = 2. All patients were anti-coagulated as per protocol with anti-platelet agents (aspirin and/or clopidogrel bisulfate [Plavix] and warfarin (therapeutic international normalized ratio 2.0 to 3.5). There was no prior history of gastric bleeding in this group; 10 episodes of bleeding requiring blood transfusion occurred in 5 patients. Some patients had multiple episodes (1 × 5, 1 × 2, 3 × 1). The events occurred at varying times post-VAD implantation (days 14, 21, 26, 107, 152, 189, 476, 582, 669, and 839). Octreotide (a long-acting somatostatin analog that reduces splanchnic arterial and portal blood flow) was administered subcutaneously or intravenously; 3 patients received infusions of adrenaline at 1 μg/min to enhance pulsatility. Anti-coagulation was interrupted during bleeding episodes but successfully introduced post-bleeding event.

Rennyson et al (2013) stated that left ventricular support devices (LVADs) are associated with a propensity toward GI bleeding. A postulated mechanism is related to GI arterio-venous malformations (AVMs) secondary to non-pulsatile flow. The authors describe a case of LVAD-related, GI bleeding successfully treated with a combination of subcutaneous and intra-muscular depot formulations of octreotide.

Coutance et al (2014) reported the case of a 64-year old Jarvik 2000 recipient with a high risk of bleeding (anti-coagulation treatment and acquired von Willebrand disease), who presented with intractable GI bleeding due to severe gastric angiodysplasia. He was successfully treated with long-acting octreotide.

Loyaga-Rendon et al (2015) stated that GI bleeding is the most common cause of re-admission in patients supported by continuous flow LVAD (CF-LVAD). These investigators described their experience in the off-label use of octreotide in the management of recurrent GI bleed in this population. Of 116 patients implanted with a CF-LVAD at the authors' institution, 7 had recurrent GI bleeding unresponsive to conventional management and were started in chronic octreotide injections. Hospitalizations due to GI bleeding, number of packed red blood cells (RBCs) transfused, and number of endoscopic procedures were compared 3 months before and after octreotide treatment. In the overall cohort, there were no differences in these 3 end-points. When 1 patient with differing characteristics was excluded from the analysis there was a trend ($p = 0.06$) to a reduction of hospitalizations due to GI bleeding, number of blood transfusions, and number of endoscopic procedures. The authors concluded that octreotide exhibited a favorable trend in the frequency of admissions, blood transfusions, and endoscopic procedures in most patients with recurrent GI bleed. Moreover, they stated that further prospective studies are needed to clarify its benefits in this population.

Malhotra et al (2017) noted that patients with implanted continuous, non-pulsatile, LVADs have increased the occurrence of GI bleeding (GIB). Although the pathophysiology is multi-factorial, there are few treatments beyond supportive care. Octreotide acetate is a somatostatin analog that reduces GIB in various patient populations. However, there are sparse case series that suggest octreotide acetate may reduce GIB in LVAD patients. This 10-patient, 28 week phase-I study evaluated the safety and tolerability of octreotide acetate long-acting release (LAR) 20 mg depot injection every 4 weeks until week 16 after LVAD placement. Secondary aims were occurrence of GIB and measurement of vascular endothelial growth factor, fibrinogen, von Willebrand factor, and platelet aggregation across the study period. A total of 10 patients were enrolled, and 8 completed the study. The 2 study drop-outs were not related to octreotide. None of the patients experienced side effects or safety concerns related to octreotide nor did GIB occur in the study population. Vascular endothelial growth factor (VEGF) levels were maintained in the reference range throughout the duration of the study. There did appear to be laboratory evidence of acquired von Willebrand syndrome, with mildly

low platelet aggregation studies. The authors concluded that octreotide acetate LAR 20 mg depot injection was safe and effective in this population. This was a phase-I study with a small sample size (n = 8).

Shah et al (2017) stated that GI bleeding is one of the most common complications after CF-LVAD implantation. More than 1/3 of patients with incident bleed go on to develop recurrent GI bleeding. Octreotide is proposed to reduce the risk of recurrent GI bleeding in this population. In a multi-center, retrospective analysis, these researchers evaluated 51 CF-LVAD patients who received secondary prophylaxis with octreotide after their index GI bleed from 2009 to 2015. All patients had a hospitalization for GI bleed and received octreotide after discharge. Patient demographics, medical and medication history, and clinical characteristics of patients who re-bled after receiving octreotide were compared with non-re-bleeders. These data were also compared with matched historical control patients previously enrolled in the HMII (HeartMate II) clinical trials, none of whom received octreotide, to provide a context for the bleeding rates; 12 patients (24 %) who received secondary octreotide prophylaxis developed another GI bleed, whereas 39 (76 %) did not. There were similar inter-group demographics; however, significantly more bleeders had a previous GI bleeding history before LVAD placement (33 % versus 5 %; p = 0.02) and greater frequency of angio-dysplasia confirmed during endoscopy (58 % versus 23 %; p =0.03). Fewer patients in this study experienced a recurrent GI bleed compared with a matched historical control group that did not receive octreotide (24 % versus 43 %; p = 0.04). The authors concluded that patients with CF-LVAD receiving secondary prophylaxis with octreotide had a significantly lower GI bleed recurrence compared with historical controls not treated with octreotide. Moreover, they stated that additional prospective studies are needed to confirm these data.

Molina et al (2018) stated that LVADs offer a therapeutic strategy for patients with end-stage heart failure. Increased device utilization has also increased the incidence of device-related complications including GIB. Multiple mechanisms have been proposed in the pathophysiology of CF-LVAD-associated GIB including physiologic changes associated with high shear and non-pulsatile flow such as GI AVMs and acquired von Willebrand syndrome. Strategies to minimize the morbidity and mortality of LVAD-associated GIB are needed. Octreotide has been described as

an adjunct to current therapies and interventions. Factors that contribute to LVAD-associated GIB may be targeted by the pharmacologic effects of octreotide, including improved platelet aggregation, increased vascular resistance, and decreased splanchnic circulation. Octreotide has demonstrated clinical benefit in several case series and clinical trials for the treatment of LVAD-associated GIB.

Juricek et al (2018) noted that recurrent GIB is one of the most significant adverse events in patients with LVADs. These researchers enrolled LVAD patients who had received an intra-muscular injection of 20 mg octreotide every 4 weeks as secondary prevention for recurrent GIB despite conventional medical therapies and repeated transfusions. The frequency of GIB and other associated clinical outcomes before and during octreotide therapy were compared. A total of 30 LVAD patients (66.4 ± 8.8 years old, 16 men [53 %]) received octreotide therapy for 498.8 ± 356.0 days without any octreotide-associated adverse events (AEs). The frequency of GIB was decreased significantly during octreotide therapy (from 3.4 ± 3.1 to 0.7 ± 1.3 events/year; $p < 0.001$), accompanied by significant reductions in RBC and flesh frozen plasma transfusions, days in hospital, and need for endoscopic procedures ($p < 0.05$ for all). The authors concluded that octreotide therapy reduced the frequency of recurrent gastrointestinal bleeding and may be considered for secondary prevention.

The authors stated that this study had several drawbacks. This was a prospective study with a moderate cohort size (n = 30)from a single center. Furthermore, the study was non-randomized, and pre-treatment data from the same patients were used to assess the prospective effects of octreotide. A randomized control study would be best method to evaluate the use of octreotide in this patient population, but may not be practical given the severe consequences of refractory GI bleeding on patient quality-of-life. The timing of initiation of octreotide therapy (both in terms of time from LVAD implant and in terms of number of prior GI bleeds) varied widely among patients. These time biases may have affected the outcomes. Most of the enrolled patients were treated with HeartMate II or HVAD. These findings may not simply be adopted in patients with other devices such as HeartMate 3.

Octreotide for the Treatment of Idiopathic Intracranial Hypertension

In a prospective, open-label trial, Panagopoulos and colleagues (2007) examined the effects of octreotide in patients with idiopathic intracranial hypertension (IIH). This study included 26 patients with symptoms and signs of IIH; and were investigated by means of brain MRI and lumbar puncture. Octreotide was administered subcutaneously, at an initial dose of 0.3 mg/day; and was gradually increased until headache was relieved (upper-dose limit: 1 mg/day). Treatment with octreotide at 1 mg/day was administered for a maximum of 6 to 8 months and afterwards the dose was gradually tapered. Patients were followed prospectively every month for 3 years; cerebrospinal fluid (CSF) opening pressure was measured before commencement of the treatment and again in the first follow-up examination, on month 1. In all follow-up visits the presence of papilledema was evaluated by fundoscopy; visual fields and visual acuity (VA) were also examined. Overall 24/26 patients improved significantly (92 %). Headache was relieved within days (1 to 10, median of 7 days). Papilledema subsided in all 24 patients, in up to 2 months (35 to 68, median of 45 days). Visual disturbances, initially presenting in 20 of the patients, improved in 18 (90 %). The mean reduction in CSF pressure following treatment was 20.72A +/- 10.7 cmH2O (range of 2 to 48). Patients were followed-up for 3 years after cessation of treatment. No recurrence of papilledema, or any other symptoms, has been observed. The authors concluded that octreotide resulted in a significant and sustained improvement of IIH in these patients. These researchers stated that the findings of this study results suggested that it may be an effective alternative to existing treatments for IIH. These preliminary findings need to be validated by well-designed studies.

In a pilot study, Salpietro and associates (2014) examined the potential IIH endocrine-metabolic co-morbidities by studying the natural (and targeted drug-modified) history of disease in children. Retrospective study (years 2001 to 2010) of clinical records and images and prospective follow-up (years 2010 to 2013) in 15 children (11 girls, 4 boys; aged 5 to 16 years) diagnosed previously as "IIH", according to the criteria for pediatric IIH proposed by Rangwala, at 3 university pediatric centers in northern, central, and southern Italy were carried out. These researchers identified 6 potential endocrine-metabolic co-morbidities including, weight

gain and obesity (n = 5), recombinant growth hormone therapy (n = 3), obesity and metabolic syndrome (n = 1), secondary hyperaldosteronism (n =1), hypervitaminosis A (n = 1), and corticosteroid therapy (n = 1). Response to etiologically targeted treatments (e.g., octreotide, spironolactone,) was documented. The authors concluded that IIH is a protean syndrome caused by various potential (risk and) associative factors. Several conditions could influence the pressure regulation of CSF. An endocrine-metabolic altered homeostasis could be suggested in some IIH patients, and in this context, etiologically targeted therapies (spironolactone) should be considered.

House and Stodieck (2016) noted that IIH is characterized by elevated intracranial pressure without a space-occupying cerebral lesion, venous sinus thrombosis or hydrocephalus and with normally composited CSF. Main symptoms are headache, sight disturbances and potential visual impairment. Weight loss, carbonic anhydrase inhibitors, lumbar punctures with CSF drain, CSF shunting, optic nerve sheath fenestration, and venous sinus stenting are common IIH therapies. These investigators presented the findings of treatment with octreotide on 5 female patients with IIH and a history of failed therapies. Octreotide was administered everyday subcutaneously for 6 months with identified doses high enough to suspend all clinical IIH symptoms. After tapering for 2 months, the further clinical course was to be monitored. All patients were IIH symptom-free under octreotide. After tapering, 1 patient remained IIH symptom-free; 1 patient became IIH symptom-free under IM octreotide after failure of former therapies; 1 patient became IIH symptom-free on low-dose carbonic anhydrase inhibitors; 1 patient had an allergic reaction and paused octreotide, after successful desensitization, toothache developed, forcing octreotide tapering; 1 patient had another shunt revision alleviating IIH symptoms. The authors confirmed that clinical IIH symptoms were suspended during octreotide exposure; 6-month administration could sustainably abolish IIH symptoms; desensitization was possible for octreotide allergy. When IIH symptoms reoccurred following limited-time octreotide administration, re-application of formerly ineffective carbonic anhydrase inhibitors could suspend IIH symptoms. These researchers stated that IM octreotide is a promising, long-term therapeutic option for the treatment of IIH.

Scotton and co-workers (2019) stated that the management of IIH focuses on reducing intracranial pressure to preserve vision and reduce headaches. There is sparse evidence to support the use of some of the drugs commonly used to manage IIH. These researchers evaluated the efficacy of these drugs at lowering intracranial pressure in healthy rats. These investigators measured intracranial pressure in female rats before and after subcutaneous administration of acetazolamide, topiramate, furosemide, amiloride and octreotide at clinical doses (equivalent to a single human dose) and high doses (equivalent to a human daily dose). In addition, they measured intracranial pressure after oral administration of acetazolamide and topiramate. At clinical and high doses, subcutaneous administration of topiramate lowered intracranial pressure by 32 % ($p = 0.0009$) and 21 % ($p = 0.015$), respectively. There was no significant reduction in intracranial pressure noted with acetazolamide, furosemide, amiloride or octreotide at any dose. Oral administration of topiramate significantly lowered intracranial pressure by 22 % ($p = 0.018$), compared to 5 % reduction with acetazolamide ($p = > 0.999$). The authors concluded that these in-vivo studies demonstrated that both subcutaneous and oral administration of topiramate significantly lowered intracranial pressure. Other drugs tested, including acetazolamide, did not significantly reduce intracranial pressure. These researchers stated that future clinical trials evaluating the efficacy and side effects of topiramate in IIH patients would be of interest.

Furthermore, an UpToDate review on "Idiopathic intracranial hypertension (pseudotumor cerebri): Prognosis and treatment" (Lee and Wall,2019) does not mention octreotide as a therapeutic option.

Octreotide for the Treatment of Pheochromocytoma / Paraganglioma

National Comprehensive Cancer Network's Drugs & Biologics Compendium (2019) lists pheochromocytoma / paraganglioma as a recommended indication of octreotide acetate. It is indicated for the treatment of locally unresectable disease or distant metastases if somatostatin receptor positive imaging and symptomatic.

Octreotide for the Treatment of Polycystic Kidney Disease

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 colelithiasis and asthenia, respectively. In the remaining 12 patients octreotide was well-tolerated. Kidney volume increased by 71 +/- 107 ml ($p < 0.05$) on octroetide and by 162 +/- 114 ml ($p < 0.01$) on placebo. The percent increase was significantly lower on octroetide (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.

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.

Meijers and colleagues (2018) noted that autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive cyst formation in both kidneys and loss of renal function, eventually leading to a need for kidney replacement therapy. There are limited therapeutic options. In an open-label, randomized clinical trial with blinded end-point assessment, these researchers examined the effect of lanreotide on the rate of kidney function loss in patients with later-stage ADPKD. This trial included 309 patients with ADPKD from July 2012 to March 2015 at 4 nephrology out-patient clinics in the Netherlands. Eligible patients were 18 to 60 years of age and had an estimated GFR (eGFR) of 30 to 60 ml/min/1.73 m2. Follow-up of the 2.5-year trial ended in August 2017. Patients were randomized to receive either lanreotide (120 mg subcutaneously once every 4 weeks) in addition to standard care (n = 153) or standard care

only (target blood pressure <of less than 140/90 mm Hg; n = 152). Primary outcome was annual change in eGFR assessed as slope through eGFR values during the 2.5-year treatment phase. Secondary outcomes included change in eGFR before versus after treatment, incidence of worsening kidney function (start of dialysis or 30 % decrease in eGFR), change in total kidney volume and change in QOL (range of 1 [not bothered] to 5 [extremely bothered]). Among the 309 patients who were randomized (mean [SD] age of 48.4 [7.3] years; 53.4 % women), 261 (85.6 %) completed the trial. Annual rate of eGFR decline for the lanreotide versus the control group was -3.53 versus -3.46 ml/min/1.73 m2 per year (difference, -0.08 [95 % CI: -0.71 to 0.56]; p = 0.81). There were no significant differences for incidence of worsening kidney function (HR, 0.87 [95 % CI: 0.49 to 1.52]; p = 0.87), change in eGFR (-3.58 versus -3.45; difference, -0.13 ml/min/1.73 m2 per year [95 % CI: -1.76 to 1.50]; p = 0.88), and change in QOL (0.05 versus 0.07; difference, -0.03 units per year [95 % CI: -0.13 to 0.08]; p = 0.67). The rate of growth in total kidney volume was lower in the lanreotide group than the control group (4.15 % versus 5.56 %; difference, -1.33 % per year [95 % CI: -2.41 % to -0.24 %]; p = 0.02); AEs in the lanreotide versus control group included injection site discomfort (32 % versus 0.7 %), injection site papule (5.9 % versus 0 %), loose stools (91 % versus 6.6 %), abdominal discomfort (79 % versus 20 %), and hepatic cyst infections (5.2 % versus 0 %). The authors concluded that among patients with later-stage ADPKD, treatment with lanreotide compared with standard care did not slow the decline in kidney function over 2.5 years of follow-up. These researchers stated that these findings did not support the use of lanreotide for treatment of later-stage ADPKD.

Lanreotide (Somatuline Depot)

U.S. Food and Drug Administration (FDA)-Approved Indications

- Somatuline Depot is indicated for the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option.
- Somatuline Depot is indicated for the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced

or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.
- Somatuline Depot is indicated for the treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analog rescue therapy.

Compendial Uses

- Neuroendocrine tumors (NETs):

  - Tumors of the gastrointestinal (GI) tract, lung, and thymus (carcinoid tumors)
  - Tumors of the pancreas
  - Pheochromocytoma and paraganglioma
  - Zollinger-Ellison syndrome

Lanreotide is an octapeptide analog of natural somatostatin. The mechanism of action is believed to be similar to that of natural somatostatin.

Somatuline Depot (lanreotide) is indicated for: the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy the treatment of adult patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic tumors (GEP-NETs) to improve progression-free survival

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 can not 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.

Lanreotide may reduce gallbladder motility and lead to a gallstone formation therefore, patients may need to be monitored periodically.

Patients treated with lanreotide may experience hypoglycemia or hyperglycemia. Blood glucose levels should be monitored when lanreotide treatment is initiated or when the dose is altered, and antidiabetic treatment should be adjusted accordingly.

Decrease in heart rate may occur. Use with caution in at-risk patients.

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 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.

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.

In December 2014, Somatuline Depot was FDA-approved to improve progression-free survival (PFS) in patients with unresectable, well- or moderately- differentiated locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs). FDA approval for the treatment of GEP-NETs indication was based on a multicenter, randomized, double-blind, placebo-controlled trial of 204 patients (median age 63 yrs) with unresectable, well or moderately differentiated, metastatic or locally advanced, gastroenteropancreatic neuroendocrine tumors. "Patients were randomized to receive Somatuline Depot 120 mg (n=101) or placebo (n=103) every 4 weeks until disease progression, unacceptable toxicity, or a maximum of 96 weeks of

treatment. Randomization was stratified by the presence or absence of prior therapy and by the presence or absence of disease progression within 6 months of enrollment. The major efficacy outcome measure was progression-free survival, defined as time to disease progression as assessed by central independent radiological review using the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) or death. Disease progression was present in 9 of 204 patients (4.4%) in the 6 months prior to enrollment and 29 patients (14%) received prior chemotherapy. Ninety-one patients (45%) had primary sites of disease in the pancreas, with the remainder originating in the midgut (35%), hindgut (7%), or unknown primary location (13%). The majority (69%) of the study population had grade 1 tumors. Baseline prognostic characteristics were similar between arms with one exception; there were 39% of patients in the Somatuline Depot arm and 27% of patients in the placebo arm who had hepatic involvement by tumor of greater than 25%. Patients on the Somatuline Depot arm had a statistically significant improvement in progression-free survival compared to patients receiving placebo" (FDA, 2017).

Lanreotide for the Prevention and Management of High-Output Ileostomy after Colorectal Cancer Surgery

Cuyle and colleagues (2018) stated that patients with stage III and high-risk stage II colorectal cancer (CRC) are advised to initiate adjuvant treatment as soon as feasible and certainly before 8 to 12 weeks after resection of the tumor. A protective ileostomy is often constructed during surgery to protect a primary anastomosis "at risk", especially in rectal cancer surgery. However, up to 17 % of patients with a stoma suffer from high-output, a major complication that can prevent adjuvant treatment implementation or completion. To avoid delay or cancellation of adjuvant therapy after CRC resection, effective strategies must be implemented to successfully treat and/or prevent high-output stoma (HOS). These investigators reported 2 clinical case reports demonstrating the impact and management of HOS in this setting; they also provided a review of the available literature and ongoing clinical studies. The clinical cases described patients with advanced stage CRC and focused on the different strategies for HOS management, presenting their outcome and how each strategy affected the implementation of adjuvant treatment. The patient population with the highest risk of developing HOS was described, along with the rationale for using somatostatin analogs, such as lanreotide, to

treat and prevent high-output. The authors concluded that in patients with CRC and protective ileostomies after primary resection, HOS could be treated with somatostatin analogs in combination with dietary recommendations and Saint Mark's solution. Moreover, these researchers stated that the role of this therapeutic approach as a preventive strategy in patients at high risk of developing HOS, deserves further examination in a prospective, randomized clinical trial.

The authors noted that several clinical trials are currently examining the benefits of somatostatin analogs (SSAs) other than octreotide in HOS. The ongoing LIFE study (EudraCT: 2013-003998-10) is investigating the use of lanreotide to reduce output in patients with high-output enterocutaneous fistula or enterostomy, compared to the standard of care. The ILEHOS study (NCT02354768) is an ongoing multi-center, randomized trial evaluating the efficacy of lanreotide combined with anti-diarrheal drugs as 1st-line treatment in HOS, compared to anti-diarrheal drugs alone. The SOMILEO study (NCT02713776) is an upcoming pilot, double-blind, randomized, placebo-controlled trial that will assess the effect of the SSA pasireotide on the effluent volume of patients with enterostomas. These researchers stated that data coming from these and new clinical studies in the next several years will provide experts with more evidence to create official, consistent guidelines for HOS treatment, and to implement new strategies for the prevention of ileostomy-related complications.

Lanreotide for the Treatment of Focal Forms Congenital Hyperinsulinemia

Dastamani and colleagues (2019) noted that lanreotide is used in the management of a diazoxide-unresponsive diffuse form of congenital hyperinsulinism (CHI). However, no reports of its use in patients with the focal form of CHI exist. These investigators described the use of lanreotide in 3 children with focal forms of DHI. Case 1: A 1-month old boy diagnosed with diazoxide-unresponsive CHI due to a paternal heterozygous ABCC8 gene mutation showed partial response to octreotide; 18F-DOPA-PET/CT scan revealed a focal lesion in the pancreatic head. Surgical removal of the lesion was unsuccessful. He was switched to monthly lanreotide treatment at the age of 11 months, which stabilized his blood glucose over a 12-month period. Case 2: A 1-

month old boy with diazoxide-unresponsive CHI due to a paternal heterozygous KCNJ11 gene mutation was partially responsive to octreotide; 18F-DOPA-PET/CT scan confirmed a focal pancreatic head lesion. Over 6 months, he underwent 3 lesionectomies and afterwards responded to octreotide. At the age of 9 months, treatment was switched to monthly lanreotide. Currently, he is 3-year old , with stable glycaemia, and improved fasting tolerance. Case 3: A 3-week old girl with a paternal heterozygous ABCC8 gene mutation was unresponsive to diazoxide; 18F-DOPA-PET/CT scan confirmed a focal pancreatic head lesion. She responded to octreotide, and her parents preferred to avoid pancreatic surgery. At the age of 20 months, treatment was switched to monthly lanreotide, resulting in euglycemia over the last 7 months. The authors concluded that CHI patients with focal pancreatic head lesions are challenging, especially if not surgically amenable. Conservative treatment is preferable, and lanreotide might be an option. These researchers stated that the impact of treatment with lanreotide in patients with the focal forms of CHI should be confirmed in prospective studies with close monitoring of the side effects.

Lanreotide for the Treatment of High Output Stoma

Mesli and colleagues (2020) noted that the incidence of high-output stoma (HOS) was reported to be approximately 3 % to 16 % in the literature, and HOS can cause dehydration. This complication is often severe enough to warrant hospital re-admission and may result in renal failure. The aim of this study was to show a decrease of 50 % in ileostomy output in the experimental arm using lanreotide treatment. Patients with an ileostomy output of greater than or equal to 1.5 L/24 hours were included in this prospective, open, multi-center, randomized trial. Patients were randomly allocated between treatment arms with either lanreotide (LAN) and anti-diarrheal treatments (TAD) (LAN-TAD group) or anti-diarrheal treatments only (TADS group). The primary outcome was ileostomy output after 72 days. The secondary end-points were ileostomy output during the first 6 days, blood urea and creatinine values, hospital LOS and serious AEs. In the per-protocol analysis, there were 9 patients in the control group (TADS) and 6 patients in the experimental group (TAD-LAN group). The stoma outputs at Day 3 (D3) in the experimental and control groups were 1,900 ± 855.7 ml and 1,728.6 ± 845.5 ml, respectively (p = 0.2). No differences were found

concerning stoma output at D6, renal function, or hospital LOS between the 2 groups. The authors concluded that the trial was prematurely stopped due to the low number of patients included. The question of the usefulness of somatostatin analogs in HOS persists, especially as the cost of this treatment is high, and there is a lack of evidence of its effectiveness.

Pasireotide Diaspartate (Signifor)

U.S. Food and Drug Administration (FDA)-Approved Indications

- Signifor is indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

Pasireotide diaspartate is available as Signifor (Novartis Pharmaceuticals Corporation). Pasireotide is a somatostatin analogue that binds to multiple somatostatin receptor subtypes found in various human tissues. Binding of pasireotide to these receptors causes inhibition of adrenocorticotropic hormone (ACTH) secretion which, in turn, leads to decreased cortisol secretion. The debilitating manifestations of Cushing's disease are associated with excess cortisol.

Signifor carries warnings and precautions for risk of hypocortisolism, hyperglycemia and diabetes (occurs with initiation), bradycardia and QT prolongation, liver test elevations, and choleithiasis. The most common adverse reactions occurring in 20% or more include diarrhea, nausea, hyperglycemia, cholelithiasis, headache, abdominal pain, fatigue, and diabetes mellitus (Novartis, 2020).

Cushing's disease is a rare and life-threatening endocrine disorder that results from long-term exposure to excess levels of the hormone, cortisol. This excess is caused by a pituitary tumor that prompts the over-production of cortisol. The first-line approach is surgery to remove the tumor.

Titrate dosage based on treatment response (ie. clinically meaningful reduction in 24-hour urinary free cortisol (UFC) and/or improvements in signs and symptoms of disease) and tolerability

Testing Prior to Dosing: fasting plasma glucose, hemoglobin A1c, liver tests, electrocardiogram (ECG), and gallbladder ultrasound

Dosing Adjustments in Patients with Hepatic Impairment:

- Child Pugh B: Recommended initial dosage is 0.3 mg twice a day and maximum dosage is 0.6 mg twice a day
- Child Pugh C: Avoid use in these patients

Urinary Free Cortisol (UFC) is a biochemical marker of hypercortisolism.

Pasireotide is mainly eliminated by biliary excretion. Cholelithiasis has been frequently reported with pasireotide. Performing gallbladder ultrasounds before starting treatment and at 6-month intervals is recommended.

Pasireotide Pamoate (Signifor LAR)

U.S. Food and Drug Administration (FDA)-Approved Indications

- Treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option
- Treatment of patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative

Pasireotide pamoate is available as Signifor LAR (Novartis Pharmaceuticals Corporations),which is a long-acting cyclohexapeptide analog of natural somatostatin. The mechanism of action is believed to be similar to that of natural somatostatin which binds to somatostatin receptors on neuroendocrine tissue such as those found in growth hormone (GH) secreting pituitary adenomas. These tumors produce high levels of GH and insulin-like growth factor-1 (IGF-1) which are associated with acromegaly. As with pasireotide diaspartate, pasireotide pamoate also binds and activates the SSTRs resulting in inhibition of ACTH secretion, which leads to decreased cortisol secretion.

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.

Pasireotide is mainly eliminated by biliary excretion. Cholelithiasis has been frequently reported with pasireotide. Performing gallbladder ultrasounds before starting treatment and at 6-month intervals is recommended.

On December 15, 2014, the FDA approved Signifor LAR 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).

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%).

On June 29, 2018, the FDA also approed Signifor LAR for the treatment of patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. The FDA approved Signifor LAR for Cushing's disease based on results from a Phase 3, randomized, double-blind, multicenter study that evaluated the safety and efficacy of two dose regimens of Signifor LAR over a 12-month treatment period in patients with persistent or recurrent Cushing's disease, or de novo patients who were not considered candidates for pituitary surgery (G2304 Study group; Lacroix et al 2018) .

Lacroix et al (2018) stated Cushing's disease is a rare debilitating endocrine disorder for which few prospective interventional studies have been done. The authors report results of the first phase 3 trial assessing long-acting intramuscular pasireotide in patients with Cushing's disease. This trial recruited patients aged 18 years or older with persistent, recurrent, or de-novo (non-surgical candidates) Cushing's disease who had a mean urinary free cortisol (mUFC) concentration (from three 24 h samples) of 1·5-5·0 times the upper limit of normal (ULN), a normal or greater than normal morning plasma adrenocorticotropic hormone concentration, and a pituitary source of Cushing's syndrome, from 57 sites across 19 countries. Patients were excluded if they had received previous pasireotide treatment, mitotane therapy within 6 months, and pituitary irradiation within 10 years. The patients were randomly allocated 1:1 (block size of four) using an interactive-response-technology system to intramuscular pasireotide 10 mg or 30 mg every 4 weeks for 12 months (in the core phase). The authors stratified randomisation by screening mUFC concentration (1·5 to less than 2·0 × ULN and 2·0-5·0 × ULN). The dose could be uptitrated (from 10 mg to 30 mg or from 30 mg to 40 mg) at month 4 if the mUFC concentration was greater than 1·5 × ULN, and at month 7, month 9, or month 12 if the mUFC concentration was greater than 1·0 × ULN. Investigators, patients, site personnel, and those assessing outcomes were masked to dose group allocation. The primary endpoint was the proportion of patients in each group with an mUFC concentration of less than or equal to the ULN at month 7. Efficacy analyses were based on intention to treat. Between Dec 28, 2011, and

Dec 9, 2014, 150 patients were randomly allocated to receive pasireotide 10 mg (74 [49%] patients) or 30 mg (76 [51%] patients). The primary efficacy endpoint was met by 31 (41·9% [95% CI 30·5-53·9]) of 74 patients in the 10 mg group and 31 (40·8% [29·7-52·7]) of 76 in the 30 mg group.

The most common adverse events were hyperglycaemia (36 [49%] in the 10 mg group and 36 [47%] in the 30 mg group), diarrhoea (26 [35%] and 33 [43%]), cholelithiasis (15 [20%] and 34 [45%]), diabetes mellitus (14 [19%] and 18 [24%]), and nausea (15 [20%] and 16 [21%]). Serious adverse events suspected to be study drug related were reported in eight (11%) patients in the 10 mg group and four (5%) in the 30 mg group. Two (3%) patients in the 30 mg group died during the study (pulmonary artery thrombosis and cardiorespiratory failure); neither death was judged to be related to the study drug. The authors concluded that long-acting pasireotide normalised mUFC concentration in about 40% of patients with Cushing's disease at month 7 and had a similar safety profile to that of twice-daily subcutaneous pasireotide. Long-acting pasireotide is an efficacious treatment option for some patients with Cushing's disease who have persistent or recurrent disease after initial surgery or are not surgical candidates, and provides a convenient monthly administration schedule.

Signifor LAR must be reconstituted immediately before use and administered by a trained healthcare professional.

Recommended tests prior to dosing: fasting plasma glucose, hemoglobin A1c, liver tests, electrocardiogram (ECG), and gallbladder ultrasound.

Management of adverse reactions or over-response to treatment (age and sex adjusted IGF-1 less than the lower limit of normal) may require dose reduction. The dose may be decreased, either temporarily or permanently, by 20 mg decrements.

Pasireotide for the Reduction of the Development of Post-Operative Pancreatic Fistula

Young and colleagues (2018) noted that a previous study reported that peri-operative pasireotide demonstrated reduction in post-operative pancreatic fistula (POPF) following pancreatectomy, yet recent studies

question the efficacy of this drug. In this study, all patients who underwent pancreatic resection between January 2014 and August 2017 at a single institution were prospectively followed. Starting in February 2016, pasireotide was administered to all patients who underwent pancreatectomies. Pancreaticoduodenectomy (PD) patients were additionally risk-stratified using a validated clinical risk score. The primary end-point was the development of clinically relevant POPF (CR-POPF), and was compared between patients who received pasireotide and controls. Of 116 patients, 87 patients (75 %) underwent PD, and 43 patients (37.1 %) received pasireotide. CR-POPF occurred in 28.4 % patients. The use of pasireotide was not associated with reduced CR-POPF among the total cohort (25.6 % versus 30.1 %, p = 0.599), distal pancreatectomy patients (p = 0.339), PD (p = 0.274), or PD patients with elevated risk scores (p = 0.073). Pasireotide did not decrease hospital length of stay (LOS), use of parenteral nutrition, delayed gastric emptying, surgical site wound infection, or re-admission rate. The authors concluded that the use of pasireotide after pancreatic resection did not decrease CR-POPF, nor was it associated with reduced LOS or post-operative complications. These researchers stated that a randomized, multi-center trial is needed to study its true effect on outcomes following pancreatectomy.

In a prospective, single-arm trial, Elliott and associates (2018) examined if pasireotide would prevent post-operative pancreatic fistula following pancreas surgery. This study included 111 consecutive patients undergoing pancreatic resection. Beginning immediately before surgery, patients received 900 µg subcutaneous pasireotide twice-daily for up to 7 days. Fistula rates were compared to 168 historical controls from July 2013 to March 2015. The primary outcome was grade B/C fistula, as defined by the International Study Group on Pancreatic Fistula (ISGPF). There were no significant differences between the pasireotide-treated group and historical controls in demographics, co-morbidities, operation type, malignancy, gland texture, or pancreatic duct size. Pasireotide did not reduce fistula rate (15.5 % control versus 17.1 % pasireotide, p = 0.72). In subgroup analyses of pancreaticoduodenectomy or distal pancreatectomy, or patients with soft gland texture and/or small duct size, there was no decrease in fistulas; 39 patients (38 %) experienced dose-

limiting nausea. The authors concluded that in an appropriately-powered, single-institution prospective study, pasireotide was not validated as a preventive measure for pancreatic fistula.

Pasireotide for the Treatment of Dopamine-Resistant Prolactinoma

Lasolle and associates (2019) stated that approximately 10 % of prolactinomas are resistant to dopamine-agonists (DAs). The only alternatives for tumor and prolactin control are surgery or radiotherapy. While studies on 1st generation somatostatin analogs have shown no efficacy against prolactinomas, no study has been conducted on the new multi-receptor-targeted somatostatin receptor ligand (SRL) pasireotide, which presents high affinity for 5, 3, 2 and 1 receptor subtypes. These investigators described the case of a 41-year old woman who presented with a macroprolactinoma showing resistance to all available DAs. She was first diagnosed at 17 years old after which she had undergone 2 incomplete debulking surgeries. Under pasireotide long-acting release (PAS-LAR) treatment, plasma prolactin levels normalized and symptoms disappeared within 1 month after initiation of pasireotide therapy. The clinical benefits of the monotherapy (specifically, prolactin levels within normal range and stable tumor volume) were maintained for 7 years. Glucose tolerance was satisfactory. Pathological analysis of the tumor revealed high SSTR5 and low SSTR2 expression (25 % and 5 % of cells, respectively). The authors concluded that this is a promising first report of a patient with a DA-resistant macroprolactinoma who achieved long-term control, in terms of prolactin normalization and tumor volume, under pasireotide treatment alone. These researchers stated that pasireotide could thus be an alternative in prolactinomas resistant to DA.

Coopmans and colleagues (2019) noted that prolactinomas are the most commonly encountered pituitary adenomas in the clinical setting. While most can be controlled by DAs, a subset of prolactinomas are dopamine-resistant and very aggressive. In such tumors, the treatment of choice is neurosurgery and radiotherapy, with or without temozolomide. These investigators reported a patient with an highly aggressive, dopamine-resistant prolactinoma, who only achieved biochemical and tumor control during PAS-LAR therapy. Interestingly, cystic degeneration, tumor cell necrosis, or both was observed following PAS-LAR administration suggesting an anti-tumor effect. The authors concluded that the findings

of this study showed that PAS-LAR therapy holds clinical potential in selective aggressive, dopamine-resistant prolactinomas that express SSTR5 and appeared to be a potential new therapeutic option before starting temozolomide. In addition, PAS-LAR therapy may induce cystic degeneration, tumor cell necrosis, or both in prolactinomas. These preliminary findings need to be validated in well-designed studies.

Pasireotide for the Treatment of Dumping Syndrome after Bariatric or Upper Gastro-Intestinal Cancer Surgery

Tack and colleagues (2018) stated that dumping syndrome is a prevalent complication of esophageal and gastric surgery characterized by early (post-prandial tachycardia) and late (hypoglycemia) post-prandial symptoms. In a multi-center, open-label, single-arm, intra-patient dose-escalation, phase-II clinical trial, these researchers examined the safety and efficacy of pasireotide in patients with dumping syndrome after bariatric or upper GI cancer surgery. This study had 4 phases: screening, 3-month SC (subcutaneous), 3-month IM (intramuscular) and 6-month optional extension IM phase. Primary end-point was the proportion of patients without hypoglycemia (plasma glucose less than 3.3 mmol/L [60 mg/dL] during an oral glucose tolerance test, OGTT) at the end of 3-month SC phase. A greater than or equal to 50 % response rate was considered clinically relevant. A total of 43 patients with late dumping were enrolled; 33 completed the 3-month SC phase and 23 completed the 12-month study. The proportion of patients without hypoglycemia at month 3 (primary end-point) was 60.5 % (26 of 43; 95 % CI: 44.4 % to 75.0 %). Improvement in QOL was observed during SC phase, which was maintained in the IM phase. The proportion of patients with a rise in pulse rate of greater than or equal to 10 beats/min during OGTT reduced from baseline (60.5 %) to month 3 (18.6 %) and month 12 (27.3 %). Overall (month 0 to 12), the most frequent (greater than 20 % of patients) AEs were headache (34.9 %); diarrhea, hypoglycemia (27.9 % each); fatigue, nausea (23.3 % each); and abdominal pain (20.9 %). The authors concluded that these results suggested that pasireotide is a promising therapeutic option in patients with dumping syndrome following bariatric or upper GI cancer surgery.

Pasireotide for the Treatment of Gastrointestinal Angiodysplasias

Benamouzig and colleagues (2018) noted that gastrointestinal angiodysplasias (GIADs) could be responsible for recurrent bleeding and severe anemia. Somatostatin analogs could reduce transfusion requirements in these patients but no RCT is available. The main objective of the ANGIOPAS phase-II, double-blinded, randomized, non-comparative study was to examine the effectiveness of PAS-LAR in reducing transfusion requirements in patients with refractory GIADs bleeding. A total of 22 patients with transfusion requirements greater than or equal to 6 units of packed red blood cells (pRBCs) during the 6 months prior to inclusion were randomized to receive PAS-LAR 60-mg (n = 10) or placebo (n = 12) every 28 days for 6 months. Patients were then followed for an additional 6 months after stopping treatment. The PAS-LAR and placebo groups were equivalent for age, sex, co-morbidities and transfusion requirement during the reference period (median of 13 and 9.5 pRBCs). A 50 % and 83 % success rate (success defined as a decrease of at least 30 % of transfused pRBCs) was observed in the PAS-LAR arm in the intent-to-treat (ITT) and per protocol (PP) analysis, respectively. The need for transfusion during the intervention period was 3 pRBC units in the PAS-LAR group (range of 0 to 26) and 11.5 pRBC units in the placebo group (range of 0 to 23). Overall, 3 cases with glycemic control impairment were observed in the PAS-LAR group including 1 de-novo diabetes. The authors concluded that the findings of this randomized, double-blinded, non-comparative, phase-II trial suggested, for the first time, the effectiveness of PAS-LAR 60-mg every 28 days to decrease the transfusion requirement in patients with recurrent bleeding due to GIADs. These researchers stated that a multi-center collaborative network involving specialized centers will allow performing the needed phase-III clinical trial to confirm these findings.

The authors stated that the main drawback of this study was its limited recruitment. The initial recruitment ANGIOPAS target has not been achieved. Only 25 patients were selected and 22 included despite 50 were initially considered. Several factors may explain this limited recruitment: scarcity of the pathology at the desired stage (refractory bleeding after endoscopic therapy with transfusion requirement of more than 6 pRBC units during the last 6 months), exclusion criteria as QTcF greater than 450 ms, which was frequently observed in these elderly patients with vascular co-morbidities and the geographical remoteness of some patients that did not allow regular monitoring according to the

protocol. This difficulty was also described by another team. Despite this limited recruitment and the restrictive attribution method for missing data, the observed success rates allowed the rejection of a futile effect ($p < p0$ hypothesis when $p0 < 15$ % with a 0.037 true error rate). Furthermore, the PP analysis of the patients exposed to PASLAR suggested the true effectiveness of PAS-LAR in reducing the transfusion requirement ($p \geqslant p1$ hypothesis with $p1 \geqslant 40$ %).

Pasireotide for the Treatment of Hepatic Cysts

In a double-blind, placebo-controlled trial, Wijnands and associates (2018) examined if complementary use of the pasireotide would augment efficacy of aspiration sclerotherapy of hepatic cysts. This trial included patients who underwent aspiration sclerotherapy of a large (greater than 5 cm) symptomatic hepatic cyst. Patients were randomized to either IM injections of 60-mg PAS-LAR (n = 17) or placebo (sodium chloride 0.9 %, n = 17). Injections were administered 2 weeks before and 2 weeks after aspiration sclerotherapy. The primary end-point was proportional cyst diameter reduction (%) from baseline to 6 weeks. Secondary outcomes included long-term cyst reduction at 26 weeks, patient-reported outcomes including the polycystic liver disease-questionnaire (PLD-Q) and safety. A total of 34 patients (32 women; 53.6 ± 7.8 years) were randomized between pasireotide or placebo. Pasireotide did not improve efficacy of aspiration sclerotherapy at 6 weeks compared to controls (23.6 % [inter-quartile range [IQR] 12.6 to 30.0] versus 21.8 % [9.6 to 31.8]; p = 0.96). Long-term cyst diameter reduction was similar in both groups (49.1 % [27.0 to 73.6] and 45.6 % [29.6 to 59.6]; p = 0.90). Mean PLD-Q scores improved significantly in both groups ($p < 0.01$) without differences between arms (p = 0.92). The authors concluded that in patients with large symptomatic hepatic cysts, complementary pasireotide to aspiration sclerotherapy did not improve cyst reduction or clinical response.

The authors stated that this study had several drawbacks. First, the primary end-point was measured by ultrasonography, which introduced variability as it was operator-dependent; CT or MRI may reduce variability, but would have led to unnecessary exposure to radiation and/or costs as this study required multiple measurements within short intervals. To minimize bias, all measurements were performed by the same investigator following standardized operating procedures. As a

result, these researchers found excellent intra-class coefficients of intra- and inter-observer variability. Second, these researchers powered the study assuming a large beneficial effect from pasireotide. Possible smaller differences between these groups cannot be ruled out. However, the authors believe that such small differences would not be relevant for clinical practice, given the costs of pasireotide. Finally, these investigators included both sporadic hepatic cysts and dominant hepatic cysts within PLD. The genetic background of both congenital cyst types corresponded as somatic loss of PLD-type alleles from cyst epithelium is required to drive cyst formation. Indeed, both cyst types have a thin wall lined by a single layer of aberrant cholangiocytes, which are targetable by somatostatin analogs. However, it was unclear if germline mutations in PLD patients alter susceptibility to these agents. In this study, these researchers found no differences in efficacy between patients with or without underlying PLD, as reflected in the previous literature.

Pasireotide for the Treatment of Hepatocellular Carcinoma

In a phase-II clinical trial, Feun and colleagues (2018) examined the safety and efficacy of pasireotide in the treatment of advanced or metastatic hepatocellular carcinoma (HCC). Patients with advanced HCC and Child-Pugh score less than or equal to 7 received PAS-LAR 60-mg intramuscularly every 28 days. Primary end-point was disease control rate; secondary end-points were time to tumor progression, response rate, treatment-related AEs, and OS. Serum insulin-like growth factor-1 (ILGF-1) was measured before and after pasireotide. A total of 20 patients were treated and evaluable; 18 patients (90 %) had prior therapy; 16 patients (80 %) had multiple therapies. Median age was 65 years, 75 % had Barcelona Clinic Liver Cancer stage C, and 55 % had metastatic disease. The main toxicity was hyperglycemia. Rare adverse effects included reversible grade-4 elevation in alanine transaminase/aspartate transaminase in 1 patient. The best response was stable disease in 9 patients (45 %). Median time to tumor progression for the 20 patients was 3 months, and median survival was 9 months. The authors concluded that although the findings in this study showed very modest disease control in advanced, unresectable HCC as a 2nd- or 3rd-line treatment, future trials may select patients most likely to benefit, such as using pre-treatment octreotide image scanning and testing available tumor samples for SSTR expression. Unfortunately, due to costs of

octreotide scanning and insurance issues, these researchers were unable to select out the best patients to benefit from this therapy. Baseline serum ILGF-1 levels and decreasing ILGF-1 after treatment may have value in assessing tumor control or possibly predict better clinical outcome; further studies will be needed to confirm its utility in this setting.

Pasireotide for the Treatment of Medullary Thyroid Cancer

Faggiano and colleagues (2018) noted that medullary thyroid cancer (MTC) is a neuroendocrine tumor of the thyroid C cells. Pasireotide and everolimus showed anti-tumor properties in neuroendocrine tumors. In an open-label, single-center, phase-II, proof-of-concept study, these researchers examined pasireotide alone and in combination with everolimus in patients with MTC. Patients with progressive metastatic or persistent post-operative MTC received pasireotide LAR 60 mg/month for at least 6 months. Patients exhibiting progressive disease received everolimus 10 mg/day as combination therapy. Primary end-point was PFS; secondary end-points included OS, objective response rates (ORR), change in circulating markers, safety. A total of 19 consecutive patients were enrolled. Median follow-up was 31 months. Median PFS with pasireotide was 36 months (95 % CI: 19.5 to 52.5); 9 patients (47 %) had tumor progression: 7 of them started everolimus in combination with pasireotide, achieving a median PFS of 9.0 months (95 % CI: 0 to 21.83); 5 of them (71 %) had further tumor progression, 1e objective response (14.3 %), 1 stopped treatment because of pulmonary embolism. Pasireotide alone and with everolimus was safe and required withdrawal only in 1 case. Diarrhea and hyperglycemia were the most frequent AEs with pasireotide (grade 3 in 5.3 % each). Hyperglycemia was the most frequent grade-3 toxicity with the combination therapy (28.6 %). The authors concluded that pasireotide therapy showed anti-proliferative effects in persistent post-operative MTC suggesting further investigation on larger series of patients. In progressive MTC lesions, the combination pasireotide plus everolimus may be of benefit; both schemes were safe and well-tolerated.

Pasireotide for the Treatment of Metastatic Melanoma

Dummer and colleagues (2018) stated that somatostatin analogs exert anti-tumor activity via direct and indirect mechanisms. In a phase-I, open-label study, these researchers examined the safety and efficacy of pasireotide in patients with BRAF-wild type (WT) and NRAS-WT metastatic melanoma. Patients with unresectable and/or metastatic melanoma or Merkel cell carcinoma were eligible. Pasireotide was administered at different doses for less than or equal to 8 weeks in dose-escalation phase, followed by PAS-LAR 80-mg or lower dose in case of toxicity in follow-up phase up to 6 additional months. Primary end-point was safety in the first 8 weeks of dose-escalation phase. The study was terminated early due to slow recruitment. Of the 10 patients with metastatic melanoma enrolled, only 4 reached the high-dose level: 2 patients reached 3,600-µg in dose-escalation and follow-up phases; and 2 patients reached 3,600-µg in dose-escalation and PAS-LAR 80-mg in follow-up phases and were stable for greater than 5 months. Most common AEs during dose-escalation phase in greater than or equal to 2 patients (20 %) were: diarrhea (50 %), nausea (50 %), fatigue (20 %), hyperglycemia (20 %), hypophosphatemia (20 %), chills (20 %) and tumor pain (20 %); grade-3 or grade-4 study drug-related AEs were diarrhea and nausea, reported in 1 patient. Partial response was documented in 1 patient and stable disease (SD) in another. The authors concluded that pasireotide was well-tolerated, and safety results were similar to those previously reported in other indications. Moreover, these researchers stated that further prospective randomized trial are needed to evaluate the efficacy of pasireotide in BRAF-WT and NRAS-WT melanoma; pasireotide may also be potentially used in combination with other therapeutic agents in the treatment of patients with BRAF-WT and NRAS-WT melanoma.

The authors stated that possible limitations of this study included the following: insufficient study drug exposure as patients were dropping out during the dose-escalation phase due to disease progression. Some patients received a lower dose for a shorter period of time and disease progression occurred early. Nevertheless, the patients who continued to the follow-up phase received high doses of pasireotide for more than 5 months and showed stable disease/partial response or stable disease in target lesions.

Pasireotide for the Treatment of Prostate Cancer

Thakur and colleagues (2018) stated that pasireotide is a multi-targeted somatostatin receptor analog likely to treat the neuroendocrine, and docetaxel resistant components within metastatic castrate-resistant prostate cancer (mCRPC). In a phase-I clinical trial, these investigators examined the effects of combination of pasireotide, docetaxel, and prednisone in pre-treated mCRPC. Chemotherapy naive mCRPC patients received docetaxel 75 mg/m^2 intravenously every 21 days and pasireotide intramuscularly every 28 days at escalating dose levels of 40-, 60-, and 80-mg. Maximum tolerated dose (MTD) and recommended phase-II dose (RP2D) were assessed. A total of 18 patients were enrolled with a median age of 65 (range of 49 to 75) years, and pre-therapy prostate-specific antigen (PSA) of 259.9 ng/ml. The dose-limiting toxicities (DLTs) were grade-4 hyperglycemia unresponsive to therapy and grade-4 neutropenia lasting for greater than 7 days in 1 patient each occurring at the 80-mg dose level of pasireotide. The RP2D was determined at 60 mg every 28 days. Four patients at the 60-mg dose had grade-3 or grade-4 hyperglycemia that responded adequately to therapy. Median time to progression and survival were 7.2 and 18.3 months, respectively; 3 of 6 patients with circulating tumor cells greater than or equal to 5 converted to circulating tumor cells of less than 5 post-therapy. The ILGF-1 levels revealed a median 51 % decrease following therapy. The neuron-specific enolase and chromogranin did not show any marked change. The authors concluded that the addition of pasireotide to docetaxel and prednisone was clinically feasible at a dose level of 60 mg every 28 days. The combination showed potential for clinical efficacy but needs to be compared with the standard docetaxel and prednisone regimen.

The authors stated that this study had major limitations in determining efficacy. It is a phase-I clinical trial designed to evaluate the recommended phase-II dose as the primary end-point. The sample size was very limited (n = 18) and the study design was not conducive and adequately powered to determine efficacy. The omission of prednisone might have decreased the risk of hyperglycemia noted, however it was ethically concerning to deviate from an approved standard regimen of docetaxel and prednisone. The efficacy results could be entirely attributable to docetaxel and prednisone and the next step should be to compare the combination with a control arm of the standard docetaxel and prednisone regimen. The combination of an SSTR analog-based

combination therapy in mCRPC is worthy of further investigation.

Treatment-related neuroendocrine-like prostate cancer has evolved into a well-recognized entity. This condition has been reported typically after therapy with an androgen receptor axis targeted agent such as abiraterone or enzalutamide. This is an aggressive variant of prostate cancer that has a dismal prognosis with a reported median OS of less than 6 months. The molecular features of amplification of N-MYC (MYCN) gene and aurora kinase A expression have been well-described, although clinical trials attacking these genomic targets have shown only modest efficacy. Therapeutic strategies that would preempt or treat the clinical manifestation of neuroendocrine prostate cancer, represent a currently unmet need and the addition of pasireotide to chemotherapy is worthy of future exploration.

Pasireotide for the Treatment of Unresectable Neuroendocrine Tumors with Hepatic Metastases

Kimand colleagues (2018) stated that neuroendocrine tumors (NETs) metastasize to the liver. Everolimus and selective internal radioembolization (SIRT) are approved treatments. Pasireotide is a somatostatin analog with an affinity for SSTR 1, 2, 3, and 5 subtypes. Everolimus and pasireotide may potentiate SIRT radio-sensitization and inhibit rebound angiogenesis. In a phase-1b clinical trial, these researchers examined the safety of pasireotide, everolimus, and SIRT for the treatment of unresectable neuroendocrine tumors with hepatic metastases. This 3 + 3 phase-I trial evaluated 3 dose levels of everolimus (2.5, 5, and 10 mg/day), pasireotide (600 µg twice-daily), and SIRT (SIR-Spheres dose on days 9 and 37). Eligibility criteria included well or moderately differentiated NETs, bi-lobar liver metastases, and progression on long-acting octreotide. Toxicities and responses were evaluated with the Common Terminology Criteria for Adverse Events and the Response Evaluation Criteria in Solid Tumors (version 1.1); DLTs were defined in the first 28 days. Correlative markers – angiopoietin 1, angiopoietin 2, basic fibroblast growth factor, collagen V, ILGF binding protein 1, interleukin 8, M30, M65, placenta growth factor, and VEGF receptor 2-were assessed. The Norfolk Quality of Life-Neuroendocrine Tumor Questionnaire was used to assess the QOL. A total of 13 patients were enrolled; 1 was not evaluable for the primary end-point; 11 patients had well-differentiated tumors. The primary sites included small bowel (n

= 4), pancreas (n = 3), lung (n = 2), colon (n = 1), gastric (n = 1), and unknown primary (n = 2) were unknown; 4 had liver-only disease; 12 completed the planned treatment. No DLTs were observed. There was no treatment-related mortality. The most common toxicity was hyperglycemia. Clinically significant liver toxicity was not observed; 1 patient had liver progression; QOL improved on treatment. The median PFS and OS were 18.6 and 46.3 months, respectively. The authors concluded that the recommended phase-II dose of everolimus is 10 mg daily in combination with pasireotide and SIRT. The regimen is well-tolerated; preliminary activity appeared promising.

Acromegaly

Acromegaly is an uncommon chronic progressive disorder in adults resulting from the hypersecretion of growth hormone (GH) and resultant elevated circulating insulin like growth factor-1 (IGF-1). This hypersecrection of growth hormone is most commonly caused by a benign tumor of the pituitary gland. It results in gradual enlargement of body tissues including the bones of the face, jaw, hands, feet and skull. Acromegaly can result in substantial morbidity and mortality rates due to cardiovascular, pulmonary, and malignant diseases two-to-four times higher than the general population if not treated.

Acromegaly occurs in about six out of 100,000 people. It occurs in frequency equally among men and women. The mean age of onset for women is 34.9 years and 32.7 years in men. The mean age for diagnosis in men is 42.3 years and 43.8 for women.

Conventional therapy is aimed at reducing GH and IGF-1 levels to normal, eliminating or reducing tumor growth, and alleviating clinical signs and symptoms to reduce comorbidities. Standard therapy is transphenoidal surgery, dopamine agonists, somatostatin analogues, GH receptor antagonists, and radiotherapy. Patients who are not eligible for surgery or who have had an inadequate response to dopamine agonist or radiation would instigate a trial of somatostatin analogues. A randomized, double-blind, placebo controlled, multicenter trial of 115 acromegalic patients demonstrated the effectiveness of 100 micrograms subcutaneously every 8 hours for a six month period.(Ezzat et al, 1992). About half of the patients experienced a reduction in GH and about two

thirds in IGF-1. Three principal studies were performed providing up to 30 months of exposure to octreotide LAR depot who had previously responded to octreotide injection s.c. Growth hormone and IGF-1 levels were at least as well controlled on octreotide LAR depot as they were on octreotide injection s.c.

Associated or Induced Diarrhea

Chemotherapy or radiation induced diarrhea is a debilitating and potentially lifethreatening side effect of cancer treatments. Severe diarrhea often results in delay of treatment or dose reductions. In a multicenter, randomized trial of long-acting octreotide for prevention of CID, 147 patients were randomized to receive 30 mg or 40 mg octreotide LAR with chemotherapy. The first dose was given seven-to-14 days before Day 1 of the next chemotherapy cycle and the second dose coincided with the initiation of the chemotherapy cycle. Subsequent treatment was give q28 days. 124 patients were efficacy evaluable. Among respondents at study end (n=74) 56% treated with either dose of LAR reported satisfaction to extreme satisfaction with therapy. Fewer patients experienced severe diarrhea, required less IV fluid supplementation, and had fewer diarrhea-related healthcare visits. (Rosenoff S. et al.)

Treatment of AIDS related diarrhea is often difficult because the cause of the diarrhea may be multifactorial and resistant to current therapy. In a review article evaluating the use of octreotide in the treatment of refractory diarrhea, Fried (1999) evaluated seven uncontrolled and three controlled studies of treatment of AIDS-related diarrhea. In the study with the highest number of patients, stool frequency and volume decreased significantly with the use of octreotide in all patients. This was typical in all the studies.

Cecal Arterio-Venous malformation

Sami and colleagues (2014) stated that angio-dysplasia (AD) of the GI tract is an important condition that can cause significant morbidity and rarely mortality. These investigators provided an up-to-date comprehensive summary of the literature evaluating this disease entity with a particular focus on pathogenesis as well as current and emerging

diagnostic and therapeutic modalities. Recommendations for treatment will be made on the basis of the current available evidence and consensus opinion of the authors. These researchers performed a systematic literature search, which used the keywords "angiodysplasia" or "arteriovenous malformation" or "angioectasia" or "vascular ectasia" or "vascular lesions" or "vascular abnormalities" or "vascular malformations" in the title or abstract. Most AD lesions (54 to 81.9 %) were detected in the caecum and ascending colon. They may develop secondary to chronic low-grade intermittent obstruction of submucosal veins coupled with increased vascular endothelial growth factor (VEGF)-dependent proliferation. Endo-therapy with argon plasma coagulation resolved bleeding in 85 % of patients with colonic AD. In patients who failed (or were not suitable for) other interventions, treatment with thalidomide or octreotide could lead to a clinically meaningful response in 71.4 % and 77 % of patients, respectively. The authors concluded that AD is a rare cause of both overt and occult GI bleeding especially in the older patients. Advances in endoscopic imaging and therapeutic techniques have led to improved outcomes in these patients. The choice of treatment should be decided on a patient-by-patient basis. They stated that further research is needed to better understand the pathogenesis and identify potential therapeutic targets.

Cirrhosis-Associated Hyponatremia

Patel and colleagues (2017) stated that hyponatremia in the setting of cirrhosis is a common electrolyte disorder with few therapeutic options. The free water retention is due to non-osmotic vasopressin secretion resulting from the cirrhosis-associated splanchnic vasodilatation. Thus, vaso-constrictive therapy may correct this electrolyte abnormality. In an observational study, these researchers evaluated effectiveness of midodrine and octreotide as a therapeutic approach to increasing urinary electrolyte-free water clearance (EFWC) in the correction of cirrhosis-associated hyponatremia. This trial consisted of 10 patients with cirrhosis-associated hyponatremia; hypovolemia was ruled out as the cause of the hyponatremia with a 48-hour albumin challenge (25 g IV q6 h). Patients whose hyponatremia failed to improve with albumin challenge were started on midodrine and octreotide at 10 mg po tid and 100 µg sq tid, respectively, with rapid up-titration as tolerated to respective maximal doses of 15 mg tid and 200 µg tid within the first 24

hours. These investigators assessed urinary EFWC and serum sodium concentration before and 72 hours after treatment. Pre-treatment serum sodium levels ranged from 119 to 133 mmol/L. The mean pre-treatment serum sodium concentration ± SEM was 124 mmol/L ± 1.6 versus 130 mmol/L ± 1.5 post-treatment (p = 0.00001). The mean pre-treatment urinary EFWC ± SEM was 0.33 L ± 0.07 versus 0.82 L ± 0.11 post-treatment (p = 0.0003). The authors concluded that these findings showed a statistically significant increase in serum sodium concentration and urinary EFWC with the use of midodrine and octreotide in the treatment of cirrhosis-associated hyponatremia. Moreover, they stated that larger randomized controlled trials (RCTs) are needed to validate these observations that treatment with midodrine and octreotide can improve cirrhosis-associated hyponatremia. This study had several drawbacks: (i) small sample size (n = 10), (ii) the study was neither randomized nor blinded but rather observational in nature, and (iii) the findings were confounded by the combined use of midodrine and octreotide.

Congenital Hyperinsulinism

Vieira et al (2010) noted that congenital hyper-insulinism (CHI) of infancy is the most common cause of hypoglycemia in newborns and infants. Several molecular mechanisms are involved in the development of CHI, but the most common genetic defects are inactivating mutations of the ABCC8 or KCNJ11 genes. The classical treatment for CHI has been pancreatectomy that eventually leads to diabetes. More recently, conservative treatment has been attempted in some cases, with encouraging results. Whether or not the patients with heterozygous ABCC8 mutations submitted to conservative treatment may spontaneously develop type 2 diabetes in the long run, is a controversial issue. These investigators reported a family carrying the dominant heterozygous germ line E1506K mutation in ABCC8 associated with persistent hypoglycemia in the newborn period and diabetes in adulthood. The mutation occurred as a de-novo germ line mutation in the mother of the index patient. Her hypoglycemic symptoms as a child occurred after the 4th year of life and were very mild, but she developed glucose metabolism impairment in adulthood. On the other hand, in her daughter, the clinical manifestations of the disease occurred in the neonatal period and were more severe, leading to episodes of tonic-clonic

seizures that were well controlled with octreotide or diazoxide. The authors concluded that these findings corroborated the hypothesis that the dominant E1506K ABCC8 mutation, responsible for CHI, predisposed to the development of glucose intolerance and diabetes later in life.

Bas et al (2012) stated that the most common reason for refractory hypoglycemia in newborns is CHI. These researchers reported a girl with CHI due to novel homozygous mutation (c.2041-25 G>A; aberrant splicing mutation) in the ABCC8 gene encoding SUR1 and during somatostatin analog (octreotide) discontinuation developed by non-hypoglycemic seizures. The newborn (birth weight of 3,750 g) was referred to the authors' clinic because of hypoglycemic seizures at 4 hours post-natal. On admission, blood glucose was 24 mg/dL and intravenous glucose infusion was started. The patient's insulin level was 27 mIU/ml during the hypoglycemic period. Phenobarbital (5 mg/ kg/day) was added because of short-acting generalized clonic seizures. Although the patient received high doses of diazoxide, esidrex, and octreotide approximately for 2 months, hypoglycemic episodes continued. Then the patient had near-total pancreatectomy, and pathology confirmed a diffuse form of CHI. There was homozygous mutation in the ABCC8 gene encoding SUR1, which confirmed the diagnosis of autosomal recessive CHI. During octreotide discontinuation, the patient developed non-hypoglycemic seizures, which were controlled by re-starting the previous doses. In the light of in-vitro and in-vivo studies on anti-epileptic effects of somatostatin, the authors believed that seizures in this case have developed secondary octreotide discontinuity.

Celik et al (2013) stated that CHI denotes an inappropriate secretion of insulin from pancreatic β-cells in the presence of a low blood glucose level due to various genetic causes. Diazoxide is the first-line medical treatment for CHI. In case of failure, a somatostatin analogue called octreotide is used. A prolonged QT interval is an unusual side effect of octreotide which can be lethal if unrecognized. These investigators reported on a 35-day old infant who was diagnosed with CHI on the 3rd day of his life and underwent pancreatectomy due to failure of medical treatment at 8 months. His genetic analysis revealed a compound heterozygosity for a novel missense mutation (p.Met115Val) and a nonsense mutation (p.Trp1339X) in the ABCC8 gene. Furthermore, at the 6th month of follow-up, a long QT (0.49 s) was determined by ECG

examination, which was normalized following discontinuation of octreotide treatment after pancreatectomy. Thus, the long QT was considered to be secondary to octreotide medication. The authors recommended ECG monitoring before and during octreotide treatment in order to recognize a prolonged QT interval and to prevent related complications in cases with CHI.

Durmaz et al (2014) noted that hyperinsulinemic hypoglycemia (HH) is the commonest cause of persistent hypoglycemia in the neonatal and infancy periods. Mutations in the ABCC8 and KCNJ11 genes, which encode subunits of the ATP-sensitive potassium channel in the pancreatic beta cell, are identified in approximately 50 % of these patients. The first-line drug in the treatment of HH is diazoxide. Octreotide and glucagon can be used in patients who show no response to diazoxide. Nifedipine has been shown to be an effective treatment in a small number of patients with diazoxide-unresponsive HH. These researchers reported a HH patient with a homozygous ABCC8 mutation (p.W1339X) who underwent a near-total pancreatectomy at 2 months of age due to a lack of response to diazoxide and octreotide treatment. Severe hypoglycemic attacks continued following surgery, while the patient was being treated with octreotide. These attacks resolved when nifedipine was introduced. While this patient responded well to nifedipine, the dosage could not be increased to 0.75 mg/kg/day due to development of hypotension, a reported side effect of this drug. This patient, now aged 4 years, is receiving a combination of nifedipine and octreotide treatment. He is under good control and shows no side effects. The authors concluded that nifedipine treatment can be started in patients with HH who showed a poor response to diazoxide and octreotide treatment.

Minute et al (2015) stated that CHI due to diffuse involvement of the pancreas is a challenging and severe illness in children. Its treatment is based on chronic therapy with diazoxide and/or octreotide, followed by partial pancreatectomy, which is often not resolutive. Sirolimus, a mammalian target of rapamycin inhibitor, was reported to be effective in treating CHI in infants. These investigators reported the case of an 8-year old boy affected by a severe form of CHI due to a bi-allelic heterozygous ABCC8 mutation who responded to sirolimus with a dramatic improvement in his glucose blood level regulation and quality of life, with no serious adverse events after 6 months of follow-up. The

authors concluded that this was the first report of a successful intervention in an older child. It provided a promising basis for further studies comparing sirolimus with other treatments, particularly in older children.

Furthermore, an UpToDate review on "Treatment and complications of persistent hyperinsulinemic hypoglycemia of infancy" (Sunehag and Haymond, 2017) states that "Pharmacologic therapy for hyperinsulinism may involve treatment with diazoxide (a specific ATP-dependent potassium [KATP] channel agonist in normal beta cells), somatostatin analogues (e.g., octreotide), or calcium channel blockers (e.g., nifedipine) …. Somatostatin analogues (e.g., octreotide) can be tried as a second-line therapy to reduce insulin secretion if treatment with diazoxide is unsuccessful".

Congenital Lymphedema

An UpToDate review on "Prevention and treatment of lymphedema" (Mohler and Mondry, 2015) does not mention octreotide as a therapeutic option.

Crohn's Disease-Associated Refractory Diarrhea

Martelli and associates (2017) stated that diarrhea is one of the main symptoms of Crohn's disease (CD). It is usually significantly improved with specific CD treatments, loperamide or cholestyramine. However, in some cases, diarrhea becomes refractory. In an uncontrolled, open-label study, these researchers evaluated the safety and effectiveness of octreotide in this situation. A total of 15 patients with CD refractory diarrhea defined by at least an average of 5 smooth or liquid stools per day despite an optimized CD treatment were included from 3 Belgian centers; 2 patients were lost to follow-up. A subcutaneous injection of 100 µg octreotide was administered 3 times a day for 3 days. When the drug had been well-tolerated, an intramuscular injection of 30 mg octreotide (Sandostatin® LAR 30) was realized; evaluation was carried out at day 31. The primary end-point was to assess the effect on the mean number of smooth or liquid stools per day. A significant reduction ($p = 0.0001$) of the average number of smooth or liquid stools over the last 7 days was observed between baseline and day 31. The maximum number

of smooth or liquid stools also significantly decreased (p = 0.0009); 4 patients (26.7 %) presented mild non-specific adverse events (AEs) but no serious AE. These investigators also observed a significant decrease (p = 0.0006) of the Harvey-Bradshaw Index (HBI) and a significant improvement (p = 0.0012) of the inflammatory bowel disease questionnaire (IBDQ). The authors concluded that octreotide appeared safe and effective in CD refractory diarrhea, in addition to CD treatments. It significantly improved the number of liquid or smooth stools, the HBI and the IBDQ. These preliminary findings need to be validated by well-designed studies.

Dumping Syndrome

Didden and colleagues (2006) stated octreotide therapy is effective in controlling severe dumping symptoms during short-term follow-up but little is known about long-term results. These investigators reported on the long-term results of patients with severe dumping syndrome treated with subcutaneous or depot IM (long-acting release) octreotide. They followed-up 34 patients with severe dumping syndrome refractory to other therapeutic measures treated between 1987 and 2005 with octreotide subcutaneous/long-acting release. At regular intervals symptoms, quality of life (QOL), weight, fecal fat excretion and gallstone formation were evaluated. All patients had excellent initial relief of symptoms during octreotide subcutaneous therapy. However, during follow-up 16 patients stopped therapy because of side effects (n = 9) or loss of efficacy (n = 7); 4 patients died. A total of 14 patients (41 %) remained using octreotide (follow-up 93 +/- 15 months), 7 were on octreotide subcutaneous and 7 on octreotide long-acting release. Patients with severe dumping (both early and late) fared better on subcutaneous than long-acting release despite the inconvenience of frequent injections. Dumping symptoms were reduced by 50 % even in long-term users. Body weight continued to increase during therapy despite more pronounced steatorrhea. The authors concluded that the long-term the efficacy of octreotide was much less favorable compared with short-term treatment.

Peeters and associates (2010) evaluated the research that has been conducted into the use of Sandostatin to control the debilitating symptoms of diarrhea in a number of different etiologies. These were cancer-related diarrheas, including diarrhea related to chemotherapy, radiotherapy,

neuroendocrine tumor carcinoid syndrome, VIP-secreting tumors and also non-cancer related diarrhea, including SBS, ileostomy and jejunostomy, dumping syndrome, graft versus host disease (GVHD) and AIDS-related diarrhea. There is an increasing recognition of the need to balance the cost of care with patient outcome. It is becoming clear that although the cost of a therapeutic regimen with Sandostatin is substantially greater than the current non-specific therapy, the overall cost is potentially greater without the use of Sandostatin for patients with refractory diarrhea due to the inevitable need for further treatment and/or hospitalization with intravenous fluid supplementation. Initial trials and reports from pre-clinical testing and clinical practice have shown promising results and, although in the majority of cases they strengthened the view taken in the published consensus guidelines for the use of Sandostatin for refractory diarrhea. The authors stated that further, larger scale, comparative clinical trials are needed for any evidence-based definition of dosage and efficacy as a treatment or prophylactic agent to combat and control diarrhea.

Sato and colleagues (2013) noted that dumping syndrome, or rapid gastric emptying, is a frequent complication after gastric surgery. In this case, the patient was a 47-year old woman who 10 years previously had undergone distal gastrectomy with Billroth I reconstruction for early-stage gastric cancer. She presented with symptoms of weakness, headache, palpitation, sweating, dizziness and significant fatigue between 1 and 2 hours after a meal. Because a 75 g oral glucose tolerance test (75 g-OGTT) induced both acute post-prandial tachycardia (within 1 hour) and post-prandial hypoglycemia, these investigators diagnosed this patient with early and late dumping syndrome. Dietary measures and acarbose improved symptoms of late dumping syndrome but did not prevent the symptoms of early dumping syndrome such as post-prandial tachycardia, weakness, headache, palpitation, and dizziness. Thus, they used octreotide, which has been reported as an effective therapy for early dumping syndrome. Octreotide prevented the symptoms of early dumping syndrome, especially post-prandial tachycardia, but caused post-prandial hyperglycemia. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) were completely suppressed during the 75 g-OGTT following subcutaneous injection of octreotide. No change was observed in VIP, which is the GI peptide

hormone generally responsible for early dumping syndrome, suggesting possible contribution of incretins in early dumping syndrome of this patient.

The authors stated that this study had several drawbacks. Although octreotide improved symptoms of dumping syndrome, octreotide inhibited both insulin secretion per se, and incretins, during a 75g-OGTT. It was difficult to conclude whether the inhibitory effects of octreotide on incretins were a direct effect of GLP-1 on vasodilatation or an indirect effect via insulin secretion from pancreatic β-cells. These researchers were also unable to measure enteroglucagon, peptide YY, pancreatic polypeptide and neurotensin. It was possible that octreotide improved symptoms through one of these hormones. Further study is needed to explore this. These investigators treated this patient with octreotide for several times, but did not continue this therapy because of the past history of cholelithiasis and post-prandial hyperglycemia. The authors stated that these data suggested that increased secretion of GLP-1 and GIP might be an alternative mechanism leading to the occurrence of early dumping syndrome.

Mohammadi and co-workers (2017) noted that hypoglycemia due to late dumping is a significant problem post-esophagectomy but may not always be diagnosed sufficiently early. It can be difficult to treat and may severely compromise QOL. These investigators reported on the case of a patient who developed severe hypoglycemic episodes post-esophagectomy who failed to respond to conventional measures, but was treated with pasireotide with moderately effective hypoglycemic control. The authors concluded that the combination of diazoxide and octreotide and particularly pasireotide my transform the patient's life and should be considered in all problematic cases.

Furthermore, an UpToDate review on "Postgastrectomy complications" (Ashley, 2018) states that "Most patients with dumping can be treated conservatively with dietary changes (frequent small meals that are high in fiber and protein and low in carbohydrates, separation of liquid from solid during meals). Symptoms tend to resolve in most patients as they learn to avoid foods that aggravate the problem (e.g., simple sugar). Octreotide may also help in severe cases of dumping but is rarely required. A study of 30 patients with dumping treated with either

subcutaneous octreotide, administered 3 times a day, or its long-acting formulation (Octreotide LAR), which is given monthly, reported that both significantly reduced dumping symptoms and improved quality of life".

Gastrointestinal Bleeding from Vascular Malformations

Iannone and colleagues (2016) stated that GI vascular malformations are responsible for 2 to 8 % of all cases of bleeding and 30 to 40 % of all obscure hemorrhages, being the most frequent cause of occult bleeding in older people. These investigators provided an up-to-date review on the use of octreotide in bleeding from both hereditary and acquired vascular malformations of the GI tract. They performed a systematic literature search using the keywords "gastrointestinal vascular malformation", "octreotide", "angiodysplasia", "portal hypertensive gastropathy", "gastric antral vascular ectasia", and "hereditary vascular malformations". The 1st line therapy of acute/chronic bleeding from digestive vascular malformations is endoscopy, followed by angiographic embolization and surgical resection when this is unsuccessful. In the setting of difficult-to-treat patients, octreotide has been proposed as an alternative therapeutic strategy. Studies reported in the literature showed octreotide to be safe and effective, but described only a small number of enrolled patients, heterogeneous therapeutic schedules and short-term follow-up, with the exception of acute bleeding from esophageal varices. As a consequence, the use of octreotide is not approved in this setting and it is currently still prescribed as an off-label drug. The authors concluded that studies in larger populations are needed to confirm the promising results observed in the small case series reports, so as to provide physicians with a therapeutic option for patients without available alternatives.

Lymphorrhea Reduction in Gynecological Malignancies

Weinberger and co-workers (2017) stated that the effect of octreotide on lymphorrhea reduction in gynecological malignancies has only been examined in case studies. In 2014 there was a prospective, randomized, single-institution study. Patients underwent surgery including pelvic or pelvic and para-aortic lymphadenectomy for cervical, uterine and ovarian cancers. Octreotide was evaluated in relation to diagnosis, surgery (laparoscopy versus laparotomy), pelvic and/or para-aortic lymphadenectomy, number of removed lymph nodes and their positivity,

neoadjuvant chemotherapy, adjuvant chemotherapy, adjuvant radiotherapy, albumin, body mass index (BMI), number of days with drains post-operatively, number of days in hospital, blood loss during surgery, time of surgery, total number of drains placed into abdominal cavity. In follow up period, within 1 year after surgery, these investigators searched for lymphocele, lymph-edema of lower extremities and lymphatic ascites in relation to lymphorrhea. A total of 44 patients (9 cervical, 19 endometrial and 16 ovarian cancers) were enrolled in 2 statistically comparable randomized groups. "Octreotide group", which paradoxically showed lymphorrhea of 4,082 ml on average, (without 1,992 ml, p = 0.001), needed drainage for more days (p = 0.001). The diagnosis had no influence on lymphorrhea in both groups (p = 0.966). Neoadjuvant chemotherapy was administered (p = 0.026), the more lymph nodes were removed (p = 0.018), the more days the drainage was in place (p < 0.001), the bigger the lymphorrhea; no relationship between lymphorrhea and age (p = 0.631), albumin level (p = 0.584), BMI (p= 0.966) or number of positive nodes (p = 0.259), length of surgery (p = 0.206), blood loss (p = 0.494); nor lymphedema (p = 0.404), nor lymphocele (p = 0.086), correlated with post-operative lymphorrhea. Lymphatic ascites was associated with lymphorrhea (p = 0.048). The authors concluded that octreotide did not reduce lymphorrhea and the incidence of lymphocele, lymphedema of lower extremities and lymphatic ascites within 1 year of follow-up period after surgery. Based on these findings, the authors do not recommend the use of octreotide in oncogynecological patients following pelvic and/or para-aortic lymphadenectomy.

Neuroendocrine Tumors (NETs)

Neuroendocrine tumors (NETs) are rare, occurring in less than 1 % of the general population. NETs can begin in any part of the body, including the lung, gastrointestinal tract and pancreas. 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. Guidelines from the UKNetwork 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.

UKNetwork 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 analogues. 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.

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). 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.

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".

Carcinoid Tumors

A carcinoid tumor is a type of neuroendocrine tumor (NET) which occurs most often in the gastrointestinal tract or the lungs.

Gastroenteropancreatic tumors are also classified as carcinoid tumors. Carcinoid tumors are rare, slow-growing tumors that originate in cells of the diffuse neuroendocrine system. They occur most frequently in tissues derived from the embryonic gut. Foregut tumors, which account for up to 25% of cases, arise in the lung, thymus, stomach, or proximal duodenum. Midgut tumors, which account for up to 50% of cases, arise in the small intestine, appendix, or proximal colon, with the appendix being the most common site of origin. Hindgut tumors, which account for approximately 15% of cases, arise in the distal colon or rectum. Other sites of origin include the gallbladder, kidney, liver, pancreas, ovary, and testis.

Carcinoid Tumors are neuroendocrine tumors derived from enterochromaffin or Kulchitsky cells which are widely distributed in the body. They may be found at any location in the body but usually originate in the foregut, midgut, or hindgut. The annual incidence of carcinoid tumors is around two cases per 100,000 and it varies with age, gender and race. Under the age of 50, incidence is twice as high in females, and at older ages a male dominance is observed.

Carcinoid 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. Life-threatening hypotension may occur due to a carcinoid crisis. Rapid bolus IV may be given in emergency situations.

Conventional therapy to inhibit the severe diarrhea and flushing episodes that result from carcinoid tumors is reduction in consumption of foods and stress that cause flushing; and loperamide, diphenoxylate-atropine, serotonin antagonists, or codeine for diarrhea. Octreotide is a proper choice for patients who have not achieved adequate response from use of these prior agents. In a prospective, open, comparative study with a crossover design, octreotide 200 micrograms given subcutaneously 2 to 3 times daily for one month was well tolerated and effective in controlling symptoms in patients with carcinoid syndrome. Disappearance or improvement in flushes occurred in 68% of patients (17 of 25). In addition, 50% of patients (11 of 22) reported a disappearance or improvement of diarrhea. The mean decrease in the 24-hour urinary biochemical tumor marker level was 25%. A decrease of greater than or equal to 25% in the 24-hour level was observed in 50% of patients receiving octreotide (O'Toole et al, 2000a). In a six month clinical trial of 93 patients with metastatic carcinoid syndrome, overall mean daily flushing episodes and daily stool frequencies were as well controlled or similar in octreotide LAR depot as octreotide injection s.c.

Toumpanakis and Caplin (2013) stated that somatostatin analogs (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.

Carcinoid Syndrome

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 4rth 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 $p < \text{or} = 0.001$); 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 "[w]e usually begin therapy with octreotide LAR 20 to 30 mg every four weeks. Depot lanreotide is another alternative to octreotide LAR".

On September 18, 2017, Ipsen Biopharmaceuticals, Inc. announced the U.S. FDA approval of Somatuline Depot (lanreotide) injection 120 mg for the treatment of carcinoid syndrome, which when used, reduces the frequency of short-acting somatostatin analogue rescue therapy (Ipsen, 2017).

FDA approval for the carcinoid syndrome treatment indication was based on a multicenter, randomized, 16-week, double-blind, placebo-controlled trial (Study 4). The trial included 115 patients with histopathologically-confirmed neuroendocrine tumors and a history of carcinoid syndrome

(flushing and/or diarrhea) who were treatment naïve or stable on another somatostatin analog and who were randomized 1:1 to receive Somatuline Depot 120 mg (n=59) or placebo (n=56) by deep subcutaneous injection every 4 weeks. The mean patient age was 59 years old (range 27 to 85 years). "Patients were instructed to self-administer a short-acting somatostatin analog (octreotide) as rescue medication as needed for symptom control. The use of rescue therapy and the severity and frequency of diarrhea and flushing symptoms were reported daily in electronic patient diaries. During the 16 week double-blind phase, the primary efficacy outcome measure was the percentage of days in which patients administered at least one injection of rescue medication for symptom control. Average daily frequencies of diarrhea and flushing events were assessed secondarily." "Patients in the Somatuline Depot arm experienced 15% fewer days on rescue medication compared to patients in the placebo arm (34% vs. 49% of days, respectively; p=0.02). The average daily frequencies of diarrhea and flushing events in patients treated with Somatuline Depot (and rescue medication) were numerically lower relative to patients treated with placebo (and rescue medication), but were not statistically significantly different via hierarchical testing" (FDA, 2017).

The most common adverse reactions occurring in "greater than 10% of patient who received Somatuline Depot in the GEP-NET trial were abdominal pain (34%), musculoskeletal pain (19%), vomiting (19%), headache (16%), injection site reaction (15%), hyperglycemia (14%), hypertension (14%), and cholelithiasis (14%). Adverse reactions occurring in the carcinoid syndrome trial were generally similar to those in the GEP-NET trial. Adverse reactions occurring in greater than 5% of patients who received Somatuline Depot in the carcinoid syndrome trial and occurring at least 5% greater than placebo were headache (12%), dizziness (7%) and muscle spasm (5%)" (Ipsen, 2017).

Pancreaticoduodenectomy (Whipple's procedure)

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-pancreaticoduodenectomy.

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

Pancreatitis

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.

Pituitary Adenomas

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)".

Prevention and Treatment of Pancreatic Fistulas Following Pancreatic Surgery

Machado (2012) stated that resection of pancreas, especially pancreaticoduodenectomy, is a complex procedure, usually performed in selected patients with benign and malignant disease of the pancreas and peri-ampullary region. Despite significant improvements in the safety and effectiveness of pancreatic surgery, pancreatico-enteric anastomosis continues to be the "Achilles heel" of pancreaticoduodenectomy, due to its association with a measurable risk of leakage or failure of healing, leading to pancreatic fistula. The morbidity rate after pancreaticoduodenectomy remains high in the range of 30 % to 65 %, although the mortality has significantly dropped to below 5 %. Most of these complications are related to pancreatic fistula, with serious complications of intra-abdominal abscess, post-operative bleeding, and multi-organ failure. Several pharmacological and technical interventions have been suggested to decrease the pancreatic fistula rate, but the results have been controversial.

Kabanov et al (2013) noted that in the period from 2011 till 2012, octreotide-depot was used by the authors in treatment of 34 patients. Patients were divided into 2 groups: (i) the prevention of development and (ii) the treatment of external pancreatic fistulas. Octreotide-depot was applied in 17 patient of the first group: as part of the complex therapy of severe pancreatitis in 4 patients and after pacreaticoduodenectomy in 13 patients. Octreotide-depot was used in 17 patients of the second group: 7 cases of patients after different types of pancreatic resections and after external drainage of pancreatic cysts in 10 patients. The positive effect of using the drug was obtained in 30 patients (88.25 %): the cases of preventive application of drug in 17 patients and during the treatment of external pancreatic fistulas in 13 patients. The preventive and therapeutic usage of octreotide-depot facilitated an uncomplicated post-operative period in 13 cases and the healing of the external pancreatic fistulas in terms from 5 till 7 days in 13 patients. The authors concluded that the application of octreotide-depot could be recommended as a preventive measure against the incompetence of pancreaticojejunoanastomosis after pancreaticoduodenectomy in complex therapy of severe pancreatitis and also in treatment of external pancreatic fistulas after pancreaticoduodenectomy and percutaneous drainage of post-necrotic pseudocysts.

In a Cochrane review, Gurusamy and associates (2013) 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 2013, Issue 1), MEDLINE, EMBASE and Science Citation Index Expanded to February 2013. They included RCTs comparing prophylactic somatostatin or one of its analogs versus no drug or placebo during pancreatic surgery (irrespective of language or publication status). Two review authors independently assessed trials for inclusion and independently extracted data. They analyzed data with both the fixed-effect and random-effects models using Review Manager (RevMan). They calculated the RR, MD or 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 a per protocol analysis. They identified 21 trials (19 trials of high risk of bias)

involving 2,348 people. There was no significant difference in the peri-operative mortality (RR 0.80; 95 % CI: 0.56 to 1.16; n = 2,210) or the number of people with drug-related adverse effects between the 2 groups (RR 2.09; 95 % CI: 0.83 to 5.24; n = 1,199). Quality of life was not reported in any of the trials. The overall number of participants with post-operative complications was significantly lower in the somatostatin analog group (RR 0.70; 95 % CI: 0.61 to 0.80; n = 1,903); but there was no significant difference in the re-operation rate (RR 1.26; 95 % CI: 0.58 to 2.70; n = 687) or hospital stay (MD -1.29 days; 95 % CI: -2.60 to 0.03; n = 1,314) between the groups. The incidence of pancreatic fistula was lower in the somatostatin analog group (RR 0.66; 95 % CI: 0.55 to 0.79; n = 2,206). 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 significant difference between the 2 groups (RR 0.69; 95 % CI: 0.38 to 1.28; n = 292). The authors concluded that somatostatin analogs may reduce peri-operative complications but do not reduce peri-operative mortality. Further adequately powered trials with low risk of bias are necessary. Moreover, they stated that based on the current available evidence, somatostatin and its analogs are recommended for routine use in people undergoing pancreatic resection.

Allen and colleagues (2014) conducted a single-center, randomized, double-blind trial of peri-operative subcutaneous pasireotide (a somatostatin analog that has a longer half-life than octreotide and a broader binding profile) in patients undergoing either pancreaticoduodenectomy or distal pancreatectomy. These researchers randomly assigned 300 patients to receive 900 µg of subcutaneous pasireotide (152 patients) or placebo (148 patients) twice-daily beginning pre-operatively on the morning of the operation and continuing for 7 days (14 doses). Randomization was stratified according to the type of resection and whether the pancreatic duct was dilated at the site of transection. The primary end-point was the development of pancreatic fistula, leak, or abscess of grade 3 or higher (i.e., requiring drainage). The primary end-point occurred in 45 of the 300 patients (15 %). The rate of grade 3 or higher post-operative pancreatic fistula, leak, or abscess was significantly lower among patients who received pasireotide than among patients who received placebo (9 % versus 21 %; RR, 0.44; 95 % CI: 0.24 to 0.78; p = 0.006). This finding was consistent among 220

patients who underwent pancreaticoduodenectomy (10 % versus 21 %; RR, 0.49; 95 % CI: 0.25 to 0.95) and 80 patients who underwent distal pancreatectomy (7 % versus 23 %; RR, 0.32; 95 % CI: 0.10 to 0.99), as well as among 136 patients with a dilated pancreatic duct (2 % versus 15 %; RR, 0.11; 95 % CI: 0.02 to 0.60) and 164 patients with a non-dilated pancreatic duct (15 % versus 27 %; RR, 0.55; 95 % CI: 0.29 to 1.01). The authors concluded that peri-operative treatment with pasireotide decreased the rate of clinically significant post-operative pancreatic fistula, leak, or abscess.

Adachi et al (2015) stated that prior studies suggested that early drain removal prevented the development of pancreatic fistula (PF) after pancreatico-duodenectomy (PD), but there has been no corresponding prospective trial for distal pancreatectomy (DP). These researchers examined if the safety and effectiveness of early drain removal and triple-drug therapy (TDT) with gabexate mesilate, octreotide and carbapenem antibiotics to prevent PF after DP in patients at high-risk of developing PF. A total 71 patients who underwent a DP were enrolled. These investigators prospectively divided them into 2 groups: (i) the late-removal group, in which the drain remained in place for at least for 5 days post-operatively (n = 30) and (ii) the early-removal group in which the drain was removed on post-operative day 1 (POD1) (n = 41). For the patients with a high drain amylase level (greater than or equal to 10,000 IU/L) and patients with symptomatic intraperitoneal fluid collection, the original TDT was introduced. The primary end-point was the safety and effectiveness of this management, and the secondary end-point was the incidence of PF. The incidence of clinical PF was significantly lower in the early-removal group (0 % versus the late removal 16 %; $p < 0.001$). In the early-removal group, TDT was administered to 12 patients (29 %) and none of the patients needed additional treatment after TDT. The authors concluded that post-operative management after DP with early drain removal and TDT was safe and effective for preventing PF.

An UpToDate review on "Pancreatic fistulas: Management" (Vege and Kendrick, 2015) states that "Supportive care for PFs includes somatostatin analogue, octreotide (100 micrograms subcutaneously three times a day) in patients with high-output PFs or those that result in electrolyte abnormalities or skin breakdown. Somatostatin preparations may be effective in the reduction of fistula output but not the rate of fistula

closure. In a 2012 meta-analysis of seven randomized trials that included 297 patients of which 102 had pancreatic fistulas, closure rates were not significantly higher in patients treated with somatostatin analogues as compared with controls".

Spinal Paraganglioma

Yin et al (2017) stated that paraganglioma rarely develops in the spine. With few cases reported, little knowledge about this disease was known. These investigators illustrated the clinical features, imaging manifestations, pathological appearances and long-term outcomes of the consecutive surgeries by literature review. The clinical and follow-up data of 18 patients who were diagnosed of spinal paraganglioma and treated with surgeries in the authors' hospitals from 2003 to 2014 were retrospectively analyzed. A total of 14 patients radiographed of intra-spinal tumor underwent extra-capsular tumor resection. Of 5 patients with obvious vertebral bone damage, 4 cases underwent piecemeal resection, and the left one with sacral tumor underwent en bloc tumor excision. Spinal reconstruction was performed in all cases. Follow-up lasted for 16 to 96 months (average of 44.1 months). There was no local recurrence or distant metastasis in cases without obvious bone invasion. Of those 5 cases with vertebral bone damage, 1 case suffered and survived from the repeat relapse of T1 vertebral body tumor. Local recurrence was not observed in 1 case with T10 vertebral tumor after tumor resection, but the tumor metastasized to T2 attachment during the follow-up and was finally eradicated by re-operation. No tumor recurrence was observed in the remaining 3 cases. The authors concluded that paraganglioma, usually benign, rarely occurs. Surgical resection, especially complete surgical resection, is preferred to treat spinal paraganglioma. Chemotherapy, radiotherapy, use of octreotide and other somatostatin are selected as adjuvant therapies, but their effects remain unknown.

Tumor-Induced Osteomalacia

Ovejero and colleagues (2017) noted that tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome in which unregulated hyper-secretion of fibroblast growth factor 23 (FGF23) by phosphaturic mesenchymal tumors (PMT) causes renal phosphate wasting,

hypophosphatemia, and osteomalacia. The resulting mineral homeostasis abnormalities and skeletal manifestations can be reversed with surgical resection of the tumor. Unfortunately, PMTs are often difficult to locate, and medical treatment with oral phosphate and vitamin D analogs is either insufficient to manage the disease or not tolerated. Octreotide has been proposed as a potential treatment for TIO due to the presence of SSTR on PMTs; however, the role of somatostatin signaling in PMTs and the effectiveness of treatment of TIOs with somatostatin analogs is unclear. These researchers evaluated the effectiveness of octreotide therapy in TIO – 5 subjects with TIO were treated with octreotide for 3 days. Blood intact FGF23, phosphate, and 1,25(OH)2 D3 , and tubular reabsorption of phosphate (TRP) were measured at frequent time-points during treatment. Octreotide's effects were examined by comparing group means of the biochemical parameters at each time-point to mean baseline values. The authors reported that there were no significant changes in blood phosphate, FGF23, 1,25(OH)2 D3 , or TRP during octreotide treatment, consistent with a lack of effectiveness of octreotide in treating TIO.

Uveal Melanoma

In a phase-II clinical trial, Shoushtari and colleagues (2016) tested the hypothesis that inhibiting mammalian target of rapamycin and insulin-like growth factor-1 receptor would be effective in metastatic uveal melanoma. This was a study of everolimus 10-mg daily plus pasireotide long-acting release (LAR) 60-mg every 28 days enrolling patients with progressive, metastatic uveal melanoma to treatment until progression by RECIST 1.1 or unacceptable toxicity. The primary end-point was clinical benefit rate, defined as any objective response or RECIST 1.1 stable disease at 16 weeks. A subset of patients underwent baseline indium-111-octreotide scans. A total of 14 patients were enrolled, of which 13 were evaluable for the primary end-point, before the study was terminated due to poor accrual; 3 of 13 (26 %) patients obtained clinical benefit; 7 of 13 (54 %) had stable disease lasting for a median of 8 weeks (range of 8 to 16 weeks). Grade-3 AEs deemed at least possibly related to study drugs were hyperglycemia (n = 7), oral mucositis (n = 2), diarrhea (n = 1), hypophosphatemia (n = 1), and anemia (n = 1); 7 of 14 (50 %) patients required at least 1 dose reduction due to toxicity; 7 of 8 (88 %) patients with baseline indium-111-octreotide scans had at least 1 avid lesion, with

significant intra-patient heterogeneity. There was a trend toward an association between octreotide avidity and cytostatic response to therapy ($p = 0.078$). The authors concluded that the combination of everolimus and pasireotide had limited clinical benefit in this small metastatic uveal melanoma cohort. They stated that further investigation into the relationship between somatostatin receptor expression and cytostatic activity of somatostatin analogs is needed.

Vasoactive Intestinal Peptide Tumors

Vasoactive Intestinal Peptide Tumors are rare cancers in which tumor cells arise from certain hormone-producing cells called islet cells. These cells are most commonly located in the pancreas but may also be located in or around the adrenal glands. These VIPomas produce excessive amounts of vasoactive intestinal peptide which causes the symptoms of watery diarrhea. VIPomas are very rare cancers and very few new cases are reported each year (0.05 to 0.2 cases per million adults). Even fewer cases in children are reported. When they do develop in adults they appear most commonly between the ages of 40-50 and usually develop in the pancreas. In children they most commonly appear around the adrenal glands. Treatment goals are to reduce the symptoms of profuse watery diarrhea associated with these secreting tumors. The severe watery diarrhea responds to octreotide and improves electrolyte imbalances and overall condition of the patient.

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.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
Code	**Code Description**
Octreotide (Sandostatin, Sandostatin LAR Depot):	
Other CPT codes related to the CPB:	
33615	Repair of complex cardiac anomalies (e.g., tricuspid atresia) by closure of atrial septal defect and anastamosis of atria or vena cava to pulmonary artery (simple Fontan procedure)
33617	Repair of complex cardiac anomalies (e.g., single ventricle) by modified Fontan procedure
43204	Esophagoscopy, flexible, transoral; with injection sclerosis of esophageal varices
43400	Ligation, direct, esophageal varices
43405	Ligation or stapling at gastroesophageal junction for pre-existing esophageal perforation
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 duodenojejunostomy (pylorus-sparing, Whipple-type procedure); with pancreatojejunostomy
48154	without pancreatojejunostomy
96361 - 96379 99601 - 99602	IV therapy, subcutaneous infusion, therapeutic injection, and home infusion/specialty drug administration
HCPCS codes covered if selection criteria are met:	
Bynfezia Pen (octreotide acetate) - no specific code	
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:	
G0069	Professional services for the administration of subcutaneous immunotherapy for each infusion drug administration calendar day in the individual's home, each 15 minutes

Code	Code Description
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-10 codes covered if selection criteria are met:	
C15.3 - C15.9	Malignant neoplasm of esophagus
C16.0 - C16.9	Malignant neoplasm of stomach
C17.0 - C19	Malignant neoplasm of small intestine including duodenum, colon, and rectosigmoid junction
C25.0 - C25.9	Malignant neoplasm of pancreas
C33 - C34.92	Malignant neoplasm of trachea, bronchus and lung [non-small cell]
C37	Malignant neoplasm of thymus
C4a.0 - C4a.9 C7a.00 - C7a.8 D3a.00 - D3a.8	Neuroendocrine tumors
C74.00 - C74.92	Malignant neoplasm of adrenal gland
C75.1 - C75.2	Malignant neoplasm of pituitary gland and craniopharyngeal duct [pituitary adenomas]
C75.4	Malignant neoplasm of carotid body [paraganglioma]
C75.5	Malignant neoplasm of aortic body and other paraganglia [paraganglioma]
D13.7	Benign neoplasm of endocrine pancreas [islets of Langerhans]
D15.0	Benign neoplasm of thymus
D32.0	Benign neoplasm of cerebral meninges [unresectable meningiomas]
D35.00 - D35.02	Benign neoplasm of adrenal gland [pheochromocytoma / paraganglioma]
D35.2 - D35.3	Benign neoplasm of pituitary gland and craniopharyngeal duct (pouch)

Code	Code Description
D35.5	Benign neoplasm of carotid body [paraganglioma]
D35.6	Benign neoplasm of aortic body and other paraganglia [paraganglioma]
D44.3 - D44.4	Neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct
D44.6	Neoplasm of uncertain behavior of carotid body [paraganglioma]
D44.7	Neoplasm of uncertain behavior of aortic body and other paraganglia [paraganglioma]
E16.4	Increased secretion of gastrin
E22.0	Acromegaly and pituitarygigantism
E24.0 - E24.9	Cushing's syndrome
E34.0	Carcinoid syndrome
I85.01	Esophageal varices with bleeding
I85.11	Secondary esophageal varices with bleeding
K63.2	Fistula of intestine [enterocutaneous fistulae of small intestine with volume depletion]
K91.2	Postsurgical malabsorption, not elsewhere classified
R19.7	Diarrhea
T66.xxx+	Radiation sickness, unspecified
T81.83x+	Persistent postprocedural fistula [following pancreatic surgery]
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
C50.011 - C50.929	Malignant neoplasm of breast
C61	Malignant neoplasm of prostate [hormone refractory prostate cancer]
C73	Malignant neoplasm of thyroid gland
E08.00 - E09.9	Secondary diabetes mellitus
E10.10 - E13.9	Diabetes mellitus
E34.4	Constitutional tall stature [idiopathic]

Code	Code Description
E66.01 - E66.09, E66.8, E66.9	Obesity
G93.2	Benign intracranial hypertension
I89.8	Other specified noninfective disorders of lymphatic vessels and lymph nodes [chylothorax in neonates]
K22.8	Other specified diseases of esophagus [acute non-variceal upper gastrointestinal bleeding]
K31.84	Gastroparesis
K50.00 - K50.919	Crohn's disease
K85.90 - K85.92	Acute pancreatitis, unspecified
K90.41 - K90.49, K90.89	Malabsorption due to intolerance and other intestinal malabsorption [protein-losing enteropathy following the Fontan operation]
K91.1	Postgastric surgery syndromes [Dumping syndrome]
K92.0	Hematemesis
K92.1	Melena
K92.2	Gastrointestinal hemorrhage, unspecified
M83.8	Other adult osteomalacia [tumor-induced osteomalacia]
Q27.33	Arteriovenous malformation of digestive system vessel [cecal arterio-venous malformation]
Q44.0 - Q44.1 Q44.4 - Q44.5 Q44.7	Anomalies of gallbladder, bile ducts, and liver [vascular (arterio-venous) malformations of the gastrointestinal tract]
Q61.11 - Q61.3	Polycystic kidney
Q82.0	Hereditary lymphedema
T82.598A - T82.599S	Other mechanical complication of other cardiac and vascular devices and implants

Code	Code Description
T82.897A - T82.897S	Other specified complication of cardiac prosthetic devices, implants and grafts
Z95.811	Presence of heart assist device [GI bleeding in left ventricular assist device recipients]
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-10 codes covered if selection criteria are met:	
C25.0 - C25.9	Malignant neoplasm of pancreas
C7A.010 - C7B.8	Malignant neuroendocrine tumors
D37.1 - D37.9	Neoplasm of uncertain behavior of digestive organs [unresected gastrinoma]
E16.4	Increased secretion of gastrin [Zollinger-Ellison syndrome]
E22.0	Acromegaly and pituitary gigantism [with inadequate response to or cannot be treated with surgery and/or radiotherapy]
E24.0 - E24.9	Cushing's syndrome
E34.0	Carcinoid syndrome
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
C22.0 -C22.1	Malignant neoplasm of liver and intrahepatic bile ducts
C61	Malignant neoplasm of prostate [castration resistant]
E16.1	Other hypoglycemia [congenital hyperinsulinemia]
E34.4	Constitutional tall stature [idiopathic]
K92.0	Hematemesis
K92.1	Melena
K92.2	Gastrointestinal hemorrhage
K94.19	Other complications of enterostomy [prevention and management of high-output ileostomy after colorectal cancer surgery]

Code	Code Description
Q61.11 - Q61.3	Polycystic kidney
Pasireotide Pamoate (Signifor LAR):	
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:	
J2502	Injection, pasireotide long acting, 1 mg
ICD-10 codes covered if selection criteria are met:	
E22.0	Acromegaly and pituitary gigantism
E24.0 - E24.9	Cushing's syndrome
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
C22.0	Liver cell carcinoma
C43.0 - C43.9	Malignant melanoma of the skin
C61	Malignant neoplasm of prostate
C69.30 - C69.32	Malignant neoplasm of choroid
C69.40 - C69.42	Malignant neoplasm of ciliary body
C73	Malignant neoplasm of thyroid gland [medullary thyroid cancer]
C7A.00 - C7B.8	Secondary malignant neoplasm of liver and intrahepatic bile duct [unresectable neuroendocrine tumors with hepatic metastases]
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct [unresectable neuroendocrine tumors with hepatic metastases]
D35.2	Benign neoplasm of pituitary gland [treatment of dopamine-resistant prolactinoma]
K31.811 - K31.819	Angiodysplasia of stomach and duodenum
K55.20 - K55.21	Angiodysplasia of colon

Code	Code Description
K76.89	Other specified diseases of liver [hepatic cysts]
K91.1	Postgastric surgery syndromes [dumping syndrome]
Q44.6	Cystic disease of liver [hepatic cysts]
R63.8	Other symptoms and signs concerning food and fluid intake [constitutional (idiopathic) tall stature]
Pasireotide Diaspartate (Signifor SAR):	
Other CPT codes related to the CPB:	
80420	Dexamethasone suppression panel, 48 hour This panel must include the following: Free cortisol, urine (82530 x 2) Cortisol (82533 x 2) Volume measurement for timed collection (81050 x 2)
82530	Cortisol; free
82533	Cortisol; total
HCPCS codes covered if selection criteria are met:	
Pasireotide Diaspartate (Signifor SAR) - no specific code:	
ICD-10 codes covered if selection criteria are met:	
E24.0 - E24.9	Cushing's syndrome
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
C22.0	Liver cell carcinoma
C43.0 - C43.9	Malignant melanoma of the skin
C61	Malignant neoplasm of prostate
C69.30 - C69.32	Malignant neoplasm of choroid
C69.40 - C69.42	Malignant neoplasm of ciliary body
C73	Malignant neoplasm of thyroid gland [medullary thyroid cancer]
C7A.00 - C7B.8	Secondary malignant neoplasm of liver and intrahepatic bile duct [unresectable neuroendocrine tumors with hepatic metastases]
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct [unresectable neuroendocrine tumors with hepatic metastases]

Code	Code Description
D35.2	Benign neoplasm of pituitary gland [treatment of dopamine-resistant prolactinoma]
E34.4	Constitutional tall stature
K31.811 - K31.819	Angiodysplasia of stomach and duodenum
K55.20 - K55.21	Angiodysplasia of colon
K70.0 - K70.9	Alcoholic liver disease [severe liver disease]
K76.0 - K76.9	Other diseases and specified diseases of liver [severe liver disease]
K91.1	Postgastric surgery syndromes [dumping syndrome]
Q44.6	Cystic disease of liver [hepatic cysts]

The above policy is based on the following references:

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