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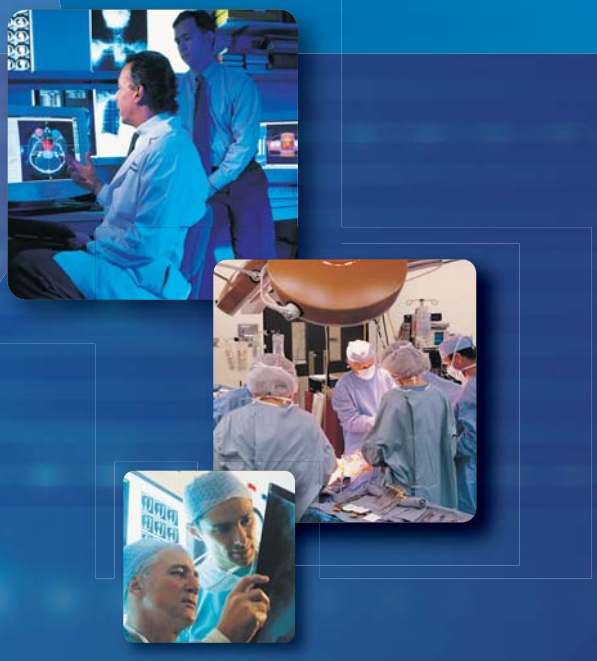
Octreotide for Endocrine, Oncologic, and Gastrointestinal Disorders: Systematic Review and Budget Impact Analysis



Supporting Informed Decisions

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Canadian Agency for Drugs and Technologies in Health

Octreotide for Endocrine, Oncologic, and Gastrointestinal Disorders: Systematic Review and Budget Impact Analysis

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July 2008

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This report is a review of existing literature, studies, materials, and other information and documentation (collectively the "source documentation") that are available to CADTH. The accuracy of the contents of the source documentation on which this report is based is not warranted, assured, or represented in any way by CADTH, and CADTH does not assume responsibility for the quality, propriety, inaccuracies, or reasonableness of any statements, information, or conclusions contained in the source documentation.

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Industry: *Novartis Pharmaceuticals Canada Inc. was provided with an opportunity to comment on an earlier version of this report. Comments were received and were considered when preparing the final report.*

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Gaetanne Murphy participated in the development of the protocol, selection of studies, and extraction of study data. She was the principal author of the clinical methods, variceal bleed, and

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Conflicts of Interest

Stella Chen, Christine Cripps, Brigitte Desjardins, Derek Jonker, Shaila Mensinkai, Kristen Moulton, Gaetanne Murphy, Kusiel Perlman, Christine Perras, and Becky Skidmore have no conflicts of interest to declare.

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REPORT *IN BRIEF*

July 2008

Octreotide for Endocrine, Oncologic, and Gastrointestinal Disorders: Systematic Review and Budget Impact Analysis

Technologies

Octreotide, which is a synthetic analogue of somatostatin, inhibits endocrine and exocrine secretions.

Condition

Octreotide is approved by Health Canada for use in acromegaly, neuroendocrine tumours, pancreatic surgery, and emergency bleeding of gastroesophageal varices. Octreotide is also being used for other unapproved indications.

Issue

Given the growing use of octreotide and the availability of a long-acting somatostatin analogue (lanreotide), a review of the clinical and cost-effectiveness evidence on the approved uses and on six selected unapproved uses of octreotide is timely.

Methods and Results

Relevant meta-analyses or systematic reviews, randomized controlled trials (RCTs), controlled clinical trials, and economic analyses were identified. Eight-two RCTs were included. Meta-analysis was possible for outcomes in five indications. Data from the non-randomized controlled clinical trials were used for the assessment of harms only. For the economic analysis, a narrative synthesis of eight identified economic evaluations (four in a Canadian context) was conducted, and a budget impact analysis for five publicly funded drug plans was completed.

Implications for Decision Making

- **Substantial uncertainty remains.** An effect on mortality has not been observed. Octreotide improved surrogate markers of efficacy or short-term symptom control in patients with acromegaly, neuroendocrine tumours, esophageal bleeding, and bowel obstruction**.** For patients with hepatocellular carcinoma, pancreatic cancer, or refractory diarrhea related to HIV-AIDS or chemotherapy, no consistent clinical effect was found. Octreotide is not associated with substantial harm in the short term. The impact on health-related quality of life, the efficacy of short-acting versus long-acting octreotide, or the optimal duration of octreotide therapy is largely unknown.
- **The use of octreotide in pancreatic surgery warrants consideration.** Octreotide reduced the risk of some complications after pancreatic surgery and is more effective and less costly compared to placebo.
- **A potential for increased expenditures exists.** The coverage of unapproved indications could double the expenditures on octreotide for publicly funded drug plans. If only palliative care programs are funded, reimbursement for approved and unapproved indications results in a smaller budget increase.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): Murphy G, Perras C, Desjardins B, Chen S, Moulton K, Jonker D, Perlman K, Pasieka J, Ezzat S, Cripps C, Mensinkai S, Skidmore B. *Octreotide for endocrine, oncologic, and gastrointestinal disorders: systematic review and budget impact analysis.*

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EXECUTIVE SUMMARY

Issue

Octreotide, which is a synthetic analogue of somatostatin, inhibits endocrine and exocrine secretions. Health Canada has approved octreotide for use in four indications. It is, however, also being used for other conditions. Publicly funded drug programs are seeing an increasing number of requests to cover these off-label uses. A new long-acting somatostatin analogue (lanreotide) has received Health Canada approval for the treatment of acromegaly. Given the growing use of octreotide and the availability of lanreotide, it is timely to review the evidence regarding the clinical effectiveness and cost-effectiveness of octreotide.

Objectives

The aim of the review was to examine the clinical and cost-effectiveness of octreotide for Health Canada-approved and unapproved uses, compared with placebo, no treatment, or active comparators. The indications that were reviewed included acromegaly; gastroenteropancreatic neuroendocrine tumours (GEPNETs); prevention of complications after pancreatic surgery; emergency management of bleeding esophageal varices; refractory diarrhea related to chemotherapy, HIV-AIDS, Crohn's disease, or ileostomy; hepatocellular or pancreatic cancer; inoperable bowel obstruction; short bowel syndrome; and pediatric idiopathic or persistent hyperinsulinism.

The review tries to meet these objectives by addressing five research questions.

- What is the evidence regarding the clinical effectiveness of octreotide therapy for the selected indications?
- What is the evidence regarding the clinical effectiveness of the long-acting intramuscular depot formulation (OCT-LA) of octreotide compared with that of the short-acting subcutaneous or intravenous formulation (OCT-SA) for the selected indications?
- What is the optimal length of octreotide therapy for the selected indications?
- What is the evidence regarding the cost-effectiveness of octreotide therapy for the selected indications and regarding the cost-effectiveness of OCT-LA compared with that of OCT-SA?
- What is the budget impact on publicly funded drug programs in Canada of funding octreotide for the approved and unapproved indications?

Methods

A search for meta-analyses or systematic reviews, randomized controlled trials (RCTs), controlled clinical trials (cohort or case-control studies), and economic analyses was conducted. Data analysis was conducted based on accepted methodology for systematic reviews and meta-analyses. Data from the non-randomized controlled clinical trials were only used for the assessment of harms. For the economic analysis, a narrative synthesis of economic evaluations was conducted. A budget impact analysis was also completed.

Clinical Review

None of the systematic reviews or meta-analyses that were identified met the study criteria for quality. As a result, we conducted a new systematic review. For four indications (pediatric

hyperinsulinism, diarrhea related to ileostomy or to Crohn's disease, and short bowel syndrome), no RCTs were identified, or the trials had data that could not be analyzed. Of the 82 included RCTs, seven (9%) had adequate allocation concealment, and 31 (38%) were of higher methodological quality (Jadad score of three or higher). Meta-analysis was possible for outcomes in five indications (acromegaly, variceal bleeding, prevention of pancreatic surgery complications, bowel obstruction, and refractory diarrhea). The ability to analyze data was limited by the poor reporting of some studies; for example, the measures of dispersion were not reported clearly.

The evidence was strongest for the management of acute variceal bleeding and the prevention of complications after pancreatic surgery. The limited data available for other indications should be interpreted with caution.

- In acromegaly, OCT-SA improved surrogate endpoints (growth hormone and insulin-like growth factor-1 levels) when it was compared with placebo or no treatment.
- In esophageal variceal bleeding, OCT-SA reduced the risk of failing initial hemostasis when it was compared with placebo, no treatment, terlipressin, or vasopressin. It reduced the risk of rebleeding when it was compared with placebo or no treatment. No significant difference in the number of deaths was detected when OCT-SA was compared to any other treatment.
- In GEPNETs, limited data suggest that octreotide and lanreotide show similar results for the relief of symptoms.
- In patients undergoing pancreatic surgery, OCT-SA reduced the risk of post-operative fluid collection, pancreatic fistulas, and overall complications when it was compared with placebo or no treatment. No significant difference was detected between groups for length of hospital stay, abscess, bleeding, infection, pancreatitis, or death.
- In bowel obstruction, OCT-SA reduced vomiting and nausea when it was compared with hyoscine butylbromide.
- In refractory diarrhea related to chemotherapy, limited data suggest that OCT-SA was superior to placebo in resolving symptoms. The benefit of octreotide was unclear when it was compared with loperamide. OCT-SA was no different from placebo or placebo plus anti-diarrheal agents in patients with HIV-AIDS.
- For hepatocellular carcinoma, no consistent effect with octreotide was observed. Two small studies showed a benefit in survival with octreotide when it was compared to placebo. No benefit was detected in the other five studies.
- For pancreatic cancer, one study showed a benefit in survival with OCT-SA when it was compared with no treatment. No benefit was detected in three other studies.
- Adverse events were mainly gastrointestinal symptoms and pain at the injection site. The incidence could not be determined because of deficiencies in the reported data.

Areas of further research include comparing the formulations of octreotide in head-to-head trials and determining the optimal duration of therapy.

Economic Review

Eight economic evaluations (four of which were Canadian) met the inclusion criteria. There was sufficient information to inform formulary decisions for one indication. In patients undergoing pancreatic surgery, OCT-SA was more effective and less costly when it was compared to placebo.

Because of limitations in the studies of patients with acromegaly and GEPNETs, it is not possible to draw conclusions about the cost-effectiveness of octreotide. No studies assessed the cost-effectiveness of OCT-SA or OCT-LA in unapproved indications. Data were also lacking for patients with acute variceal bleeding.

Health Services Impact

When the prevalence rate corresponding to each approved indication was applied to the Canadian population, an estimated number of possible beneficiaries of the use of octreotide was fewer than 8,500. For the unapproved indications, the number of potential beneficiaries was more than 180,000.

The results of the budget impact analyses based on the publicly funded drug plans of British Columbia, Saskatchewan, Manitoba, Nova Scotia, and New Brunswick showed that market expansion for the unapproved indications would lead to an estimated 76% to 137% increase in octreotide expenditures in 2009-2010. For palliative care beneficiaries, reimbursement for approved and unapproved indications resulted in a smaller budget increase. Coverage for the approved indications of acromegaly and GEPNETs could be provided at a lower budget impact; for example, 3% and 16% increases for Saskatchewan and Manitoba respectively.

Conclusions

Octreotide demonstrated improvement in surrogate markers of efficacy or short-term symptom control in patients with acromegaly, GEPNETs, esophageal bleeding, and bowel obstruction. Octreotide reduced the risk of some complications after pancreatic surgery. No overall benefit was detected in death rate or survival time for variceal bleeding, pancreatic surgery, or pancreatic cancer. No conclusions could be drawn about the impact of octreotide on health-related quality of life, the efficacy of OCT-SA compared to that of OCT-LA, or the optimal duration of octreotide therapy. A descriptive review of adverse events suggested that octreotide was not associated with substantial harm in the short term.

We could not assess four indications (pediatric hyperinsulinism, short bowel syndrome, diarrhea related to ileostomy or to Crohn's disease) because of a lack of RCTs. Conclusions about the efficacy of octreotide in hepatocellular carcinoma or refractory diarrhea related to chemotherapy or HIV-AIDS could not be drawn.

In our review of economic evaluations, there were sufficient data to draw conclusions for one indication. For patients undergoing pancreatic surgery, OCT-SA was more effective and less costly than placebo. For publicly funded drug plans, the expansion of listing criteria to include unapproved indications could double the expenditures on octreotide.

ACRONYMS AND ABBREVIATIONS

5-FU	5-fluorouracil
5-HIAA	5-hydroxyindole acetic acid
AFP	α fetoprotein
AIDS	acquired immune deficiency syndrome
ARD	absolute risk difference
CI	confidence interval
CCT	controlled clinical trial (non-randomized clinical trials)
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
GEPNET	gastroenteropancreatic neuroendocrine tumour
HIV	human immunodeficiency virus
IGF-1	insulin-like growth factor-1
NNT	number needed to treat
OCT-LA	octreotide long-acting (intramuscular depot formulation)
OCT-SA	octreotide short-acting (subcutaneous or intravenous formulation)
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
SD	standard deviation
SE	standard error of the mean
SMD	standardized mean difference
VIPoma	vasoactive intestinal polypeptide-secreting tumour
WMD	weighted mean difference

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1 INTRODUCTION

1.1 Background and Setting in Canada

The drug octreotide inhibits the endocrine or exocrine secretions that are associated with many disease states.[1] As a result, it is useful in different conditions. Health Canada has approved octreotide for treating acromegaly and neuroendocrine tumours (carcinoid and vasoactive intestinal polypeptide secreting tumours), for preventing complications after pancreatic surgery, and for managing emergency bleeding of gastroesophageal varices in patients with underlying cirrhosis.[1-3] Octreotide is also being used for indications that have not been approved by Health Canada. As a result, publicly funded drug plans see a growing number of requests for coverage.

This research project assesses the clinical effectiveness and cost-effectiveness of octreotide for four approved indications and for the following unapproved indications: refractory diarrhea related to HIV-AIDS, chemotherapy, Crohn's disease, or ileostomy; hepatocellular carcinoma; pancreatic cancer; inoperable bowel obstruction; short bowel syndrome; and pediatric idiopathic or persistent hyperinsulinism.

1.1.1 Acromegaly

Acromegaly is caused by overproduction of growth hormone that is often due to a tumour in the pituitary gland.[4] In Europe, three to four people per million are diagnosed every year, and the estimated prevalence is 60 patients per million.[5] The clinical manifestations include more than disfigurement. The untreated disease results in complications such as heart disease, diabetes, arthritis, sleep apnea, and premalignant colonic polyps.[6]

The estimated treatment costs are $14.7 million annually in Canada [95% confidence interval (CI), $10.6 million to $18.8 million].[7] Patients are often not diagnosed until complications arise, and then the tumour can be difficult to eradicate. A single form of treatment, such as pituitary surgery or irradiation, is effective in less than half of patients. As a result, many patients undergo long-term therapy. Monthly injections of somatostatin analogues are reportedly effective in approximately 65% of patients.[6] Some patients may require additional or alternative forms of medical therapy, such as pegvisomant, to control disease progression.[8]

1.1.2 Emergency management of acute variceal bleeding

Acute variceal bleeding is a potentially life-threatening complication of portal hypertension and chronic liver disease. Esophageal varices develop in approximately 30% of patients with cirrhosis. Of these, approximately one third will experience bleeding.[9] The mortality rate with each bleeding episode is approximately 20% to 30%, depending on the severity of the underlying liver disease.[9-11] Acute bleeding episodes are likely to recur if no preventative treatment is initiated to obliterate varices or reduce portal hypertension. The average direct health care cost of an episode of variceal bleeding is estimated to be US$16,715.[12]

The therapeutic management of acute bleeding includes fluid resuscitation; endoscopic ligation or sclerotherapy; vasoactive agents (for example, somatostatin analogues, terlipressin, and

vasopressin); and possibly antimicrobials.[9,10] Balloon tamponade or a transjugular intrahepatic portosystemic shunt may also be required in those who fail to respond to initial hemostasis.[9,10] Secondary prophylaxis with beta-blockers or repeat endoscopic treatments are often indicated.[9]

1.1.3 Gastroenteropancreatic neuroendocrine tumours

Gastroenteropancreatic neuroendocrine tumours (GEPNETs) account for less than 1% of all cancers. The incidence is one to three per 100,000 in the US and Europe.[13,14] GEPNETs are diverse tumours with biological behaviour that seems to depend on the site of origin, the tumour differentiation, tumour burden, and hormonal production. Because of the rarity of these tumours, most of the information about them has been gleaned from large cohort databases.[15-17] GEPNETs are often slow-growing, and most patients present late in the course of their disease. The overall five-year survival ranges from 34% to 58%. Survival curves for any of these tumours are difficult to interpret because treatment is inconsistent between institutions and between patients. Complete surgical resection, when possible, offers the only chance for cure. Unlike adenocarcinomas of the gastrointestinal tract, GEPNETS may require treatment to control hormonal production. Endocrinopathies can be life-threatening or debilitating. New treatment options such as hormonal therapy (for example, octreotide) and radionuclide therapy have been used for palliation, but their role in prolonging survival has yet to be determined.[18-20] The European community has established treatment guidelines and a similar strategy will be used to help develop North American guidelines in 2008.

1.1.4 Prevention of complications after pancreatic surgery

Complications after pancreatic surgery stem from the complexity of the surgery and from the patients' co-morbidities.[21] The mortality rate after surgery was as high as 20% in the 1970s, but it has since fallen below 5%.[22] The post-operative complication rates for pancreatico-duodenectomy, however, remain as high as 60% in the US and Europe.[21] Serious post-operative complications such as hemorrhage, infection, failure of other anastomoses, or fistulization may arise because of the leakage of digestive enzymes. Patients who experience post-operative complications stay in hospital significantly longer than those who do not experience complications, and may require intensive care and repeat surgery.[21,23] In Ontario, the average direct medical costs for patients with post-operative complications was estimated at C$32,437, compared to $11,169 for those without complications (in-hospital costs only).[24,25] Octreotide is used prophylactically during the peri-operative period to inhibit pancreatic enzyme secretion.[26]

1.1.5 Bowel obstruction

Bowel obstruction is a mechanical or functional obstruction of the intestines, preventing the normal transit of the products of digestion. It can occur at any level of the bowel distal to the duodenum. The three most common etiologies are adhesions from previous surgeries, hernias, and neoplasms. Signs and symptoms include abdominal pain, distension, vomiting, and constipation.[27,28]

Whenever possible, the underlying cause of the bowel obstruction should be treated. Some causes may resolve spontaneously, but many require operative treatment.[27] In malignant large bowel obstruction, endoscopically placed self-expanding metal stents may relieve the

obstruction. Other treatment options include limiting oral intake, maintaining intravascular volume, correcting electrolyte abnormalities, and using nasogastric suction.[27,28] These conservative measures are successful in 70% of patients.[29] It is important to manage the pain, nausea, and vomiting. Anti-secretory agents (for example, octreotide, anti-cholinergics), analgesics, and anti-emetics can all be used in the medical management of bowel obstruction.[30]

1.1.6 Refractory diarrhea due to various causes

Chemotherapy-induced diarrhea can affect quality of life and patient compliance with treatment.[31,32] With some chemotherapy regimens, such as fluorouracil or irinotecan, diarrhea can affect as many as 50% to 80% of patients, with 30% or more having severe symptoms that correspond to Grade three to Grade five diarrhea.[33] Severe gastrointestinal toxicity has been associated with an increased risk of infectious complications and death.[33] The management of mild to moderate diarrhea includes dietary modifications, fluid replacement, and the use of anti-motility agents. Those with more severe diarrhea may need to stop chemotherapy and be hospitalized and treated with intravenous fluids and octreotide.[33]

Among patients with HIV-AIDS, diarrhea can cause malabsorption and weight loss. The prevalence of diarrhea related to HIV-AIDS varies among countries. An estimated 40% to 90% of patients suffer from diarrhea at some point.[34] Most cases have an infectious etiology, but diarrhea may be a side effect of drug therapy or it may be idiopathic.[35] Antimicrobial agents are indicated if a pathogen is isolated. In non-infectious cases, a change in the antiretroviral agents used or the use of antidiarrheal agents may be beneficial. Treatment options include fluid and electrolyte replacement, nutritional support, and the use of antimotility agents (for example, loperamide, diphenoxylate, or opiates), luminal agents (for example, cholestyramine or fibre), and hormonal agents (for example, octreotide).[35]

Crohn's disease is an inflammatory disease that is characterized by ulceration, inflammation, fibrosis, and stricturing of the bowel. It may affect any part of the gastrointestinal tract, from the mouth to the anus. In an estimated 40% to 55% of patients, both small and large bowels are implicated.[36] Signs and symptoms vary depending on the site and severity but may include abdominal pain, cramping, diarrhea, fever, weight loss, fistulas, and bowel obstruction. Diarrhea may be caused by bacterial overgrowth, bile acid malabsorption, or inflammation with decreased water absorption and increased enzyme secretion. The management of Crohn's disease includes the use of anti-inflammatory agents (for example, 5-aminosalisylic acid, sulfasalazine, mesalamine), corticosteroids, immunomodulators, and biologics (for example, infliximab). Surgical resection may be necessary and, in some cases, this may include total proctocolectomy and ileostomy.[36] In patients with an ileostomy (due to Crohn's or other diseases), high intestinal output may persist because of the underlying disease, partial bowel obstruction, intra-abdominal sepsis, or ileal resection.[37] Conventional anti-diarrheal medications may help some patients. For others, options such as octreotide may be tried.[37]

1.1.7 Hepatocellular carcinoma

In North America, the incidence of hepatocellular carcinoma is less than 10 per 100,000. The evidence suggests that the rate is rising.[38,39] The known causes are chronic viral hepatitis B, C, and D; alcohol; hereditary metabolic liver disease; non-alcoholic liver disease; and autoimmune

hepatitis.[38] If diagnosed during the early stages, the median survival is 23 to 69 months.[38] The diagnosis, however, is often not made until later when the prognosis is poor and the treatment options are limited. Surgical and percutaneous treatments have been shown to improve survival in suitable candidates. Liver resection or transplant offers a five-year survival rate of 60% to 70%, although tumour recurrence is frequent after resection.[40] For patients who are unsuitable for surgery, percutaneous alcohol injection or radiofrequency ablation may result in a five-year survival rate of 40% to 50%.[40] Other treatments, such as transarterial embolization or chemoembolization may delay tumour progression and have improved survival rates in these patients.[39] Systemic chemotherapy and drug therapies such as octreotide have been tried.[38,39,41] Many drugs have not led to promising results. Sorafenib, however, has shown a modest survival benefit.[41,42] Research is underway to find new treatment options.

1.1.8 Pancreatic cancer

Adenocarcinoma of the pancreas, which is the second most common gastrointestinal malignancy, affects approximately 29,000 new patients per year in North America.[43] The symptoms, which are often insidious, may be present for months before a diagnosis is made. Complete resection of the tumour is the only effective treatment, but only 10% to 15% of patients are diagnosed early enough to undergo surgery.[44] As nearly all patients develop metastatic disease and the efficacy of chemotherapy is modest, there is a need for more effective treatment.[45-47] The efficacy of somatostatin analogues in non-endocrine gastrointestinal malignancies is still unclear.[48]

1.1.9 Pediatric idiopathic or persistent hyperinsulinism

Persistent hyperinsulinemic hypoglycemia of infancy, which is also known as congenital hyperinsulinism and which was called nesidioblastosis, is the most common cause of persistent hypoglycemia in infancy.[49] The incidence in the US is approximately one per 25,000 to 50,000 live births,[50] while in populations with a higher incidence of consanguinity, it is approximately 10 times more common.[51]

In children with persistent hyperinsulinemia, the reciprocal relationship between blood glucose and insulin secretion is disturbed by an abnormal functioning or regulation of the adenosine triphosphate-dependent potassium channel of the beta cell. The result is uncontrolled over-secretion of insulin.[52]

The goal of therapy is to prevent the neurological symptoms and sequelae (for example, epilepsy, mental retardation, microcephaly) of prolonged or recurrent hypoglycemia.[53] In a study that reported the outcome of 114 infants with congenital hyperinsulinism, the incidence of neurodevelopmental retardation was 44%.[54]

Whenever possible, medical therapy is preferable to surgical treatment, which may involve partial or complete pancreatectomy. Oral diazoxide is the first line of medical therapy[55] and octreotide is the second line.[56] Because the use of diazoxide requires a functional potassium-adenosine triphosphate channel, infants with abnormalities in these channels do not usually respond well to oral therapy. When the use of diazoxide is unsuccessful, then octreotide can be administered subcutaneously. Surgery, with its short- and long-term complications, such as diabetes, should be reserved for infants who fail to respond to medical therapy.

1.1.10 Short bowel syndrome

Short bowel syndrome describes the complications that occur after a resection of the small intestine. The symptoms vary depending on the length and type of bowel that has been removed, the presence or absence of the underlying disease, and the degree of adaptation of the remaining bowel. After the resection, the bowel changes in structure and function, and the ability of the patient to absorb lipid, fluid, and electrolytes may be unknown for months. Severe diarrhea, which is one potential complication, is more often associated with the removal of the ileum rather than the jejunum. Its management includes dietary changes, the use of opiates to reduce stool volume, and the use of bile-binding agents (for example, cholestyramine) and proton pump inhibitors to reduce gastric acid secretion. Octreotide has been tried in some cases to reduce effluent volume and minimize fluid and electrolyte losses.[57,58] Patients who cannot maintain an adequate state of hydration will require intravenous fluids, electrolytes, and in extreme cases, parenteral nutrition.[59]

1.2 Overview of Technology

Octreotide is a synthetic octapeptide analogue with a similar pharmacologic action to that of somatostatin, but with a prolonged duration of action. It has a half-life of 100 minutes after subcutaneous administration.[1] Its effects include the inhibition of the release of pituitary growth hormone and secretion of peptides (for example, insulin, glucagon, gastrin, and other peptides) and serotonin produced in the gastroenteropancreatic (GEP) endocrine system.[1] It alters gastrointestinal motility, splanchnic blood flow, and gastrointestinal absorption.[60] Somatostatin analogues have also been used in an attempt to suppress tumour growth through the inhibition of cell proliferation, stimulation of apoptosis, inhibition of the release of circulating tumour growth-promoting humoral effectors, and reduction in the blood supply to tumours.[61,62]

In Canada, octreotide is available for subcutaneous or intravenous injection as Sandostatin® or generic Octreotide Acetate Omega in 50 µg, 100 µg, 200 µg, and 500 µg per mL injection formats (octreotide short-acting injection or OCT-SA). It is also available in a long-acting depot formulation for intramuscular injection as Sandostatin® LAR® 10 mg, 20 mg, or 30 mg per vial injection (octreotide long-acting injection or OCT-LA) (Table 1).[2,3,63]

The dose of OCT-SA varies depending on the indication and route of administration. Doses may range from 50 µg daily to a maximum of 1,500 µg split into two to four subcutaneous doses per day. Intravenous infusions of 25 µg to 50 µg/hour have been used in acute variceal bleeding. Sandostatin® LAR® is supplied in kits containing the drug (microspheres for depot suspension), diluent, and syringe. The recommended dose is 10 mg to 30 mg every four weeks by deep intragluteal injection.[1] The cost of four weeks of OCT-SA therapy ranges from C$112 to C$2,975 and from C$1,272 to C$2,124 for OCT-LA, depending on the dosage.[64]

Table 1: Somatostatin analogues available in Canada			
Product (Generic name) ATC Code, Manufacturer	**Strength**	**DIN**	**Unit Cost* (C$)**
Sandostatin® (octreotide) H01CB02, Novartis	50 µg/mL (1 mL)	00839191	5.36
	100 µg/mL (1 mL)	00839205	10.13
	200 µg/mL (5 mL)	02049392	97.40
	500 µg/mL (1 mL)	00839213	47.59
Octreotide acetate Omega (octreotide) H01CB02, Omega	50 µg/mL (1 mL)	02248639	3.99
	100 µg/mL (1 mL)	02248640	7.54
	200 µg/mL (5 mL)	02248642	72.48
	500 µg/mL (1 mL)	02248641	35.42
Sandostatin® LAR® (octreotide) H01CB02, Novartis	10 mg/vial	02239323	1,272
	20 mg/vial	02239324	1,697
	30 mg/vial	02239325	2,124
Somatuline® Autogel® (lanreotide) H01CB03, Ipsen Limited	60 mg/syringe	02283395	1,102
	90 mg/syringe	02283409	1,470
	120 mg/syringe	02283417	1,840

*Unit cost data for octreotide products from Alberta Drug Benefit List.[64] Lanreotide price from Canadian Expert Drug Advisory Committee (CEDAC) recommendation on lanreotide.[65] Other sources: Product descriptions and DINs[2,3,63,66], World Health Organization ATC/DDD 2007 index[67]
ATC code=anatomic therapeutic chemical code; DDD=defined daily doses; DIN=drug identification number; mg=milligram; mL=millilitre; µg=microgram

Alternatives to octreotide vary, depending on the indication. In July 2006, Health Canada[66] approved a new somatostatin analogue, lanreotide (Somatuline® Autogel®) for the long-term treatment of patients with acromegaly. It is available in 60 mg, 90 mg, and 120 mg syringes for deep subcutaneous injection at four-week intervals.[68]

Somatostatin (Stilamin®), which is manufactured by Serono, is available in Canada as ampoules containing 250 µg or 3 mg of somatostatin (DIN 02125269 and 02125277, respectively).[69] The use of somatostatin in clinical practice is limited because of its short half-life (less than three minutes).[30]

Expenditures on octreotide are increasing for Canadian publicly funded drug programs. In 1999-2000, when OCT-LA was first reimbursed by some provincial drug plans, the total expenditure for octreotide in British Columbia, Saskatchewan, Manitoba, Nova Scotia, and New Brunswick was C$510,000. In 2005-2006, the total expenditure was C$2.3 million. Over the same period, the number of claimants increased from 142 to 267 and the cost per claimant doubled, up to approximately C$8,670 in 2005-2006 (data provided by the publicly funded drug plans of British Columbia, Saskatchewan, Manitoba, Nova Scotia, and New Brunswick).

2 ISSUE

Health Canada has approved octreotide for use in four indications. It is, however, also being used for other conditions. Publicly funded drug programs are seeing an increasing number of requests to cover these off-label uses. Given the growing use of octreotide and the recent availability of

lanreotide for the treatment of acromegaly, it is timely to review the evidence for the clinical and cost-effectiveness of octreotide for approved and unapproved indications.

3 OBJECTIVES

The review tries to meet these objectives by addressing five research questions:

- What is the evidence regarding the clinical effectiveness of octreotide therapy for the selected indications?

Approved Indications	Unapproved Indications
▪ treatment of acromegaly ▪ emergency management of bleeding esophageal varices ▪ treatment of GEPNETs ▪ prevention of complications after pancreatic surgery	▪ inoperable bowel obstruction ▪ diarrhea related to chemotherapy, HIV-AIDS, Crohn's disease, or ileostomy ▪ hepatocellular carcinoma ▪ pancreatic cancer ▪ pediatric idiopathic (or persistent) hyperinsulinism ▪ short bowel syndrome

- What is the evidence regarding the clinical effectiveness of the long-acting intramuscular depot formulation (OCT-LA) compared with that of the short-acting subcutaneous or intravenous formulation (OCT-SA) for the selected indications?
- What is the optimal length of octreotide therapy for the selected indications?
- What is the evidence regarding the cost-effectiveness of octreotide therapy for the selected indications and regarding the cost-effectiveness of OCT-LA compared with that of OCT-SA?
- What is the budget impact on publicly funded drug programs in Canada of funding octreotide for the approved and unapproved indications?

4 CLINICAL REVIEW

4.1 Methods

A protocol for the review was written a priori and followed throughout the review process.

4.1.1 Literature search strategy

A comprehensive search strategy was designed to identify published and unpublished (grey) literature (Appendix 1). Electronic searches were conducted using Ovid for MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE and BIOSIS Previews. The Cochrane Library 2006, Issue 2, was searched for systematic reviews and economic studies while Issue 3 was searched for randomized controlled trials (RCTs). All Cochrane searches were updated as new issues arrived. Searches were staged, with the systematic review and meta-analysis search performed on May 16, 2006, the economic search on May 30, 2006, and the search for RCTs on July 26, 2006. All searches were systematically updated and results

incorporated on a biweekly basis until the first week of February 2008. There were no language or publication date restrictions. All searches, except the economic search, were limited to human studies.

Grey literature was identified by searching the web sites of health technology assessment agencies and related organizations and their databases. Search engines included Google™ and other Internet tools. Web-based proceedings of key conferences were searched, as were evidence-based resources (for example, Bandolier). Electronic searches were supplemented by manual searches of the bibliographies and abstracts of selected publications and through contact with selected experts and agencies. Novartis, the manufacturer of Sandostatin®, was contacted for information about unpublished studies**.**

4.1.2 Selection criteria

a) Study design

- Systematic reviews (including health technology assessments)
- Meta-analyses
- RCTs – parallel or crossover design
- Non-randomized controlled clinical trials (CCTs) (cohort or case control studies)

A systematic review is "a review of the evidence on a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant primary research, and to extract and analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used."[70]

A search for systematic reviews and meta-analyses was conducted first to determine if a relevant high-quality systematic review had been published. The quality of systematic reviews was assessed using the Oxman and Guyatt scale.[71] In addition, the literature search strategy was reviewed to determine if it was current and complete. If an appropriate systematic review was found, an update of the review was planned. If no high-quality systematic reviews were identified, a new systematic review would be conducted.

RCTs, by design, are restricted to selected patient groups and are often of short duration. They may be unable to detect uncommon or unexpected adverse effects that may be experienced in larger and more diverse patient populations. To supplement the adverse event data from RCTs, we included CCTs for the analysis of harm outcomes only.

b) Population groups

- Patients with Health Canada-approved and -unapproved indications (Table 2).

c) Interventions

- OCT-SA (subcutaneous, intravenous)
- OCT-LA (intramuscular)

Any dose, route of administration, or treatment duration of octreotide (when used as primary treatment, adjuvant therapy, or prophylactic therapy) was included. Studies that included a combination of treatment modalities were only considered if it was possible to extract data on

octreotide. Dosing studies where the treatment and comparator consisted of different doses of octreotide were excluded (for example, OCT-SA low dose versus OCT-SA high dose), except for those comparing OCT-SA with OCT-LA. Studies were excluded when the specific effectiveness of octreotide could not be determined.

d) Comparators

- Placebo or no treatment
- Indication-appropriate active controls (Table 2)
- Studies comparing OCT-SA with OCT-LA formulation

e) Outcomes

- Indication-specific outcomes (Table 2)
- Health-related quality of life
- Adverse events
- Serious adverse events (untoward medical occurrences that result in death, are life-threatening, require hospitalization or prolongation of hospitalization, or result in persistent or severe disability)[72]

Table 2: Study selection criteria

Approved Indications	Population	Comparators	Outcomes
Acromegaly due to pituitary tumour	Patients with diagnosis of pituitary acromegaly	Surgery, lanreotide, and other active controls	▪ survival ▪ change in symptom severity ▪ change in tumour size ▪ growth hormone level ▪ IGF-1 level ▪ complications of acromegaly
Emergency management of acute variceal bleeding	Patients with suspected or known bleeding esophageal varices	Endoscopic therapy, vasopressin, terlipressin, balloon tamponade, and other active controls	▪ survival ▪ arrest of first bleeding ▪ prevention of rebleeding ▪ need for other interventions ▪ blood transfusion requirements ▪ length of hospital stay
GEPNET	Patients with diagnosis of GEPNETs that could not be surgically removed; symptomatic or asymptomatic	Antidiarrheal agents, lanreotide, and other active controls	▪ survival ▪ change in symptom severity ▪ change in urinary 5-HIAA ▪ reduction in complications ▪ change in tumour size
Prevention of complications after pancreatic surgery	Patients who underwent pancreatic surgery	Active controls	▪ death ▪ length of hospital or ICU stay ▪ rate of post-operative complications such as bleeding, infection, pancreatitis, or fistula

Table 2: Study selection criteria			
Unapproved Indications	**Population**	**Comparators**	**Outcomes**
Bowel obstruction	Patients with inoperable bowel obstruction who require symptomatic management	Analgesics, mechanical decompression (nasogastric suction), antiemetics, and other active controls	▪ survival ▪ symptom control ▪ length of hospital stay ▪ need for nasogastric tube insertion
Chemotherapy-induced diarrhea	Patients with intractable diarrhea related to chemotherapy, where other etiological causes ruled out	Antidiarrheal agents (for example, loperamide, diphenoxylate, codeine) and other active controls	▪ diarrhea control ▪ survival ▪ need for intravenous fluid, electrolyte, or nutritional replacement ▪ need for hospital admittance and length of hospital stay ▪ return to work
HIV-AIDS-related diarrhea	Patients with intractable diarrhea related to HIV-AIDS, where other etiological causes ruled out	Antidiarrheal agents (for example, loperamide, diphenoxylate, codeine) and other active controls	▪ diarrhea control ▪ survival ▪ need for intravenous fluid, electrolyte, or nutritional replacement ▪ need for hospital admittance and length of hospital stay ▪ return to work
Crohn's disease-related diarrhea	Intractable diarrhea related to complications of Crohn's disease; for example, fistulas, short bowel, or ileostomy	Antidiarrheal agents (for example, loperamide, diphenoxylate, codeine) and other active controls	▪ diarrhea control ▪ survival ▪ need for intravenous fluid, electrolyte, or nutritional replacement ▪ need for hospital admittance and length of hospital stay ▪ return to work
Ileostomy-associated diarrhea	Patients with intractable post-ileostomy diarrhea, where other etiological causes ruled out	Antidiarrheal agents (for example, loperamide, diphenoxylate, codeine) and other active controls	▪ diarrhea control ▪ survival ▪ need for intravenous fluid, electrolyte, or nutritional replacement ▪ need for hospital admittance and length of hospital stay ▪ return to work
Hepatocellular carcinoma	Patients with unresectable hepatocellular carcinoma	Chemotherapy and other active controls	▪ survival ▪ tumour size and response rate ▪ AFP levels ▪ time to progression
Pancreatic cancer	Patients with advanced pancreatic cancer	Chemotherapy and other active controls	▪ survival ▪ tumour size and response rate ▪ time to progression

Table 2: Study selection criteria			
Pediatric hyperinsulinism	Pediatric population with congenital hyperinsulinism	May not have appropriate comparator (octreotide is second-line therapy when patients do not respond to diazoxide)	▪ survival ▪ avoidance of disease complications; for example, disabilities, cerebral palsy, blindness ▪ blood glucose ▪ need for pancreatectomy ▪ reduction in long-term and short-term surgical complications (diabetes and biliary tract damage)
Short bowel syndrome	Patients with short bowel syndrome	Antidiarrheal agents (for example, loperamide, diphenoxylate, codeine) and other active controls	▪ diarrhea control ▪ need for intravenous fluid therapy or TPN ▪ need for hospital admittance and length of hospital stay ▪ return to work ▪ nutritional status

5-HIAA=5-hydroxyindole acetic acid; AFP= α fetoprotein; GEPNETs=gastroenteropancreatic neuroendocrine tumours; HIV-AIDS=human immunodeficiency virus and acquired immune deficiency syndrome; IGF-1=insulin-like growth factor 1; ICU=Intensive Care Unit; OGTT=Oral Glucose Tolerance Test; TPN=total parenteral nutrition

f) Publication characteristics

- Trial reports published as abstracts or conference proceedings were included if they contained sufficient detail on the study characteristics and results.
- Narrative reviews, case series, case reports, and editorial articles were excluded.
- Grey literature was included if it met the selection criteria. Permission to cite was obtained for unpublished studies.
- The search was not limited by publication date or language. Articles written in any language were screened. Because of the limited translation budget, foreign language articles without an English or French abstract were excluded.

4.1.3 Selection method

Systematic reviews and meta-analyses were selected by reviewers who used a hard copy form. TrialStat systematic review software (SRS)[73] was used during study selection, quality assessment, and data extraction from RCTs and CCTs. Study selection forms were developed a priori.

Two review authors (RB, SC, KM, GM, or CP) assessed titles and abstracts independently. Full text copies were obtained for those studies that met the selection criteria or when there was uncertainty or disagreement about the eligibility of a study. The reviewers then applied the eligibility criteria to the full texts. Disagreements were resolved through consensus or a neutral third party (TC).

Because of resource issues, we were unable to translate articles that were not written in English or French. These articles were screened based on English or French abstracts. If it was written in a language other than English or French, we used the expertise that was available in CADTH.

Those articles that met the selection criteria and had an English or French abstract were included in the analysis.

4.1.4 Data extraction strategy

At least two reviewers (RB, SC, KM, GM, or CP) independently extracted data from the selected papers using structured forms that were developed a priori. Data were collected on report characteristics, study design, patients' demographic and clinical characteristics, interventions and comparators, adverse events, and outcomes. Disagreements were resolved through consensus or a neutral third party (TC).

4.1.5 Strategy for validity assessment

A minimum of two reviewers independently assessed the quality of included studies. Systematic reviews and meta-analyses were evaluated using the Oxman and Guyatt scale.[71] A review was considered to be of higher quality if it obtained a score of five or higher. The quality of RCTs was assessed using the Jadad Scale (randomization, blinding, and reporting of withdrawals).[74] Studies with a score of zero to two were considered to be of lower quality, and those with a score of three to five were considered to be of higher quality. Allocation concealment was assessed as adequate, inadequate, or unclear.[75] No quality assessment was conducted for the CCTs that were included in the safety analysis.

4.1.6 Data analysis methods

The decision as to whether to update a systematic review or to conduct a new one was based on the answers to five questions:

- Has a systematic review been published that meets our selection criteria?
- Is the systematic review of higher methodological quality (with a score of five or higher on the Oxman and Guyatt scale[71])?
- Did the authors conduct a search strategy that meets CADTH's standards?
- Is the systematic review up-to-date?
- Are there RCTs that were published after the systematic review's last search date and that will likely change the results?

When a new systematic review was conducted, data from RCTs were used to assess efficacy. RCT and CCT data were used for the safety analysis. For clinical trials with a crossover design, data before the switching point were used in the synthesis. The clinical effectiveness of OCT-SA and OCT-LA were examined separately.

Where appropriate, a meta-analysis was performed according to the Cochrane handbook for systematic reviews of interventions[76] and using Cochrane Review Manager 4.2.10.[77] Data were pooled only if heterogeneity was low to moderate. Heterogeneity was assessed using the Higgins' I^2.[78] An I^2 of less than 25% was considered to be a low degree of heterogeneity, 25% to 75% was considered to be a moderate degree of heterogeneity, and greater than 75% was considered to be a high degree of heterogeneity. In cases with low heterogeneity, a fixed-effects model was used. For cases with moderate heterogeneity, a random-effects model was used.

When heterogeneity was more than 75%, a narrative description was provided. In all cases, an attempt was made to explain the heterogeneity based on the patient or study characteristics.

For continuously distributed outcomes, the weighted mean difference (WMD) or standardized mean difference (SMD) was calculated. When the standard deviation (SD) was not reported, it was calculated from the standard error ($SE = SD / \sqrt{N}$, N=number of participants). Study authors were contacted if the report did not state if the variance was SE or SD.

For dichotomous outcomes, the relative risk (RR) and, in some cases, the absolute risk difference (ARD) or number needed-to-treat (NNT) was calculated. The NNT was calculated using Visual Rx 2.0 (http://www.nntonline.net/ebm/visualrx/try.asp).[79] The precision of results was expressed by a 95% CI whenever possible. For individual patient data, descriptive statistics were calculated using SPSS 15.0 software.[80]

Wherever possible, an intention-to-treat analysis was conducted. Authors were asked to provide more information if patient data were missing. If data could not be obtained, the analysis was conducted on available cases for continuous and dichotomous outcomes. For dichotomous outcomes with missing data, the best and worst case scenarios were also calculated.

Sensitivity or subgroup analyses were conducted only if there were more than four studies for comparison. These analyses were based on the quality of the included RCTs, treatment dose, and other clinical parameters relevant to the indication.

A narrative synthesis was conducted if the data were unsuitable for meta-analysis.

4.2 Results

4.2.1 Quantity of research available

a) Systematic reviews or meta-analyses

In the search for systematic reviews and meta-analyses, 103 reports were identified from electronic databases and six from other sources (Appendix 3, Figure A1). Of these, 67 were retrieved as full text. A total of 52 articles did not meet our inclusion criteria and were excluded (Appendix 2).

Fifteen reports met the selection criteria: acromegaly (3);[81-83] variceal bleeding (8);[84-91] refractory diarrhea (2);[92,93] hepatocellular carcinoma, pancreatic cancer, and bowel obstruction (1);[93] prevention of complications after pancreatic surgery (3).[93-95] Three indications were reviewed in one report.[93] One report[90] was identified as an earlier version of another systematic review[84] and was excluded.

The remaining 14 reports were assessed using the Oxman and Guyatt scale. For variceal bleeding, five studies were of higher quality and received a score of seven (2),[84,85] six (1),[86] or five (2).[87,88] The others received a score of three,[89] and one.[91] For the prevention of complications after pancreatic surgery, one report was of higher quality with a score of seven;[94]

the others were rated as lower quality with a score of three.[93,95] The remaining reports were given scores of two,[92] three,[81,83] or four.[82]

Of the five higher quality systematic reviews that assessed octreotide for acute variceal bleeding, one report[87] included all the comparators that were relevant to our research questions. We scrutinized the search strategy of this report and the higher quality systematic review for pancreatic surgery prophylaxis.[94] In both reports, the search strategy was not updated or not comprehensive. Thus, for all indications, no published reports were considered to be acceptable for an update and we would subsequently conduct a new systematic review.

While the systematic review of RCTs was in progress, we identified three new systematic reviews that were relevant. One evaluated octreotide for the management of bowel obstruction[96] and two evaluated prophylactic use in patients undergoing pancreatic surgery.[97,98]

b) Randomized or controlled clinical trials

Our search identified 2,180 RCTs and CCTs of which 1,730 were excluded based on the title and abstract. Another 35 were identified from other sources. We tried to retrieve the full text of the remaining 485 papers. Of these, 321 were excluded (Appendix 3, Figure A2). All excluded studies appear in Appendix 2.

Among the 485 papers, 69 were written in a language other than English. Based on the expertise available in CADTH, or on an English or French title or abstract, we determined that 17 met the inclusion criteria: 15 for variceal bleeding and two for prevention of complications after pancreatic surgery. Of these 17, three studies had an English abstract and were included in the review.[99-101] Because we were unable to translate the remaining articles, they were excluded.[102-115] Because of the language, it was not possible to assess the eligibility of two papers; these were excluded.[116,117]

A total of 164 reports met the selection criteria and were included in the study. These included 24 CCTs and 140 reports of 99 unique RCTs. Seventeen RCTs[57,57,58,101,118-131] and 15 CCTs[132-146] could not be used in the analysis because of the treatment comparator, duration of therapy, or incomplete data. Data from 82 RCTs and nine CCTs were used in the analysis.

From the included studies, efficacy data were extracted from RCTs. We assumed that any study that did not report the blinding of participants was open label.

Harms data were extracted from CCTs and RCTs. Adverse event reporting in the included studies was sparse and poorly reported. No trial described a systematic attempt to collect adverse event information. As a result, a narrative synthesis was provided.

The trial and patient characteristics, and the reported outcomes, appear in Appendix 4, Tables A1 to A28.

4.2.2 Acromegaly

a) Study characteristics

Ten RCTs compared octreotide to another treatment in patients with acromegaly. Of these, three studies compared OCT-LA with lanreotide;[147-149] five studies (in eight publications) compared

OCT-SA with placebo or no treatment;[150-157] one study compared OCT-SA with bromocriptine;[158] and one study compared OCT-LA with surgery[159] (Appendix 4, Tables A1 to A4).

Three studies were double-blinded[152,154,155] and the others were open label. One used a cross-over design.[152] The sample sizes varied from 12 to 125 patients with half the trials having fewer than 30 patients. These were included in the review for pooling or for descriptive purposes. Treatment duration ranged from 14 days to 24 months. Five trials[148-150,153,159] obtained a Jadad score of two or less (indicating poorer quality). Allocation concealment could not be determined for all ten studies.

Three studies had no drop-outs or withdrawals.[150,152,155] Another three reported that three to five patients had not completed the trial.[147,154,158] One of these used intention-to-treat analysis[154] (Appendix 4, Table A3). The remainder of the studies did not report on withdrawals during the study period of interest.

In our search, we identified seven single-dose RCTs that met the inclusion criteria.[123,125-129,160] These were excluded from the analysis given the disease's chronic nature.

Sixteen non-randomized trials were identified. Of these, four provided harms data.[161-164] The remaining trials were excluded because they had a cross-over design and did not report data before the cross-over,[132,133,136,138,141-143,145] or they were single-dose studies.[134,135,144,146]

b) Data analysis and synthesis

A meta-analysis of the data and comparisons between studies were not always possible because the treatment or control groups were different, the number of patients in each group was not reported, or outcome data such as variance or end-point values were not reported. Attempts to contact the authors to obtain missing data were successful in one case. One study provided individual patient data on growth hormone and insulin-like growth factor-1 levels.[150] From these data, we calculated means and standard deviations using the computer program SPSS 15.0.[80] Finally, sub-group analyses were not possible because of the small number of trials included in this review.

These results must be interpreted given that most of the included studies had small sample sizes. Some studies had missing data or provided a narrative description of the results. Some studies did not use intention-to-treat analysis. This was an issue when continuous variables are involved. Hence, we only present results that are based on available case data. For dichotomous variables, we calculated best- and worst-case scenarios to assess the impact of missing patients.

Death

Two studies reported the number of deaths that occurred during the trial.[149,150]

OCT-LA versus lanreotide: One death due to pulmonary embolism occurred during the first three months of treatment in the Chanson et al. study.[149] However, the authors did not specify the group in which the death occurred.

***OCT-SA versus no treatment*:** In the Colao et al. study,[150] one death from cardiorespiratory arrest occurred in the "no treatment" group 20 hours after surgery.

No conclusions can be drawn about whether octreotide has an impact on death in patients with acromegaly.

Change in symptom severity
Two studies looked at the effect of octreotide on the alleviation of symptoms (for example, headache, perspiration, paresthesia, carpal tunnel syndrome).[149,158]

OCT-LA versus lanreotide: Chanson et al.[149] used a five-point verbal rating scale (0=symptoms not present, 4=symptoms severe and incapacitating) and found no significant change from baseline for OCT-LA or lanreotide.

OCT-SA versus bromocriptine: Another study with a small sample size (23 patients, Table 3) obtained a severity score (0=absent, 3=severe) for 19 symptoms. It found a significant difference in composite severity score ($p<0.02$) at eight weeks, but not at ten weeks, in favour of OCT-SA compared with bromocriptine.[158]

Table 3: Composite severity symptom scores for OCT-SA versus bromocriptine

Study (Timing of Endpoint)	Treatment (Sample Size)	Control (Sample Size)	Results for Treatment Group*	Results for Control Group*
Halse, 1990[158] (8 weeks)	OCT-SA (12)	bromocriptine (11)	baseline: 18.6 8 weeks: 10.3 change: 8.3	baseline: 22.4 8 weeks: 15.6 change: 6.8, p<0.02
(10 weeks)			10 weeks: 17.0 change: 1.6	10 weeks: 21.0 change: 1.4, p=NS

NS=not significant; OCT-SA=octreotide short-acting
*Results are based on available case analysis

There is insufficient information to determine if there is a difference between OCT-LA and lanreotide in improving the symptoms of patients with acromegaly. We also cannot make a statement about the use of OCT-SA in the management of symptoms.

Change in pituitary tumour size
Four studies measured the change in pituitary tumour size[147,149,158,159] (Table 4). One study with a small sample size[147] showed no difference between OCT-LA and lanreotide at 12 and 24 months in the percentage decrease in tumour volume. A second study[149] showed no difference between baseline and end-point tumour sizes, but provided no information to compare the two groups. In the two trials that compared OCT-SA versus bromocriptine[158] and OCT-LA versus surgery,[159] the data reported were insufficient to draw any conclusions. Therefore, it is not possible to make a statement about the efficacy of octreotide in reducing the pituitary tumour size.

Growth hormone levels
Nine of ten studies measured growth hormone levels, but some did not report mean end-point levels, and provided a description of results instead.

Table 4: Change in pituitary tumour size					
Study	**Treatment (Sample Size)**	**Control (Sample Size)**	**Results for Treatment Group**	**Results for Control Group**	**WMD (95% CI)**
OCT-LA versus lanreotide					
Amato, 2002[147] at 12 months	OCT-LA (8)*	lanreotide (12)	% volume reduction (mean±SD) 31.1±16.1	% volume reduction (mean±SD) 26.5±17.3	4.6 (−10.2, 19.4)
at 24 months			34.8±16.5	30.0±17.2	4.8 (−10.2, 19.8)
Chanson, 2000[149]	OCT-LA (98)	lanreotide (27)	NS from baseline	NS from baseline	NA
OCT-SA versus bromocriptine					
Halse, 1990[158]	OCT-SA (12)*	bromocriptine (11)*	NR	1 patient had reduction in tumour size	NE
OCT-LA versus surgery					
Colao, 2006[159]	OCT-LA (NR)	surgery (NR)	73% of patients had >20% reduction in tumour size	95% of patients had significant tumour volume reduction	NE

CI=confidence interval; NE=not estimable; NR=not reported; NS=not significant; OCT-LA=octreotide long-acting; OCT-SA= octreotide short-acting; SD=standard deviation; WMD=weighted mean difference
*Results are based on available case analysis

OCT-LA versus lanreotide: Of the three studies comparing OCT-LA to lanreotide, one reported growth hormone levels at end-point.[149] No statistical difference was detected between the two drugs in growth hormone levels at end-point (Table 5).

OCT-SA versus no treatment or placebo: Of the five studies comparing OCT-SA with placebo or no treatment, one study did not provide end-point data[155] and one study[152] did not provide the number of patients in each group before the cross-over occurred (Table 5). We performed a meta-analysis for the other three studies[150,153,154] and found a significant difference in growth hormone levels at end-point in the OCT-SA group compared with control [WMD= −9.25 (95%CI: −17.33, −1.16)] (Figure 1).

OCT-SA versus bromocriptine: One study with a small sample size showed that growth hormone levels were significantly lower in the OCT-SA group compared with bromocriptine at 10 weeks, but not at eight weeks (Table 5).[158]

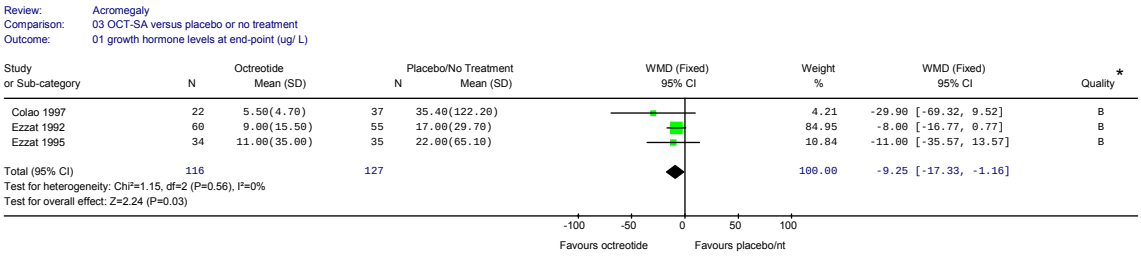
Patients attaining normal growth hormone levels

Seven studies measured the number of patients who attained normal growth hormone levels (2 µg/L or 5 mU/L).[147,148,150,152,154,155,158] Relative risk could not be calculated for one study[152] because the number of patients in each sample was not reported. The Ezzat et al. study in 1992 reported that in a subgroup of 39 patients who were treated with octreotide and who had abnormal growth hormone levels at two weeks, 49% (95% CI: 36% to 62%) had attained normal levels at end-point.[154] A meta-analysis of the data extracted from the other five studies was not possible because the duration of the studies varied too much. Separate relative risks are presented

Table 5: Growth hormone levels at end-point					
Study (Timing of End-point)	**Treatment (Sample Size)**	**Control (Sample Size)**	**End-point Value for Treatment**	**End-point Value for Control**	**WMD (95% CI)**
OCT-LA versus lanreotide					
Chanson, 2000[149] (3 months)	OCT-LA (98)	lanreotide (27)	6.6±7.9 mU/L (mean±SD)	8.1±17.7 mU/L (mean±SD)	−1.5 (−8.4, 5.4)
OCT-SA versus placebo or no treatment					
Andersen, 1995[152] (1 month)	OCT-SA (NR)	placebo (NR)	13±2 mU/L (mean±SE)	47±14 mU/L (mean±SE)	NE
Fredstorp, 1990[155] (2 weeks)	OCT-SA (10)	placebo (10)	significant reduction in treatment group compared to placebo		NE
OCT-SA versus bromocriptine					
Halse, 1990[158] (8 weeks)	OCT-SA (12)*	bromocriptine (11)*	2.9± 2.4 µg/L (mean±SD)	5.4±4.0 µg/ L (mean±SD)	−2.5 (−5.2, 0.2)
(10 weeks)			1.3±15.2 µg/L	13.8±14.6 µg/L	−12.5 (−24.7, −0.3)

CI=confidence interval; mU/L=milliunits per litre; µg/L=micrograms per litre; NE=not estimable; NR=not reported; OCT-LA=octreotide long-acting; OCT-SA=octreotide short-acting; SD=standard deviation; SE=standard error; WMD=weighted mean difference
*Results are based on available case analysis

Figure 1: Pooled data for growth hormone levels



CI=confidence interval; OCT-SA=octreotide short-acting; placebo/nt=placebo or no treatment; SD=standard deviation; WMD=weighted mean difference
*Quality score: B=allocation concealment unclear

for these studies (Table 6). Four of the five studies had small sample sizes.[147,148,155,158] Three studies did not use intention-to-treat analysis. Worst- and best-case scenarios were analyzed to account for missing patients. This did not change the finding of no statistical differences between patients in the treatment and control groups (data not shown).

Insulin-like growth factor-1 levels: Nine studies measured insulin-like growth factor-1 levels, but some did not report mean end-point levels and provided a description of the result instead.[147-150,152-155,158]

Table 6: Comparison of patients attaining normal growth hormone levels at end-point			
Study (Timing of End-Point)	**Number of Patients Attaining Normal Growth Hormone Levels**		**RR (95% CI)**
	Treatment Group	**Control Group**	
OCT-LA versus lanreotide			
Amato, 2002[147] (12 months)	3/ 8*	4/ 12	1.1 (0.3, 3.7)
Amato, 2002[147] (24 months)	4/ 8*	7/ 12	0.9 (0.4, 2.0)
Jenkins, 2000[148] (4 weeks for treatment and 10 days for control)	8/ 18	1/ 11	4.9 (0.7, 34.0)
OCT-SA versus placebo or no treatment			
Colao, 1997[150] (3 to 6 months)	15/ 22	13/ 37	1.9 (1.2, 3.3), p=0.01
Fredstorp, 1990[155] (14 days)	4/ 10	0/ 10	NE
OCT-SA versus bromocriptine			
Halse, 1990[158] (2 months)	4/ 12*	2/ 11*	1.8 (0.4, 8.1)

CI=confidence interval; NE=not estimable; OCT-LA=octreotide long-acting; OCT-SA=octreotide short-acting; RR=relative risk
*Results are based on available case analysis

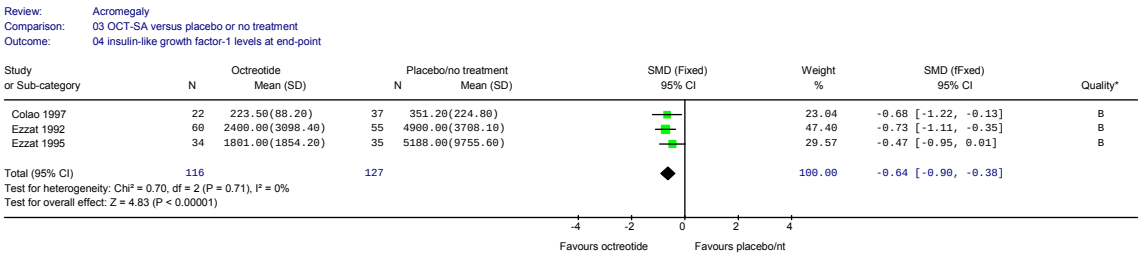
OCT-LA versus lanreotide: Of the three studies comparing OCT-LA with lanreotide, one reported growth hormone levels at end-point.[149] It found no statistical difference between the two drugs in insulin-like growth factor-1 levels at end-point (Table 7).

Table 7: Insulin-like growth factor-1 levels at end-point					
Study (Timing of End-point)	**Treatment (Sample Size)**	**Control (Sample Size)**	**End-point Value for Treatment (Mean±SD)**	**End-point Value for Control (Mean±SD)**	**WMD (95% CI)**
OCT-LA versus lanreotide					
Chanson, 2000[149] (3 months)	OCT-LA (98)	lanreotide (27)	48±29.7 nmol/L	49±26.0 nmol/L	−1.0 (−12.4, 10.4)
OCT-SA versus placebo					
Fredstorp, 1990[155] (two weeks)	OCT-SA (10)	placebo (10)	significant reduction in treatment group during treatment phase compared to placebo		NE
OCT-SA versus bromocriptine					
Halse, 1990[158] (2 months)	OCT-SA (12)	bromocriptine (11)	1.43±0.36 units/mL*	2.13±0.27 units/mL*	−0.7 (−1.0, −0.4)

CI=confidence interval, NE=not estimable; nmol/L=nanomoles per litre; OCT-SA=octreotide short-acting; OCT-LA=octreotide long-acting, SD=standard deviation; WMD=weighted mean difference
* Reported as somatomedin-C levels, the former name for insulin-like growth factor-1

OCT-SA versus no treatment or placebo: One study comparing OCT-SA with placebo did not provide end-point data[155] (Table 7). A meta-analysis was performed for the other three studies.[150,153,154] Insulin-like growth factor-1 levels were significantly lower at end-point in the OCT-SA group compared with placebo or no treatment [SMD=−0.64 (95% CI: −0.90, −0.38)] (Figure 2).

Figure 2: Pooled data for insulin-like growth factor-1 levels



CI=confidence interval; OCT-SA=octreotide short-acting; placebo/nt=placebo or no treatment; SD=standard deviation; SMD=standardized mean difference
*Quality score: B=allocation concealment unclear

OCT-SA versus bromocriptine: Somatomedin-C levels were significantly lower with OCT-SA compared to bromocriptine in the Halse et al. study (Table 7).[158]

Patients attaining normal insulin-like growth factor-1 levels

Seven studies measured the number of patients who attained normal insulin-like growth factor-1 levels.[147-150,154,155,158] Ezzat et al. (1992)[154] reported that 58% (95% CI: 44% to 72%) of patients in the OCT-SA group with abnormal insulin-like growth factor-1 values at two weeks attained normal levels at end-point. A meta-analysis of the data extracted from the other five studies was not possible because the studies varied too much in duration. Separate relative risks are presented for these studies in Table 8. Four studies had small sample sizes.[147,148,155,158] Worst- and best-case scenarios were calculated to account for the missing patients in the Amato et al. study.[147] This did not change the finding of no statistical differences between patients in the OCT-LA versus lanreotide groups, or the OCT-SA versus placebo or no treatment groups (data not shown).

Optimal length of therapy

The RCTs included in the systematic review had treatment durations ranging from 14 days to 24 months.

There were no significant differences between OCT-LA and lanreotide at three months. The results were statistically significant for OCT-SA compared with placebo or no treatment at one to six months for two outcomes (growth hormone and insulin-like growth factor-1 levels).

There is insufficient information, however, to draw a conclusion about the optimal length of therapy.

Table 8: Comparison of patients attaining normal insulin-like growth factor-1 levels at end-point			
Study (Timing of End-point)	**Number of Patients Attaining Normal Insulin-like Growth Factor-1 Levels**		**RR (95% CI)**
	Treatment Group	**Control Group**	
OCT-LA versus lanreotide			
Amato, 2002[147] (12 months)	3/8*	6/12	0.8 (0.3, 2.2)
Amato, 2002[147] (24 months)	4/8*	8/12	0.8 (0.3, 1.7)
Chanson, 2000[149] (3 months)	14/86*	0/21*	NE
Jenkins, 2000[148] (4 weeks for treatment and 10 days for control)	3/18	4/11	0.5 (0.1, 1.7)
OCT-SA versus placebo or no treatment			
Colao, 1997[150] (3 to 6 months)	12/22	11/37	1.8 (1.0, 3.4)
Fredstorp, 1990[155] (14 days)	3/10	0/10	NE
OCT-SA versus bromocriptine			
Halse, 1990[158] (2 months)	8/12†	4/11†	1.8 (0.8, 4.4)

CI=confidence interval; NE=not estimable; OCT-LA=octreotide long-acting; OCT-SA=octreotide short-acting; RR=relative risk
*Results are based on available case analysis; †reported as somatomedin-C levels, former name for insulin-like growth factor-1

Harms data

Of the 10 RCTs included in the systematic review, four provided descriptions of adverse events (Appendix 4, Table A4).[148,154,155,158] All four reported gastrointestinal disorders, including abdominal discomfort and pain, loose stools and diarrhea, nausea, and flatulence. In one study,[154] the percentage of patients reporting nausea and diarrhea was as high as 88% compared with 33% in the placebo group ($p<0.001$). A few patients reported discomfort on injection.[148] In one study, one patient had to discontinue octreotide because of throat spasms, flushing, and shallow breathing after injections.[158] The symptoms resolved when treatment was stopped. In another study, one patient discontinued octreotide because of headaches.[154]

Three non-randomized studies[161-163] measured the frequency of gallstones in patients with acromegaly on long-term octreotide therapy. One study showed no significant difference between 13 patients on OCT-SA (3.4±2.1 years of treatment) compared with 20 patients on bromocriptine or 25 patients on no treatment.[162] There was no significant difference in the presence of gallstones when the OCT-SA group was compared to healthy volunteers. Another study showed that more patients on octreotide (total of 39 patients on 20 months of treatment) had gallstones when they were compared to 38 untreated patients ($p<0.005$).[161] In the third study, seven untreated patients with acromegaly were compared with six patients with acromegaly who were treated with octreotide 500 μg per day for a mean of 16 months, and to eight patients with acromegaly who were treated with octreotide 1 mg per day for 33 months. Gallbladder contractility decreased when the untreated patients were given one dose of octreotide. Chronic octreotide therapy reduced the rate of bile secretion. Gallstones developed in all patients on high dose octreotide but not in those on the low dose. The gallstones disappeared in three patients after treatment was stopped.

One non-randomized trial with 24 patients (16.5±10 weeks of treatment) mentioned two treatment discontinuations due to adverse events. One participant developed symptoms of dependency, and one participant had repeated hypoglycemia.[164]

4.2.3 Emergency management of acute variceal bleeding

a) Study characteristics

We identified 37 RCTs (53 articles) that compared OCT-SA to placebo, no treatment, or active comparators for the emergency management of variceal bleeding.[99-101,165-197] In one article, the comparator treatment was described as "posterior pituitary." Because this treatment is not currently in use, this study was excluded.[101]

Details about the trial and patient characteristics, withdrawals, and outcomes that were extracted from the 36 RCTs appear in Appendix 4, Tables A5 to A8. No CCTs met the inclusion criteria for this indication.

OCT-SA versus placebo or no treatment: We identified 31 reports on 21 RCTs[99,165-182,187] that compared OCT-SA with placebo or no treatment. Three studies had a third treatment group.[99,173,187] Freitas et al.[178] conducted two randomizations to different treatment regimens. As a result, this study is counted as two RCTs reported in one paper. Of the 21 RCTs, seven were available only as an abstract.[165,166,173-175,177,187] The data for the Silva et al. study[99] were extracted from the English abstract and some Spanish tables. The document was not translated.

All the studies were parallel design. They enrolled a total of 2,953 patients (2,967 episodes of variceal bleeding; range of 52 to 564 patients). Five studies[165,167,170,175,176] were double-blind, the remainder were open label. Allocation concealment was adequate in three[167,170,176] studies and unclear in the others. Of the 21 studies, six[167,168,170,171,176,181] received a Jadad score of three to five. The others were judged to be lower quality with a score of one or two.

In two RCTs, patients were randomized to receive OCT-SA, and either placebo[165] or no treatment.[166] No other interventions to control the acute bleeding were stated in these abstracts. In the remaining 19 RCTs, patients received additional interventions. Patients in both treatment groups received sclerotherapy at the time of randomization in 12 studies,[167-176,178,187] ligation in one study,[182] and ligation or sclerotherapy in one study.[99] In four studies, patients in the control group received sclerotherapy at the time of randomization, while those in the treatment group received sclerotherapy after 48 to 72 hours.[178-181] In one study,[177] endoscopic therapy was delayed in the treatment group until the patients' level of consciousness improved.
Three studies[170,173,177] were excluded from the meta-analysis because of differences in the population that was randomized, differences in study treatments, or incomplete data. In the Primignani et al.[170] trial, all patients received vasoactive agents or endoscopic treatment to control the acute bleeding and were hemodynamically stable for 24 hours before randomization. In the Abd-Elrazek et al[177] study, the patients who were enrolled had impaired consciousness due to encephalopathy and a worse prognosis than the patients in other studies. The data were incomplete in the Signorelli et al. 1996 abstract and could not be used.[173]

In the other 18 studies, the patients who were enrolled had acute variceal bleeding. In two studies,[165,175] the patients were enrolled before endoscopy. As a result, some patients had bleeding from non-variceal sources. The dose of OCT-SA varied from 300 µg per day subcutaneously to 50 µg/hour intravenously for 12 hours to five days. The patients were followed for three days to 120 days.

The authors of six studies reported on the number of patients who were lost to follow-up (Appendix 4, Table A8). In two studies, the patients were enrolled before endoscopy and those who did not have variceal bleeding were excluded.[165,175] In four studies,[168,170,181,182] patients were excluded because of protocol violations, withdrawal of consent, adverse events, or loss to follow-up. Of these six studies, one conducted an intention-to-treat analysis.[170] In one trial, patients were missing from one outcome measure[178] but no explanation was provided by the authors. In two studies,[167,171] the authors stated that all patients were included in the final analysis. In the remaining studies, it was not stated if any patients withdrew or were lost to follow up. Attempts to contact the authors for missing data were unsuccessful.

OCT-SA versus sclerotherapy: We retrieved seven RCTs (eight articles) that compared OCT-SA with sclerotherapy.[99,183-188,198] Two trials[99,187] had a third treatment arm – sclerotherapy or ligation plus OCT-SA. Of the reports, four were available only as abstracts.[184-187] For the Shaikh et al. study,[187] we extracted the data from the abstract because we were unable to obtain the full text report. For the Silva et al.[99] report, we extracted data from the English abstract and from some tables in Spanish. Full translation was not conducted.

All the studies were open label, parallel design with unclear allocation concealment. The Bildozola et al. study[183] received a Jadad score of three. The remaining studies obtained a score of one.

The studies enrolled 43 to 564 patients (total 1,043) with acute variceal bleeding. El-Jackie et al.[184] randomized 100 patients with schistosomal portal hypertension. These patients have a different prognosis than those with cirrhosis due to alcoholic liver disease or viral hepatitis. As a result, this study was excluded from the meta-analysis.

The dose of OCT-SA varied from 200 µg per day[188] to 50 µg/hour,[99,183-187] administered for one to five days. The patients were followed for one to 42 days. Bildozola et al.[183] reported that eight patients withdrew from the analysis because they did not meet the inclusion criteria or there were protocol violations. Intention-to-treat analysis was possible for one outcome (death). One patient was missing from the Poo et al. study[186] in the data for the mortality outcome (Appendix 4, Table A8). The other studies did not report whether patients withdrew or were lost to follow-up.

OCT-SA versus balloon tamponade: Two studies compared OCT-SA with balloon tamponade.[189,195] Both were open label, parallel design and enrolled 92 patients in total (101 episodes of bleeding). One study was available as an abstract only.[195]

In both trials, OCT-SA was administered as a 25 µg/hour infusion. The duration varied from eight to 48 hours. In the McKee et al. study,[189] both treatment groups also received sclerotherapy 48 hours after randomization. The Kusumobroto et al.[195] study had a third treatment arm – vasopressin. Patients were followed for 24 hours[195] or nine days.[189] One study did not report the number of patients who withdrew.[195] In the second study, none were lost to follow-up.[189] The allocation concealment was unclear in both studies. One study[189] received a Jadad score of two, the other[195] received a score of one.

OCT-SA versus somatostatin: Three RCTs compared OCT-SA with somatostatin.[173,196,197] In the Signorelli et al. trial (1996),[173] 94 patients in all treatment groups received sclerotherapy in addition to OCT-SA, somatostatin, or placebo. The results were presented as percentages that did not correspond to the number enrolled, indicating that there were some losses to follow-up. Because the attempts to contact the author for clarification were unsuccessful, these data were not pooled.

The Zhang et al. trial[196] compared OCT-SA with somatostatin or with vasopressin.

The third study was a double-blind, parallel trial comparing OCT-SA to somatostatin.[197] Both treatments were administered intravenously for five days at a dose of 50 µg/hour for OCT-SA and 250 µg/hour for somatostatin. All patients received either sclerotherapy or ligation. A total of 33 patients were enrolled and followed for 42 days. The study received a Jadad score of two, and the allocation concealment was unclear.

OCT-SA versus terlipressin: Five abstracts[191,199-202] and three full text reports[100,190,192] describe four RCTs that compare OCT-SA to terlipressin. Two studies were open label,[100,192] and two were single blind.[190,191] The allocation concealment was unclear in all four. The Jadad scores were one,[100,191] two,[192] and three.[190] The data that were extracted from the Cho et al.[100] study were based on information in the abstract and in some tables that were presented in English. The main text was written in another language and was not translated.

The studies enrolled a total of 441 patients (444 bleeding episodes). The number of patients who were enrolled ranged from 60 to 209. The patients had cirrhosis and active or recent variceal bleeding. The treatment duration was 24 hours,[192] three days,[191] five days,[100] and seven days.[190] The dose of OCT-SA was 25 µg/hour in three trials [100,190,192] and 50 µg/hour in one.[191] In one study, patients who were treated with terlipressin also received transdermal nitroglycerin.[192] In two studies, the treatment and control groups underwent esophageal ligation.[100,191] The length of follow-up was 30 days to 67 days in three studies and not reported in one. One trial reported no drop outs or withdrawals.[190] It was unclear if patients were lost to follow-up in the other three studies.[100,191,192] The Silvain et al. study was ended early because of adverse events in the terlipressin group.[192]

OCT-SA versus vasopressin: Four trials[193-196] compared OCT-SA with vasopressin in patients with acute variceal bleeding. One study also compared OCT-SA with balloon tamponade[195] and with somatostatin.[196] All were randomized, open label, parallel studies. One study was published as an abstract.[195] In all studies, the concealment of allocation was unclear. The Jadad scores were two[193,194] and one.[195,196]

The studies enrolled a total of 374 patients (from 41 to 224) with cirrhosis and variceal bleeding that were confirmed by using endoscopy. The duration of treatment was 24 hours or less in three studies[193-195] and three days in one study.[196] The dose of OCT-SA was the same in three trials (25 µg/hour)[193-195] and weight-based in the fourth.[196] In one study, patients in the vasopressin group also received glyceryl trinitrate.[196] The duration of follow-up varied from 24 hours to 42 days. In two studies,[193,194] all the patients were accounted for at the end of the trial. In the other two RCTs, the number of withdrawals was unclear.[195,196]

Details about the trial and patient characteristics, withdrawals, and outcomes that were extracted from the 36 RCTs appear in Appendix 4, Tables A5 to A8. No CCTs met the inclusion criteria for this indication.

b) Data analysis and synthesis

Results from the meta-analysis appear in Table 9, the figures in Appendix 3. Subgroup or sensitivity analyses were conducted when there were four or more studies. The subgroup analysis was based on a low dose of OCT-SA (25 µg/hour or less) or a high dose (more than 25 µg/hour infusion). The sensitivity analysis was based on lower quality studies (Jadad score of two or less and unclear or inadequate allocation concealment) or higher quality studies (Jadad score of three or higher and adequate allocation concealment).

Death

The number of deaths was reported after short-term (in-hospital) and mid-term (up to three months) follow-up times. Where data were sufficient, separate analyses were conducted for in-hospital mortality (10 days or less) and longest follow-up mortality.

OCT-SA versus placebo or no treatment: All 21 RCTs reported data on the number of deaths. When the in-hospital mortality data were pooled, the difference between groups was statistically significant [RR 0.71 (95% CI 0.54, 0.93); ARD −3% (95% CI −6, −1) I^2=0%, data not shown]. In this analysis, the follow-up time ranged from 48 hours to 10 days, or to hospital discharge in 10 studies, and was not reported in four.

No significant difference was detected between OCT-SA and placebo or OCT-SA and no treatment when the longest follow-up data were pooled [RR 0.84 (95% CI 0.70, 1.01) I^2=23.6%; Appendix 3, FigureA3]. The longest follow-up time ranged from five days to 90 days in 12 studies and not reported in four.

The results did not change when the best- and worst-case scenarios were analyzed to account for missing patients. The sensitivity and subgroup analyses showed similar results.
One of the five studies that were excluded from the meta-analysis reported a significant difference between study groups (Table 10). Abd-Elrazek et al.[177] reported a significantly higher risk of death among patients treated with OCT-SA. The patients who were enrolled in this study had a poor prognosis because they presented with impaired consciousness due to grade III or IV encephalopathy.

OCT-SA versus sclerotherapy: Meta-analysis was possible for six of the seven studies that reported the number of deaths.[99,183,185-188] No significant difference in the risk of death was found in comparing the OCT-SA and sclerotherapy groups when the in-hospital data (not shown) were pooled or when the longest follow-up data (three days to 42 days, not reported in two studies) were pooled [RR 0.86 (95% CI 0.48, 1.52) I^2=28.8%] (Appendix 3, Figure A4). The sensitivity and subgroup analyses showed similar results, as did the best- and worst-case analyses for missing patients.

El-Jackie et al.[184] reported no significant difference in deaths between the OCT-SA and sclerotherapy groups (10% and 3.5% respectively) in Child Class A and B patients with

schistosomal portal hypertension and variceal bleeding. The number of deaths was not reported among those with Child class C liver disease.

Table 9: Meta-analysis results: OCT-SA for emergency management of variceal bleeding

Comparator (Number of Studies)	Event Rate in OCT-SA Group	Event Rate in Control Group	RR (95% CI)*	ARD (95% CI)*	NNT (95% CI)†
Death					
Placebo or no treatment (16)	164/1167 (14.1%)	196/1168 (16.8%)	0.84 (0.70, 1.01) I^2=23.6%	−3% (−6, 0) I^2=23.1%	NE
Sclerotherapy (6)	29/336 (8.6%)	40/374 (10.7%)	0.86 (0.48, 1.52) I^2=28.8%	−1% (−7, 5) I^2=26.5%	NE
Terlipressin (4)	24/223 (10.8%)	26/221 (11.8%)	0.87 (0.53, 1.45)	−2% (−7, 4)	NE
Vasopressin (2)	16/44 (36.4%)	21/45 (46.7%)	0.78 (0.47, 1.28)	−10% (−31, 10)	NE
Patients failing initial hemostasis					
Placebo or no treatment (10)	58/552 (10.5%)	116/515 (22.5%)	0.48 (0.36, 0.63)	−12 (−16, −8) I^2=17.0%	9 (7, 13)
Sclerotherapy (9)	59/361 (16.3%)	54/392 (13.8%)	1.19 (0.85, 1.66) I^2=13.2%	3% (−2, 8%)	NE
Balloon tamponade (2)	5/41 (12.2%)	2/38 (5.3%)	2.30 (0.47, 11.19)	7% (−5, 19)	NE
Terlipressin (4)	20/223 (9.0%)	35/221 (15.8%)	0.54 (0.34, 0.87)	Data not pooled, I^2=83.9%	14 (10, 49)
Vasopressin (4)	22/138 (15.9%)	53/150 (35.3%)	0.45 (0.29, 0.70)	−19% (−29, −10)	6 (4, 10)
Rebleeding					
Placebo or no treatment (10)	75/724 (10.4%)	180/717 (25.1%)	0.41 (0.29, 0.60) I^2=42.4%	−14% (−19, −9) I^2=42.5%	7 (6, 10)
Sclerotherapy (8)	69/454 (15.0%)	97/499 (19.4%)	0.78 (0.59, 1.03) I^2=16.5%	−2% (−8, 3) I^2=27.2%	NE
Balloon tamponade (2)	12/41 (29.3%)	6/38 (15.8%)	1.90 (0.80, 4.50)	14% (−4, 32)	NE
Terlipressin (3)	28/121 (23.1%)	20/114 (17.5%)	1.29 (0.66, 2.51) I^2=29.5%	4% (−8, 17) I^2=44.6%	NE
Vasopressin (3)	13/65 (20%)	15/67 (22.4%)	0.89 (0.33, 2.41) I^2=46.8%	−2% (−23, 19) I^2=57.4%	NE
Patients with uncontrolled bleeding requiring additional treatments					
Sclerotherapy (5)	38/171 (22.2%)	32/176 (18.2%)	1.23 (0.80, 1.86)	4% (−4, 12)	NE

ARD=absolute risk difference; CI=confidence interval; NE=not estimable; NNT=number needed to treat; OCT-SA=octreotide short-acting; RR=relative risk

*I^2 = 0% unless specified. If I^2 <25%, fixed effects model was used for meta-analysis. Random effects model was used when I^2 ≥25% but ≤ 75%

†NNT calculations based on RR

Table 10: Deaths reported in trials excluded from meta-analysis				
Author, Year	**Comparator (Follow-up Time, N)***	**Number of Deaths n/N (%)**		**RR (95% CI)**
		OCT-SA	**Control**	
Abd-Elrazek, 2005[177]	No treatment (in-hospital, 60)	28/30 (93.3%)	21/30 (70%) SS	1.33 (1.04, 1.72)
El Sayed, 1995[166]	No treatment (2 days, 100)	NR	NR	NS
Primignani, 1995[170]	Placebo (90 days, 58)	10/26 (38.5%)	7/32 (21.9%) NS	1.76 (0.78, 3.97)
Signorelli, 1996[173]†	Placebo (5 days, 94)	15%	15%	NE
Signorelli, 1997[174]	No treatment (5 days, 86)	NR	NR	NS

CI=confidence interval; n=number of deaths; N=sample size; NE=not estimable; NR=not reported; NS=not significant; OCT-SA=octreotide short-acting; RR=relative risk; SS=statistically significant
* All treatment groups also received sclerotherapy. In the Abd-Elrazek et al. study, the patients presented with impaired consciousness due to encephalopathy. In the OCT-SA group, sclerotherapy was delayed until consciousness improved
† Included a third treatment arm: somatostatin (13% of patients died; NS when comparing all three groups)

OCT-SA versus balloon tamponade: McKee et al.[189] reported zero deaths in the OCT-SA group and five deaths in the balloon tamponade group after nine days (p=0.47). The number of deaths was not reported in the Kusumobroto et al. study.[195]

OCT-SA versus somatostatin: In the Signorelli et al. 1996[173] study, the five-day mortality rate was reported as 15%, 13%, and 15% in the OCT-SA, somatostatin and placebo groups, respectively. This was not a significant difference. The number of deaths was not reported in the Zhang et al. study.[196] In the Vlachogiannakos et al. trial, three patients died: one in the OCT-SA group and two in the somatostatin group (p=0.98).[197]

OCT-SA versus terlipressin: All four trials reported the number of deaths.[100,190-192] There was no significant difference between OCT-SA and terlipressin when the in-hospital data (not shown) were pooled, or when the longest follow-up data (30 to 67 days, not reported in one study) were pooled [RR 0.87 (95% CI 0.53, 1.45) I^2=0%] (Appendix 3, Figure A5).

OCT-SA versus vasopressin: Two trials reported the number of deaths.[193,194] There was no significant difference in risk between OCT-SA and vasopressin when the in-hospital data (not shown) were pooled, or when the longest follow-up data (in-hospital death or within 42 days) were pooled [RR 0.78 (95% CI 0.47, 1.28) I^2=0%] (Appendix 3, Figure A6).

Patients failing initial hemostasis

Assessments of hemostasis were made at different timepoints; for example, after the first sclerotherapy session or up to five days after randomization. Hemostasis was defined using different clinical criteria; for example, clear gastric lavage, stable vital signs and hematocrit levels, limited or no further blood transfusions, absence of further hematemesis, or melena or signs of bleeding at endoscopy.

OCT-SA versus placebo or no treatment: The number of patients who failed initial hemostasis was reported in 14 articles.[99,167-169,171,174-176,178-182] In three studies, this outcome was measured during the first 24 hours. In nine studies, it was measured between 24 and 48 hours. In one study,

it was measured after five days, and one trial did not specify when it was assessed. When all 14 studies were pooled, patients who were treated with OCT-SA were less likely to fail initial hemostasis than those who received placebo or no treatment [RR 0.61 (95% CI 0.49, 0.76) I^2 = 13.3%; data not shown]. This benefit was mainly observed in those trials that randomized patients to receive OCT-SA plus sclerotherapy, or placebo or no treatment plus sclerotherapy.

No significant difference was found when OCT-SA was compared to placebo in the patients who received delayed sclerotherapy. Patients in the OCT-SA group received treatment with OCT-SA and then sclerotherapy after 48 to 72 hours. The control group received sclerotherapy at the time of randomization. In these studies, hemostasis was assessed before the OCT-SA group received sclerotherapy. Thus, these patients more closely resemble those in the OCT-SA versus sclerotherapy comparison. When these studies are removed from the analysis, the results still favour OCT-SA [RR 0.48 (95% CI 0.36, 0.63) I^2 = 0%] (Appendix 3, Figure A7). Data from the four studies with delayed sclerotherapy were analyzed with the data from the OCT-SA versus sclerotherapy trials.

The results were similar in the sensitivity analyses where the data were analyzed by OCT-SA dose, by study quality, or by best- and worst-case scenarios (data not shown).

OCT-SA versus sclerotherapy: Six of the included studies reported the number of patients who failed initial hemostasis.[99,183-186,188] This outcome was measured after 12 to 48 hours in five studies and not reported in one study.[185] Data from five studies were pooled.[99,183,185,186,188] Patients in the sclerotherapy group were less likely to fail initial hemostasis than those in the OCT-SA group [RR 1.95 (95% CI 1.02, 3.73) I^2 = 0%].

There was no significant difference between the groups, however, when data from the four trials[178-181] that randomized patients to receive OCT-SA plus sclerotherapy after 48 to 72 hours or to receive sclerotherapy were added to the analysis [RR 1.19 (95% CI 0.85, 1.66) I^2=13.2%] (Appendix 3, Figure A8). In all four reports, hemostasis was assessed before the OCT-SA group received sclerotherapy.

The best- and worst-case scenarios were analyzed to account for missing patients. No significant difference between groups was detected in either scenario. The results were similar in the sensitivity analyses where the data were analyzed by OCT-SA dose or by study quality.

One study was excluded from the meta-analysis because the patients had a different prognosis. El-Jackie et al.[184] reported that bleeding was controlled within 48 hours in 58% of those in the OCT-SA group and 94% of patients in the sclerotherapy group ($p<0.05$).

OCT-SA versus balloon tamponade: Both studies reported the number of patients who failed to achieve hemostasis after four[189] or 24 hours.[195] There was no significant difference between the OCT-SA and balloon tamponade groups [RR 2.30 (95% CI 0.47, 11.16) I^2=0%] (Appendix 3, Figure A9).

OCT-SA versus somatostatin: The Signorelli et al. 1996[173] study reported that 75%, 81%, and 62% of patients in the OCT-SA, somatostatin and placebo groups, respectively, achieved control

of hemorrhage after five days. These rates were significantly different for OCT-SA or somatostatin compared with placebo ($p<0.01$).

Zhang et al.[196] reported no significant difference between the OCT-SA and somatostatin groups in the number of patients who failed hemostasis at 72 hours [RR 1.46 (95% CI 0.60, 3.56)].

This outcome was not reported in the Vlachogiannakos et al. trial.[197]

OCT-SA versus terlipressin: The number of patients who failed initial hemostasis was reported in four studies.[100,190-192] The follow-up time was 12 or 24 hours in two studies, and not reported in two studies. Patients who were treated with OCT-SA were less likely to fail initial hemostasis than those who were treated with terlipressin [RR 0.54 (95% CI 0.34, 0.87) I^2=0%] (Appendix 3, Figure A10).

OCT-SA versus vasopressin: All four studies reported the number of patients who failed initial hemostasis.[193-196] The time of follow-up for this outcome varied from six hours to 72 hours. Patients who were treated with OCT-SA were less likely to fail than those who were treated with vasopressin [RR 0.45 (95% CI 0.29, 0.70) I^2=0%] (Appendix 3, Figure A11).

Rebleeding

Moderate heterogeneity was detected for most of the comparisons. This may be partly due to the differences in how rebleeding was defined. The criteria included the recurrence of hematemesis or melena, aspiration of fresh blood, presence of unstable vital signs, decrease in hemoglobin levels, or need for blood transfusion. Many studies provided no criteria for this outcome. Rebleeding was assessed at short (in-hospital) and mid-term (up to three months) follow-up times.

Some trials removed the patients who did not achieve initial hemostasis when the outcome of rebleeding was considered. Because initial hemostasis data were not reported in all trials, we used the total number per treatment arm as the denominator when we analyzed the number of patients with rebleeding.

OCT-SA versus placebo or no treatment: The number of patients with rebleeding was reported in 14 trials.[99,167-172,175,176,179-182,187] Among the 13 trials that were included in the meta-analysis, rebleeding was reported after two to 15 days (the follow-up time was not reported in one study). Patients in the OCT-SA group were less likely to experience rebleeding than those in the placebo or no treatment groups [RR 0.49 (95% CI 0.36, 0.68) I^2=42.8%, data not shown]. The elimination of the three studies[179-181] where sclerotherapy was delayed in the OCT-SA group did not change the results [RR 0.41 (95% CI 0.29, 0.60) I^2=42.4%] (Appendix 3 Figure A12).

The results did not change when the best- and worst-case scenarios were analyzed to account for missing patients (data not shown). In the sensitivity analysis, the RCTs of lower quality showed a significant benefit that favoured OCT-SA [six trials, RR 0.35 (95% CI 0.22, 0.54) I^2=46.4%]. No significant benefit was seen for the studies of higher quality (data not shown). When the studies were analyzed by OCT-SA dose, those using a dose of 25 µg/hour or less showed no significant difference between treatment groups. The heterogeneity was high (I^2=84%) in these

two studies. The studies that used a higher dose showed a significant benefit in favour of OCT-SA (data not shown).

One study was excluded from the meta-analysis because the population differed from that of the other trials. Primignani et al.[170] reported that there was no significant difference between OCT-SA and placebo regarding the rate of rebleeding at 90 days [RR 0.90 (95% CI 0.42, 1.89)]. Based on the interim analysis, the study was ended because of a lack of efficacy.

OCT-SA versus sclerotherapy: Rebleeding was reported in five RCTs that compared OCT-SA with sclerotherapy.[99,183,186-188] Rebleeding was assessed after three to five days in four studies and 30 days in one. No significant difference was detected between groups [RR 0.74 (95% CI 0.53, 1.04) I^2 = 50.6%]. When the three trials[179-181] from the OCT-SA versus placebo comparison were added to the analysis, the pooled results were similar [RR 0.78 (95% CI 0.59, 1.03) I^2=16.5%] (Appendix 3, Figure A13). In these three trials, patients were randomized to receive OCT-SA plus sclerotherapy (after 48 to 72 hours) or to receive sclerotherapy. In all cases, rebleeding was assessed before the OCT-SA group received sclerotherapy.

The pooled results did not change when the best- and worst-case scenarios were analyzed to account for the missing patients. The subgroup analysis based on OCT-SA dose showed no significant difference between groups. In the sensitivity analysis, the trials of higher quality (Jadad score of three to five) showed no significant difference between treatment groups [two trials, RR 1.09 (95% CI 0.60, 1.99) I^2=0%]. Among those of lower quality (Jadad score of zero to two), patients who were treated with OCT-SA were less likely to have rebleeding than those treated with sclerotherapy [six trials, RR 0.71 (95% CI 0.52, 0.98) I^2=23.2%; data not shown].

The El-Jackie et al. study[184] was excluded from the meta-analysis because the patients had a different prognosis. It reported no significant difference in the rate of rebleeding between the OCT-SA and sclerotherapy groups (14.3% and 3.5%, respectively) among patients with Child class A or B liver disease. In the sclerotherapy group, 27% of Child C patients re-bled within five days. Data from the OCT-SA group were not reported.

OCT-SA versus balloon tamponade: Two studies reported the number of patients with rebleeding.[189,195] No significant difference was detected between the OCT-SA and balloon tamponade groups [RR 1.90 (0.80, 4.50) I^2=0%] (Appendix 3, Figure A14).

OCT-SA versus somatostatin: The number of patients with rebleeding was reported in one of the three trials. The Vlachogiannakos et al. study[197] reported no significant difference between groups in the rate of rebleeding within six weeks (p=0.69).

OCT-SA versus terlipressin: The numbers of patients with rebleeding were reported in three trials.[100,190,192] There was no significant difference in the risk of rebleeding between OCT-SA and terlipressin when the in-hospital (data not shown) or the longest follow-up data (30 to 67 days) were pooled [RR 1.29 (95% CI 0.66, 2.51) I^2=29.5%] (Appendix 3, Figure A15).

OCT-SA versus vasopressin: Rebleeding was reported in three trials.[193-195] The follow-up time was 24 hours in two studies[193,194] and not reported in the third.[195] There was no significant

difference in the risk of rebleeding between OCT-SA and vasopressin when data were pooled [RR 0.89 (95% CI 0.33, 2.41) I^2=46.8%] (Appendix 3, Figure A16).

Need for additional treatments

The data that were reported in the RCTs were sometimes unclear. As a result, a narrative synthesis was conducted for some comparisons. In some cases, the data represented the number of events (number of procedures) rather than the number of patients who required additional interventions. The definition of treatment failure and the length of follow up also varied between studies.

OCT-SA versus placebo or no treatment: Seven RCTs reported data on patients with uncontrolled bleeding who required additional interventions.[165,167,171,178,180-182] Data from the Sivri et al. study[180] and from the Sung et al. 1993 study,[181] where the OCT-SA group received delayed sclerotherapy, were pooled with the results of the OCT-SA versus sclerotherapy studies. In these studies, the need for additional interventions was assessed before sclerotherapy. As a result, these patients more closely resembled those in the OCT-SA versus the sclerotherapy comparison.

A narrative synthesis was provided for the remaining studies (Table 11). One study[167] reported a statistically significant benefit with OCT-SA compared with placebo. In three trials,[171,178,182] a higher number of interventions were reported in the placebo group. The statistical significance, however, was not reported. In one trial,[165] no difference was seen between treatment groups.

OCT-SA versus sclerotherapy: The number of patients with uncontrolled bleeding who required intervention was reported in three studies[183,185,186] that compared OCT-SA with sclerotherapy and in two trials[180,181] that compared OCT-SA with placebo or no treatment, plus sclerotherapy. When all five studies were pooled, no significant difference was detected between OCT-SA and the control group [RR 1.23 (95% CI 0.81, 1.86) I^2=0%] (Appendix 3, FigureA17). The results did not change when the best- and worst-case scenarios were analyzed to account for the missing patients.

OCT-SA versus balloon tamponade: In the McKee et al. study, which compared OCT-SA to balloon tamponade, no difference was detected in the number of patients who required additional procedures for uncontrolled bleeding [RR 1.20 (95% CI 0.44, 3.30)] (Table 11).[189] Kusumobroto et al.[195] did not report this outcome.

OCT-SA versus terlipressin: Two trials reported the number of patients with uncontrolled bleeding that required additional treatment.[190,192] The data were reported for different time points and may represent the number of procedures rather than the number of patients. As a result, the data were not pooled. The statistical significance of any differences between treatment groups was not reported (Table 11).

OCT-SA versus vasopressin or somatostatin: The trials that compared OCT-SA with vasopressin or somatostatin did not report the number of patients with uncontrolled bleeding who required additional treatments.

Table 11: Patients with uncontrolled bleeding requiring treatment				
Author, Year	**Comparator (Follow- up Time, N)***	**Number of Patients with Uncontrolled Bleeding Requiring Other Treatments n/N (%)**		**RR (95% CI)**
		OCT-SA	**Control**	
OCT-SA versus placebo or no treatment				
Besson, 1995[167]	Placebo (5 days, N=199)	11/98 (11%)	25/101 (25%)	0.45 (0.24, 0.87)
IOVSG, 1996[165]	Placebo (5 days, N=383)	56/87 (64%)	73/106 (69%), NS	0.93 (0.76, 1.14)
Freitas, 2000[178] group II	No treatment (NR, N=86)	Need for interventions higher in sclerotherapy group (statistical significance NR)		NE
Shah, 2005[171]	Placebo (NR, N=105)	2 sclerotherapy, 0 surgery	8 sclerotherapy, 2 surgery	NE*
Sung, 1995[182]	No treatment (NR, N=100)	1 balloon tamponade, 0 surgery	10 balloon tamponade, 2 surgery	NE*
OCT-SA versus balloon tamponade				
McKee, 1992[189]	Balloon tamponade (NR, N=40)	6/20 (30%)	5/20 (25%)	1.20 (0.44, 3.30)
OCT-SA versus terlipressin				
Pedretti, 1994[190]	Terlipressin (NR, N=60)	1 balloon tamponade (<24 h), 7 sclerotherapy (>24 h)	14 sclerotherapy (>24 h)	NE*
Silvain, 1993[192]	Terlipressin (2 days, N=87)	8 (12 h) 5 (>12 to 24 h) 3 (>24 to 48 h)	12 (12 h), 0 (>12 to 24 h), 4 (>24 to 48 h)	NE*

CI=confidence interval; IOVSG-International Octreotide Varies Study Group; n=events; N=sample at follow-up; NE=not estimable; NR=not reported; NS=not significant; OCT-SA=octreotide short-acting; RR=relative risk
*RR not calculated because data that were reported were unclear. Data may represent number of events rather than number of patients and some patients may have received more than one procedure

Blood transfusion requirements

Blood transfusion requirements were reported in 27 studies (Table 12). These data were often reported as mean or median values with the range, and sometimes with no or unclear estimates of variance (SD or SE). In many cases, the data were skewed. For these reasons, the data were not pooled.

Most studies did not report the clinical criteria for administering blood products. Two[176,197] studies provided criteria for blood transfusions.

OCT-SA versus placebo or no treatment: The number of units of blood that was transfused was reported in 16 studies. Five trials reported that patients who were treated with OCT-SA required fewer units of blood than those in the control group.[171,172,174,176,178] The remaining 11 studies reported no significant difference between treatment groups.[99,165,167,168,173,177-182]

OCT-SA versus sclerotherapy: Blood transfusion requirements were reported in four studies.[99,183,184,186] Three studies reported no significant difference between treatment groups. El-Jackie et al.[184] reported that significantly fewer units of blood were required for the sclerotherapy group than for the OCT-SA group.

OCT-SA versus balloon tamponade: Two studies reported on blood transfusion requirements. Neither detected a significant difference between treatment groups.[189,195] No details were provided in the Kusumobroto et al. study.[195]

OCT-SA versus somatostatin: The Signorelli et al. (1996)[173] study reported that patients who were treated with somatostatin required fewer blood transfusions than those treated with OCT-SA or placebo ($p<0.05$). The Vlachogiannakos et al.[197] study also reported significantly fewer blood transfusions among patients treated with somatostatin compared to those treated with OCT-SA.

OCT-SA versus terlipressin: Blood transfusion requirements were reported in three studies.[190-192] The OCT-SA group required significantly less blood than the terlipressin group in one study.[192] The difference between groups was not significant in the other two studies.[190,191]

OCT-SA versus vasopressin: Transfusion requirements were reported in three studies.[193-195] Huang et al.[193] reported significantly lower blood requirements among patients who were treated with OCT-SA versus vasopressin. The other two studies reported no statistically significant differences between treatments.[194,195] No details were provided in the Kusumobroto et al. abstract.[195]

Table 12: Blood transfusion requirements

Study (Number in OCT-SA Group/ Number in Control Group)	Unit of Measure	OCT-SA	Control	WMD (95% CI)
OCT-SA versus placebo				
IOVSG, 1996[165] (189/194)	NR	NR	No difference	NE
OCT-SA + sclerotherapy versus placebo or no treatment + sclerotherapy				
Besson, 1995[167] (98/101)	Mean units, (median, range)	1 day: 1.2 (1, 0 to 7), 5 days: 0.4 (0, 0 to 5)	24 h: 2.0 (2, 0 to 10), p=0.006; 5 d: 0.8 (0, 0 to 6), NS	NE
Freitas, 2000[178] (44/42) Group II	Mean units	0.9	2.9, p=0.01	NE
Morales, 2007[168] (40/28)	Mean units, (median)	2.05 (2)	2.08 (2), p=0.96	NE
Shah, 2005[171] (51/54)	Mean units ± SD or SE	3.88±2.80	5.37±3.15, p=0.002	NE
Shiha, 1996[172] (93/96)	Mean units ± SD or SE (range)	1.14±0.3 (0 to 4)	1.40±0.4 (0 to 6), p<0.001	NE
Signorelli, 1996[173] (31/30)	Median units (range)	3 (1 to 8)	3.5 (2 to 12)	NE

Table 12: Blood transfusion requirements				
Study (Number in OCT-SA Group/ Number in Control Group)	**Unit of Measure**	**OCT-SA**	**Control**	**WMD (95% CI)**
Signorelli, 1997[174] 44/42)	Mean units ± SD or SE	2.28±2.1	3.96±3.4, p<0.01	NE
Silva, 2004[99] (36/43)	Mean units ± SD	3.2±2.3	2.8±2.5, NS	0.40 (−0.66, 1.46)
Zuberi, 2000[176] (35/35)	Mean units ± SD	1.5±0.7	2.1±1.2, p=0.03	−0.60 (−1.06, −0.14)
OCT-SA + sclerotherapy (after 48 to 72 h) versus placebo or no treatment + sclerotherapy				
Abd-Ekrazek, 2005[177] (30/30)	NR	NR	Similar between groups	NE
Freitas, 2000[178] (58/53) Group I	Mean units	1.8	1.6, NS	NE
Jenkins, 1997[179] (73/77)	Mean units ± SD	6.9±4.4	7.5±5.2, NS	−0.60 (−2.14, 0.94)
Sivri, 2000[180] (30/36)	Mean units ± SE	4.8±2.9	4.2±1.8, NS	0.60 (−6.09, 7.29)
Sung, 1993[181] (49/49)	Median units	3.5	3, p=0.34	NE
OCT-SA + ligation versus no treatment + ligation				
Sung, 1995[182] (47/47)	Median units, (range)	3 (0 to 13)	4 (0 to 23), p=0.06	NE
OCT-SA versus sclerotherapy				
Bildozola, 2000[183] (39/37)	Mean units ± SD	0.7±1.4	0.4±1.0, NS	0.30 (−0.24, 0.84)
El-Jackie, 1998[184] (50/50)	Mean units ± SD or SE	2.9±0.79	2.1±0.41, p<0.05	NE
Poo, 1996[186] (22/21)	Mean units ± SD or SE	2.7±1.8	3.2±1.7, NS	NE
Silva, 2004[99] (13/43)	Mean units ± SD	3.4±1.4	2.8±2.5	0.60 (−0.47, 1.67)
OCT-SA versus balloon tamponade				
McKee, 1992[189] (20/20)	Mean mL ± SE	1710±252	1680±295, p=0.4	30 (−730, 790)
OCT-SA versus somatostatin				
Signorelli, 1996[173] (31/33)	Median units, (range)	3 (1 to 8)	2 (1 to 6), p<0.05	NE
Vlachogiannakos, 2007[197] (16/17)	Median units (range)	3.3 (0 to 6)	0.5 (0 to 4.5), p=0.009	NE
OCT-SA versus terlipressin				
Pedretti, 1994[190] (30/30)	Mean units ± SD	1.7±1.4	1.8±1.5, NS	−0.10 (−0.83, 0.63)
Salih, 2005[191] (102/107)	NR	4.0±2.6	3.7±2.2, NS	NE
Silvain, 1993[192] (46/41)	Mean units, (range)	1 (0 to 5)	3 (1 to 13), p=0.012	NE

Table 12: Blood transfusion requirements				
Study (Number in OCT-SA Group/ Number in Control Group)	**Unit of Measure**	**OCT-SA**	**Control**	**WMD (95% CI)**
OCT-SA versus vasopressin				
Huang, 1992[193] (20/21)	Mean units ± SD	3.4±3.2	5.2±2.7, p<0.05	−1.8 (−3.62, 0.02)
Hwang, 1992[194] (24/24)	Mean mL ± SD (range)	615±472 (250 to 2000)	771±909 (0 to 5500), NS	−156 (−566, 254)

CI=confidence interval; d=days; h=hours; IOVSG-International Octreotide Varies Study Group; NE=not estimable; NR=not reported; NS=not significant; OCT-SA=octreotide short-acting; SD=standard deviation; SE=standard error; WMD=weighted mean difference

Statistically significant difference favouring OCT-SA
Statistically significant difference favouring control
No significant difference between groups

Length of hospitalization

Because of incomplete reporting and the limited number of trials that reported the length of hospitalization, a meta-analysis was not conducted for this outcome. Data on length of hospitalization appear in Table 13.

OCT-SA versus placebo or no treatment: Three of the five studies that reported the length of hospitalization found a statistically significant difference between groups. In one trial,[177] the length of hospitalization was shorter in the placebo group, and in two trials,[171,176] the length of hospitalization was shorter in the OCT-SA group. No significant difference was detected in two other trials.[99,181]

OCT-SA versus sclerotherapy: Two studies reported the length of hospitalization. Silva et al.[99] found no significant difference between groups. El-Jackie et al.[184] found that the length of stay was significantly longer in the OCT-SA group.

OCT-SA versus terlipressin: The length of hospital stay was reported in two trials. Cho et al.[100] reported no significant difference between groups. Salih et al.[191] reported a significantly shorter length of stay in the terlipressin group.

OCT-SA versus vasopressin, somatostatin, or balloon tamponade: The length of hospitalization was not reported in any trial.

Table 13: Length of hospitalization				
Study (Number in OCT-SA Group/Number in Control Group)	**Length of Hospitalization (Days)**	**OCT-SA**	**Control**	**WMD (95% CI)**
OCT-SA + sclerotherapy versus placebo or no treatment + sclerotherapy				
Shah, 2005[171] (51/54)	Mean ± SD or SE	5.31±3.87	6.63±3.86, p=0.008	NE
Silva, 2004[99] (36/43)	Mean ± SD	10.9±6.2	10.9±5.8	0 (−2.67, 2.67)
Zuberi, 2000[176] (35/35)	Mean ± SD	5.9±1.2	6.6±1.3, p=0.04	−0.7 (−1.29, −0.11)
OCT-SA + sclerotherapy (after 48-72 h) versus placebo or no treatment + sclerotherapy				
Abd-Ekrazek, 2005[177] (30/30)	NR	11±2.9	5±2.3, SS	NE
Sung, 1993[181] (49/49)	Median (range)	6 (1 to 31)	5 (1 to 33), p=0.41	NE
OCT-SA versus sclerotherapy				
El-Jackie, 1998[184] (50/50)	Mean ± SD or SE	17.9±9	5.12±1.62, p<0.05	NE
Silva, 2004[99] (13/43)	Mean ± SD	11.8±7.4	10.9±5.8	0.90 (−3.48, 5.28)
OCT-SA versus terlipressin				
Cho, 2006[100] (45/43)	Mean ± SD or SE	13.1±9.9	10.0±6.8, NS	NE
Salih, 2005[191] (102/107)	Mean ± SD or SE	5.2±2.0	4.5±1.5, p=0.004	NE

CI=confidence interval; h=hours; NR=not reported; NS=not significant; NE=not estimable; OCT-SA=octreotide short-acting; SD=standard deviation; SE=standard error; SS=statistically significant; WMD=weighted mean difference

Statistically significant difference favouring OCT-SA
Statistically significant difference favouring control
No significant difference between groups

Optimal length of therapy

The length of therapy varied from under 24 hours to 29 days (not reported in two RCTs). The most common treatment duration was two days (11 RCTs) or five days (11 RCTs) (Appendix 4, Table A5).

While some RCTs reported statistically significant results for some outcomes, no trend was revealed by the data. It is not possible to draw any conclusions regarding the optimal length of therapy.

Harms data

Of the 36 included RCTs, 10 reported no information on adverse events.[100,165,168,171,172,174,175,177,184,187]

OCT-SA versus placebo or no treatment: Adverse event data were reported in 11 RCTs that compared OCT-SA with placebo or no treatment. In all but one study,[166] patients in both treatment groups also received sclerotherapy or ligation. In four trials,[178-181] patients in the OCT-SA group received sclerotherapy after a delay of 48 to 72 hours.

The El Sayed et al. study[166] examined patients who were randomized to receive OCT-SA or conservative therapy. No side effects were observed during the OCT-SA infusion.

Besson et al.[167] reported a similar incidence of adverse events between treatment groups. No patients stopped therapy because of adverse events. There was a higher rate of hyperglycemia in the OCT-SA group than in the placebo group (23/98 versus 13/101). The difference was not statistically significant. Other adverse events that were reported were nausea, diarrhea, abdominal pain, headache, severe encephalopathy, spontaneous bacterial peritonitis or septic shock, metabolic acidosis, esophageal ulcers, and disseminated intravascular coagulation.

In the Farooqi et al.[169] study, the most common adverse event that was associated with sclerotherapy was retrosternal pain, which was reported in 32% (23/72) of the OCT-SA plus sclerotherapy group compared with 39% (27/69) of the sclerotherapy group. Eight patients in the OCT-SA group also reported abdominal pain.

In the Primignani et al.[170] study, one patient in the placebo group withdrew because of adverse events. No patients stopped treatment because of adverse events in the OCT-SA group. No other details about adverse events were reported.

Silva et al. reported a similar incidence of side effects among three treatment groups: OCT-SA, OCT-SA plus endoscopic therapy, and endoscopic therapy alone.[99]

Zuberi et al.[176] reported a similar incidence of side effects between groups. The most common adverse events in the OCT-SA and placebo groups respectively were pharyngeal irritation (7/35 versus 5/35) followed by dysphagia (4/35 versus 3/35). Other events that were reported included pneumonia, spontaneous bacterial peritonitis, chest pain, and pleural effusion.

Freitas et al.[178] conducted two randomizations. Patients with signs of recent hemorrhage at endoscopy were randomized to receive OCT-SA plus sclerotherapy (after 48 hours, 58 patients) or to receive sclerotherapy (53 patients). No major adverse events were reported in either group. There were two cases of nausea and one case of abdominal pain in the OCT-SA group. The complications that were related to sclerotherapy were chest pain, fever, or esophageal ulcers (numbers not reported). In the second group of 86 patients with active bleeding at endoscopy, two patients in the OCT-SA group reported nausea.

Jenkins et al.[179] reported no significant difference in the incidence of adverse events between the OCT-SA group and the placebo or no treatment group (19/73 versus 15/77 respectively). Two patients in the OCT-SA group experienced serious adverse events (paralytic ileus that required treatment to be discontinued, and pulmonary edema). Hyperglycemia was reported in 15 patients in the OCT-SA group and in none in the control group. Fever (2 patients), retrosternal pain (2), esophageal ulceration (8), pleural effusions (1) and aspiration (1) were reported in the control group. Abdominal pain was reported in one patient in the OCT-SA group.

The adverse events that were reported in the control group in the Sivri et al. study[180] included esophageal ulceration (3 patients), esophageal stricture (1), retrosternal pain (1) and renal failure (1). In the OCT-SA group, one patient developed renal failure and one reported hyperglycemia.

In the Sung et al. (1993)[181] study, 18 of 49 patients in the control group reported fever and retrosternal pain after sclerotherapy. Aspiration pneumonia and pleural effusion occurred in one and three patients, respectively. In the OCT-SA group, five of 49 patients complained of nausea.

In the Sung et al. (1995) study,[182] no patients in the OCT-SA group had side effects that required cessation of therapy.

OCT-SA versus sclerotherapy: In the Bildozola et al.[183] study, four patients of the 37 in the sclerotherapy group experienced major complications [aspiration pneumonia (2), perforation (1), and pericardial effusion (1)] compared with none of the 39 patients in the OCT-SA group. This was not significant.

Lopez et al.[185] reported nine cases of thoracic pain and 12 cases of esophageal ulcer in the 33 patients who received sclerotherapy. Among the 31 patients treated with OCT-SA, hyperglycemia was the only side effect to be noted (number not reported).

In the Poo et al. trial with 43 patients, one patient in each group reported side effects.[186] Yousuf et al.[188] reported no significant difference between groups with respect to adverse events [OCT-SA: 8/48, sclerotherapy: 6/48 (fever or chest pain)].

OCT-SA versus balloon tamponade: McKee et al.[189,203] reported no symptomatic side effects in the OCT-SA group compared with the balloon tamponade group, where 17 of 20 patients complained of discomfort from the Minnesota tube. Insulin was required in one patient who was treated with OCT-SA and not required in the tamponade group. Chest infection was reported in 7/20 and 10/19 patients in the OCT-SA and balloon tamponade groups, respectively. This was not significant.

OCT-SA versus somatostatin: Data from the Zhang et al.[196] study is reported in the OCT-SA versus vasopressin section. Signorelli et al. reported in 1996 that no relevant side effects were observed.[173]

Vlachogiannakos et al.[197] reported treatment-related adverse effects in 63% of patients in the OCT-SA group (10/16) and 65% of patients (11/17) in the somatostatin group (p=0.99). The reported adverse effects were hyperglycemia, fever, and transient retrosternal pain. All patients also received sclerotherapy or ligation.

OCT-SA versus terlipressin: The Silvain et al.[192] study ended early because of serious adverse events in the terlipressin group (left ventricular failure and death in one patient, and bradycardia in another). No major adverse events were reported in the OCT-SA group. Minor adverse events that did not lead to the cessation of therapy were reported in four of the 41 patients in the terlipressin group (bradycardia, tachycardia, or hypertension) and in nine of the 46 patients in the OCT-SA group (hyperglycemia and diarrhea).

Pedretti et al. reported significantly more patients had adverse events in the terlipressin group (18/30) compared with the OCT-SA group (7/30, p=0.01).[190] Diarrhea (7), electrocardiogram

ischemia (3), and bradycardia (3) were most frequent in the terlipressin group, while in the OCT-SA group, hyperglycemia (n=3), diarrhea (2), and bradycardia (2) were most common.

Salih et al.[191] reported no cardiovascular side effects in the terlipressin group.

OCT-SA versus vasopressin: Adverse events were reported in four RCTs. In the Huang et al. study,[193] eight of 21 patients in the vasopressin group reported abdominal pain (4), bradycardia (2), chest pain (1), or ischemic purpura (1). Among those treated with OCT-SA, three of 20 patients reported abdominal fullness or nausea. This was not significant.

Hwang et al.[194] reported a significantly higher rate of adverse events among patients in the vasopressin group (11/24, 46%) compared with those in the OCT-SA group (3/24, 13% p=0.02). Three patients in the OCT-SA group reported abdominal pain, while in the vasopressin group there were headache (2), chest pain (4), or abdominal pain (5).

In the Zhang et al.[196] study, patients in the vasopressin group reported a significantly higher rate of adverse events than those in the OCT-SA or somatostatin groups [vasopressin 34/83 (41%), somatostatin 5/68 (7%), OCT-SA 6/73 (8%)]. In the vasopressin group, patients experienced tachycardia, headache, hypertension, chest discomfort, and abdominal pain. In the OCT-SA and somatostatin groups, dizziness, nausea, and tachycardia were reported.

Kusumobroto et al.[195] noted a higher incidence of adverse events in the vasopressin and balloon tamponade groups compared with the OCT-SA group. The difference was not statistically significant.

4.2.4 GEPNET

a) Study characteristics

Four RCTs (six reports) compared octreotide to another treatment in patients with GEPNETs. Of these, one study compared OCT-SA with lanreotide;[204,205] another study compared OCT-SA with various doses of OCT-LA;[206,207] and two studies compared OCT-SA with placebo.[208,209]

All studies were randomized. Three studies were double-blinded[206,208,209] and the other was an open-label study. Two studies used a cross-over design.[204,209] The sample sizes varied from 11 to 93 patients. The total number of patients was 149. Although two trials[208,209] with sample sizes of 11 and 12 were included in our review, the results must be interpreted with caution.

The treatment duration for the four RCTs ranged from 24 hours to 24 weeks. Two trials obtained a Jadad score of three or more,[208,209] and one had adequate allocation concealment.[209] The other two trials obtained a Jadad score of two (indicating poorer quality). Allocation concealment could not be determined for these studies. The study characteristics and outcomes reported appear in Appendix 4, Tables A9 and A10.

One study had no drop-outs or withdrawals.[208] The other three reported that between two and 14 patients had not completed the study. None used intention-to-treat analysis. In one study, it was mentioned that the results were similar for the intention-to-treat population, but the absolute numbers were not reported. Details appear in Appendix 4, Table A11.

Two CCTs met the inclusion criteria.[210,211] Data from these studies were included in the analysis of harm data.

b) Data analysis and synthesis

There were study results on five outcomes from the four RCTs. Because of study limitations, it was not possible to do a meta-analysis of the data and comparisons between studies. Differences existed in the treatment or control groups and the duration of treatment. In addition, the number of patients in each treatment group, or outcome data, such as variance or end-point values, were not reported. Attempts to contact the authors to obtain missing data were unsuccessful. Finally, sub-group analyses were not possible because of the small number of trials included in this review.

Death

OCT-SA versus OCT-LA: Rubin et al.[206] reported three deaths: one in the OCT-LA 20 mg group and two in the OCT-LA 30 mg group. The causes of death were respiratory distress, pulmonary embolism, and hypoglycemic episodes with renal failure. These were considered to be unrelated to the study medication.

Health-related quality of life

The two cross-over studies[204,209] that measured quality of life did not provide the results in the first period of treatment (before cross-over).

Treatment success

OCT-SA versus OCT-LA: Rubin et al.[206] measured treatment success according to symptom control. Patients who did not require rescue medication at any time were considered to be treatment successes. Those who required rescue on no more than two occasions for not more than five days total were considered to be partial successes. Four treatment groups were compared. Given that the other studies used dosage ranges, the data for OCT-LA 10 mg, 20 mg, and 30 mg were consolidated for comparison.

In this study, no difference was found between OCT-SA and OCT-LA in the reduction of the need for rescue medication (Table 14). This holds true for worst- and best-case scenarios.

Table 14: Treatment success at 24 weeks* in RCTs that compare OCT-SA to OCT-LA

Study	Analysis	OCT-SA	OCT-LA	RR (95% CI)
Rubin, 1999[206]	Base case†	14/24	36/55‡	0.9 (0.6, 1.3)
	Best scenario	16/26	36/67	1.1 (0.8, 1.7)
	Worst scenario	14/26	48/67	0.8 (0.5, 1.1)

CI=confidence interval; OCT-LA=octreotide long-acting; OCT-SA=octreotide short-acting; RCTs=randomized controlled trials; RR=relative risk
*Results were the same at 20 and 24 weeks
†Available case analysis
‡Includes partial success

Change in symptom severity

All studies measured the frequency of flushing and diarrhea.

OCT-SA versus lanreotide: In the O'Toole et al. study,[204] the change in symptoms was based on measuring the intensity of flushing and diarrhea. Table 15 shows that there were no differences between the two drugs for this outcome.

Table 15: Change in symptom severity in RCTs that compare OCT-SA to lanreotide

Study	Analysis	OCT-SA	Lanreotide	RR (95% CI)
>50% decrease in frequency of flushes				
O'Toole, 2000[204]	Base case*	5/14	4/14	1.3 (0.4, 3.7)
	Best scenario	7/16	4/17	1.9 (0.7, 5.2)
	Worst scenario	5/16	7/17	0.8 (0.3, 1.9)
>50% decrease in frequency of stools				
O'Toole, 2000[204]	Base case*	12/14	11/14	1.1 (0.8, 1.5)
	Best scenario	14/16	11/17	1.4 (0.9, 2.0)
	Worst scenario	12/16	14/17	0.9 (0.6, 1.3)

CI=confidence interval; OCT-SA=octreotide short-acting; RCTs=randomized controlled trials; RR=relative risk
*Available case analysis

OCT-SA versus OCT-LA: The reporting of data for symptom severity was incomplete in the Rubin et al. study[206] The authors did not report the number of patients per treatment group, and only provided the total number of patients in the analysis of number of stools passed per day and number of flushing episodes per day. They also did not provide variance data.

The authors reported that the median number of stools decreased significantly from baseline in all treatment groups and was similar across treatment groups. No statistical differences were noted between the OCT-LA and OCT-SA groups.

The number of flushing episodes per day was higher in the OCT-LA 10 mg group than in the OCT-SA group, but the difference was not significant.

OCT-SA versus placebo: The study[209] did not provide results for the first treatment period (before cross-over).

Saslow et al.[208] compared OCT-SA with placebo in a small sample of 12 patients. The symptoms of flushing and abdominal pain were assessed before and after meal ingestion. The results were recorded on a 10 cm analogue scale, with zero being no flushing or no abdominal pain and 10 being the worst flushing or pain. Patients had significantly less flushing with OCT-SA than with placebo. The results were not statistically different for abdominal pain (Table 16). These results should be confirmed in a larger study.

Table 16: Change in symptom severity in RCTs that compare OCT-SA to placebo

Study	Symptom	OCT-SA Mean±SE (Sample Size)	Placebo Mean±SE (Sample Size)	Mean Difference (95%CI)
Saslow, 1997[208]	Flushing	0.2±0.2 (n=6)	0.9±0.2 (n=6)	−0.7 (−1.3, −0.1)
	Abdominal pain	0.9±0.8 (n=6)	1.5±0.5 (n=6)	−0.6 (−2.5, 1.3)

CI=confidence interval; OCT-SA=octreotide short-acting; RCTs=randomized controlled trials; SE=standard error

Change in 5-HIAA levels
All four RCTs reported some change in 5-HIAA levels. The data, however, could not be used.

OCT-SA versus lanreotide: The cross-over study[204]comparing OCT-SA with lanreotide provided results for the first treatment period. These results cannot be analyzed because the number of patients in each group was not reported and only the total sample size (24 patients) was provided.

OCT-SA versus OCT-LA: The study that compared OCT-SA to OCT-LA[206] provided median results with ranges. As a result, an analysis cannot be completed. The authors reported that low patient compliance regarding the collection of urine samples reduced the ability to detect any statistically significant results.

OCT-SA versus placebo: The parallel study did not provide end-point results.[208] The cross-over study[209] did not provide results for the first treatment period (before cross-over), although the author did state that patients who started with octreotide returned to pre-treatment values when they were taking placebo.

Optimal length of therapy
The study durations ranged from 24 hours to 24 weeks. Statistically significant results were reported after 24 hours of treatment in one small study (12 patients)[208] for one outcome (decreased flushing). As a result, we cannot draw a conclusion about the optimal length of therapy.

Harms data
One RCT with 93 patients (study duration of six months)[206] that compared OCT-SA with OCT-LA reported that 17 patients experienced serious adverse events, including death (three patients). The investigators thought that these adverse events, which were not described, were unrelated to the use of OCT-SA and OCT-LA. The three deaths were attributed to respiratory distress, pulmonary embolism, or hypoglycemic episodes with renal failure. Other adverse events included application site disorder, asthenia, fever, hypothyroidism, abdominal pain, flatulence, nausea, steatorrhea, cholelithiasis, rash, taste perversion, and renal calculi.

In one non-randomized study with 20 patients (2 doses of OCT-SA or placebo), three patients reported flatulence and intestinal rumbling after receiving octreotide.[210]

One small observational study with 14 patients (mean treatment duration of 6.2 years) compared to 11 historical controls[211] reported that five patients who were treated with OCT-SA had asymptomatic gallstones that were detected using ultrasound. One female patient developed alopecia.

4.2.5 Prevention of complications after pancreatic surgery

a) Study characteristics
Twenty reports[26,212-230] assessed the effects of OCT-SA in preventing complications after pancreatic surgery. Of these, 12 were unique parallel RCTs. All trials compared OCT-SA with a

placebo or a no-treatment group. Patients in these trials had pancreatitis, had a malignant or benign tumour, had undergone transplantation, or had a combination of these conditions.

Six RCTs were double blinded,[26,215,218,219,221,222] one was single-blinded,[214] and the remainder were open-label. The sample size varied between 17 and 383 patients. In all but one study, the treatment duration ranged between five and 10 days. In one study, patients were treated for a mean of 20 to 25 days.[221] Two trials had adequate allocation concealment.[214,215] The allocation concealment was unclear for the remainder of the studies. Of the 12 trials, five scored two or less on the Jadad scale,[212,213,216,217,220] and seven scored three or more.[26,214,215,218,219,221,222] Details appear in Appendix 3, Tables A12 and A13.

Few patients withdrew from the studies in either treatment arm. Patients who withdrew because of issues regarding surgery (for example, they did not require the surgery or they required a different type of surgery that was excluded from the study protocol) were subtracted from the total sample. Their withdrawals did not affect the possibility of using intention-to-treat analyses, even if the patients had been randomized before their withdrawal. These "inoperable" patients are accounted for in Appendix 4, Table A12. Appendix 4, Table A14 shows the other withdrawals.

In a quasi-randomized trial, Lowy et al.[231] used an inappropriate method of randomization (based on the medical record number). Therefore, this trial was excluded from the efficacy analysis. The data on harms, however, were included in this review.[231] Three non-randomized trials were excluded from our systematic review because they did not provide harms data.[137,139,140]

b) Data analysis and synthesis

The 12 RCTs were pooled, when heterogeneity allowed, for one continuous outcome (length of stay in hospital) and for eight dichotomous outcomes (abscess, bleeding, fluid collection, infection, pancreatic fistula, pancreatitis, death, and overall complications). Three outcomes of interest (quality of life, survival time, and length of stay in an intensive care unit) were not reported in the studies.

All trials compared OCT-SA with placebo or no treatment. Not all the trials were included in the meta-analysis because of incomplete reporting. Efforts were made to ask each author for missing data, which were added when data were provided. For continuous data, trials were pooled if they reported standard deviations or enough data to enable a standard deviation to be calculated.

Length of stay in hospital

Four trials reported enough information to enable the pooling of the number of days spent in hospital after pancreatic surgery.[26,212,215,218] The results were not statistically different for OCT-SA compared with placebo or no treatment [WMD 0.82 (95% CI: −0.58, 2.22) I^2=0%] (Appendix 3, Figure A18).

The length of stay was reported in three other studies. The data were incomplete or could not be used in the meta-analysis (Table 17). One[216] small study (34 patients) reported a significant difference in favour of OCT-SA.

Table 17: Length of hospital stay in studies excluded from meta-analysis			
Study	**Number of Patients**	**Length of Stay (Days)**	
		Treatment	**Control**
Briceño Delgado, 1998[216]	34	Mean 13 (range 10 to 17)	26 (10 to 90), SS
Büchler, 1992[222]	246	Mean 22.1 ± 1.5 (SD or SE not indicated)	26.2 ± 1.9
Suc, 2004[214]	230	Median 17 (range 7 to 130)	19 (6 to 109), NS

NS=not significant; SD=standard deviation; SE=standard error; SS=statistically significant

Abscess
Seven trials reported on the occurrence of post-surgical abscesses.[26,215,216,218,219,221,222] Based on a fixed-effects model, there was no overall effect of OCT-SA on the rate of abscesses [RR=0.95 (95% CI: 0.59, 1.54); I^2=1.1%] (Appendix 3, Figure A19).

Bleeding
The results of the eight trials[26,212-214,216,218,219,222] that reported on bleeding were pooled using a fixed-effects model. No overall effect was found [RR=1.19 (95%CI: 0.80, 1.77); I^2=0%]. None of the eight trials found that OCT-SA significantly affected the bleeding after pancreatic surgery (Appendix 3, Figure A20).

Fluid collection
A fixed-effects model was used to pool data from the eight trials[26,214,216-220,222] reporting the incidence of fluid collection. A significant overall effect was found in favour of OCT-SA [fewer patients had intra-abdominal fluid if treated with OCT-SA, RR=0.57 (95% CI: 0.40, 0.83); I^2=0%] (Appendix 3, Figure A21).

Infection
A random-effects model was used to pool the results of seven trials[26,215-217,219,220,222] that reported on infection rates (including sepsis and wound infection) after pancreatic surgery. The overall effect was non-significant [RR=0.72 (95% CI: 0.37, 1.41); I^2=35.9%] indicating that OCT-SA had no impact on infection rates compared with placebo or no treatment (Appendix 3, Figure A22).

Pancreatic fistula
A random-effects model was used to pool the results of the nine trials[26,212-216,218,219,222] that reported on patients acquiring pancreatic fistula after surgery. The overall effect was statistically significant in favour of OCT-SA (fewer patients on OCT-SA developed a fistula) [RR=0.61 (95% CI: 0.44, 0.84); I^2=34.7%] (Appendix 3, Figure A23).

Pancreatitis
A fixed-effects model was used to pool nine trials[26,213-219,222] that reported the pancreatitis rate in patients after surgery. The overall RR was not statistically significant [RR=0.60 (95% CI: 0.31, 1.14); I^2=12.4%] (Appendix 3, Figure A24).

Death
A fixed-effects model was used to pool the data from 12 RCTs. No statistically significant difference was detected between groups on the number of deaths [RR=1.10 (0.69, 1.75); I^2=0%] (Appendix 3, Figure A25).

Overall complication rate
Data from ten trials[26,212,214-219,221,222] reporting the overall complication rates were pooled using a random-effects model. The results indicated that patients taking OCT-SA experienced significantly fewer complications after pancreatic surgery, when compared with those taking placebo or those on no treatment [RR=0.67 (95% CI: 0.53, 0.84); I^2=43.6%] (Appendix 3, Figure A26).

Table 18 summarizes the results of the meta-analysis.

Subgroup and Sensitivity Analyses
The three outcomes that showed statistically significant results favouring OCT-SA (fluid collection, pancreatic fistula, and overall complication rates) were re-analyzed in the subgroup and sensitivity analyses. Subgroup analyses were not conducted for the other outcomes because the results were non-significant.

Dose: In nine of the 12 unique trials,[26,212-214,216-219,222] patients received OCT-SA 100 μg three times daily. In another trial,[220] patients received 100 μg twice daily. Patients in two trials received a higher dose.[215,221] In one of these trials,[215] OCT-SA 250 μg was administered three times daily. In the other trial,[221] OCT-SA was titrated from 50 μg to 150 μg three times daily, over three days. Analyses for fluid collection, pancreatic fistula, and complication rates were re-done to account for the different dosages. For the three outcomes, analyzing the trials according to dosage did not affect the results (data not shown).

Study quality: The sensitivity analyses were repeated for trials scoring three or more on the Jadad scale (higher quality) and those that scored less than three. For the three outcomes (fluid collection, pancreatic fistula, and complication rates), the pooled results were statistically significant in the higher quality trials, but not in the trials that scored less than three on the Jadad scale (data not shown).

Allocation concealment was adequate in two trials[214,215] and unclear in the remainder of the trials. The trials with adequate concealment did not show statistically significant results in pancreatic fistula, fluid collection, and overall complication rate (data not shown).

Optimal length of therapy
The duration of therapy ranged from five to 10 days for 11 trials. In one trial,[221] the mean treatment duration was 20 to 25 days. Of the 12 trials, one had a treatment duration of five days[217] and seven trials had a seven day treatment duration.[212,213,215,216,218,219,222] The remaining four trials had a treatment duration greater than seven days. Individual RCTs that showed statistically significant results favouring OCT-SA were from studies with a treatment duration of seven days or longer.

No conclusions can be drawn about the optimal length of therapy. RCTs that compare treatment durations of less than seven days to those of more than seven days are needed to determine the optimal length of therapy.

Table 18: Overall event data for OCT-SA versus placebo or no treatment					
Outcome (Number of Studies)	**Event Rate**		**RR (95% CI)**	**ARD (95% CI)**	**NNT (95% CI)‡**
	OCT-SA	**Control**			
Abscess* (7)	30/610 (4.9%)	32/619 (5.2%)	0.95 (0.59, 1.54)	0% (−3, 2)	NE
Bleeding* (8)	50/694 (7.2%)	40/678 (5.9%)	1.19 (0.80, 1.77)	1.0% (−1, 4)	NE
Fluid collection* (8)	41/641 (6.4%)	69/628 (11.0%)	0.57 (0.40, 0.83)	−5% (−8, −2)	22 (16, 54)
Infection† (7)	25/512 (4.9%)	36/520 (6.9%)	0.72 (0.37, 1.41)	−2% (−6, 1)	NE
Pancreatic fistula† (9)	94/798 (11.8%)	158/785 (20.1%)	0.61 (0.44, 0.84).	−7% (−13, −1)	13 (9, 32)
Pancreatitis* (9)	12/752 (1.6%)	21/743 (2.8%)	0.60 (0.31, 1.14)	−1% (−3, 0)	NE
Death* (12)	34/831 (4.1%)	29/815 (3.6%)	1.10 (0.69, 1.75)	0% (−2, 2)	NE
Overall complication rate† (10)	191/798 (23.9%)	277/783 (35.4%)	0.67 (0.53, 0.84)	−11% (−18, −5)	9 (7, 18)

ARD= absolute risk difference; CI=confidence interval; NE=not estimable; NNT=number needed to treat; OCT-SA=octreotide short-acting; RR=relative risk
* Fixed effects model; †Random effects model;
‡ NNT calculated based on RR

Harms data

Few adverse events were reported in the 12 RCTs. The most frequently reported adverse events included pain at the injection site and gastrointestinal problems. Because of the low number of adverse events, the statistical significance could not be determined and a narrative synthesis was conducted (Appendix 4, Table A15).

Nine trials[213-216,218,219,221,222,231] reported withdrawals due to adverse events. For OCT-SA patients, the number of dropouts ranged from zero to two. For placebo patients, six trials[213-215,218,221,222] reported dropouts of zero and one. The adverse events that caused patients to abandon the trial included febrile rash (one patient taking OCT-SA), hot flashes (two patients taking OCT-SA), facial flushing (one patient taking OCT-SA), and inflammatory reaction at the injection site (one patient taking placebo).

Four trials[26,216,221,222] reported that "several" to 31 OCT-SA patients experienced pain at the injection site. Each of two trials[26,222] reported that 25 patients taking placebo also experienced this outcome.

Each of four trials[26,218,219,221] reported adverse events related to the gastrointestinal tract in one to four patients taking OCT-SA. Two trials[26,218] reported that four and eight patients on placebo experienced gastrointestinal tract-related adverse events.

Other infrequent adverse events that were reported in the octreotide groups were infection at the injection site, dysopia, rash, and biliary sludge. For the placebo groups, adverse events were

disturbance of coagulation, hyperglycemia, and prolonged copious drain output. Two patients experienced itching and temporary migrant exanthema, but the groups to which they belonged were unspecified.

Harms data were collected in one quasi-randomized trial.[231] This open-label trial randomized 120 patients to receive OCT-SA (57 patients) or no treatment (53 patients) based on the medical record number. Ten patients were excluded from the analysis because of protocol violations. In the treated group, six (11%) patients had hospital stays exceeding 21 days because of poor gastric emptying or intolerance to enteral feeding. Four patients in the control group had similar adverse events. The study reported that the difference was non-significant.

4.2.6 Bowel obstruction

a) Study characteristics

Two RCTs and no CCTs met the inclusion criteria for bowel obstruction.[232,233] One additional study was excluded because of an improper method of randomization.[118] It reported no data on adverse events and thus was excluded from the safety analysis.

The RCTs compared OCT-SA with hyoscine butylbromide in a total of 86 cancer patients with inoperable bowel obstruction. In the Mercadante et al. study,[232] patients were treated for three days. The total daily doses of OCT-SA and hyoscine butylbromide were 300 µg and 60 mg, respectively. In the Mystakidou et al.[233] study, patients were treated until death. They received OCT-SA 600 µg to 800 µg daily or hyoscine butylbromide 60 mg to 80 mg daily as a subcutaneous infusion. In both studies, patients received analgesics and other medications for symptom control.

One study was open label,[232] the other was double-blind.[233] Both trials had a Jadad score of two with unclear allocation concealment.

In the Mercadante et al.[232] trial, there were incomplete data for three patients, who were removed from the analysis. In the Mystakidou et al.[233] trial, 15 patients were withdrawn on day six because of a lack of response. Neither study conducted an intention-to-treat analysis.

The trial characteristics appear in Appendix 4, Table A16.

b) Data analysis and synthesis

The results for seven outcomes that were reported on day three of the trials appear in Appendix 4, Table A17. Colicky pain, anorexia, and dry mouth were reported in one study. A meta-analysis of the data on fatigue and drowsiness was not possible because of differences in how the outcomes were measured.

For the continuous outcomes, the endpoint data on day three were pooled. Significant heterogeneity was detected in a meta-analysis using the longest follow-up data (one day before death, taken from the Mystakidou et al. study).[233] Patients who failed to respond to treatment at day six were excluded from the study. Therefore, the patient groups were no longer comparable between the two studies.

Death
All patients in these two studies had malignant bowel obstructions. In one study, all patients died.[233] In the Mercadante et al.[232] study, the outcome of four patients was unknown. All others died.

Symptom control
Vomiting: Both studies reported vomiting severity as the mean number of events per day. Patients who were treated with OCT-SA had fewer vomiting events than those treated with hyoscine butylbromide [WMD −1.13 (95% CI: −1.73, −0.52); I2=0%] (Appendix 3, Figure A27).

Nausea: Mercadante et al.[232] measured nausea severity using a Likert scale (0=none, 1=slight, 2=moderate, 3=severe). Mystakidou et al.[233] measured the severity and duration of nausea [intensity score (1=mild, 2=average, 3=severe) multiplied by duration (hours per day)]. Because of these differences, the data were pooled using the SMD.[76] Patients who were treated with OCT-SA experienced significantly less nausea than those treated with hyoscine butylbromide [SMD −0.73 (95% CI −1.18, −0.28); I2=14.6%] (Appendix 3, Figure A28).

Pain: Mercadante et al.[232] measured pain severity using a Likert scale. Mystakidou et al.[233] used a visual analogue scale (0-10 Scott-Huskisson scale). No statistically significant effect on pain was detected with OCT-SA compared with hyoscine butylbromide [SMD −0.36 (95% CI −0.80, 0.07); I2=0%] (Appendix 3, FigureA29).

Other symptoms: No statistically significant differences were detected for anorexia, fatigue, colicky pain, drowsiness, and dry mouth when OCT-SA was compared to hyoscine butylbromide on day three of treatment (Table 19).[232,233]

Table 19: Other symptoms of bowel obstruction

Study	Outcome	OCT-SA	Hyoscine B.	
		n/N*	n/N*	RR (95% CI)
Mystakidou, 2002[233]	Anorexia	15/34	23/34	0.65 (0.42, 1.02)
	Fatigue	10/34	17/34	0.59 (0.32, 1.09)
		Mean±SD†	Mean±SD†	WMD (95% CI)
Mercadante, 2000[232]	Drowsiness	2.0 ± 0.9	1.6 ± 1.2	0.4 (−0.73, 1.53)
	Dry mouth	1.7 ± 0.9	1.6 ± 1.2	0.1 (−1.03, 1.23)
	Pain (colicky)	0.4 ± 0.9	0.2 ± 0.5	0.2 (−0.51, 0.91)

CI=confidence interval; Hyoscine B.=hyoscine butylbromide; n=events; N=sample at follow-up; OCT-SA=octreotide short-acting; RR=relative risk; SD=standard deviation; WMD=weighted mean difference
* number of patients reporting symptom severity as major
† mean symptom score as measured by Likert scale (0=none, 3=severe)

Other outcomes of interest
Outcomes such as quality of life, length of hospital stay, and need for nasogastric tube insertion were not measured in either study.

Optimal length of therapy
In one RCT, patients were treated for three days.[232] In the second,[233] only those patients who had responded to treatment by day six continued with therapy. With these limited data, it is not possible to draw conclusions about the optimal length of therapy.

Harms data
Adverse events were reported in one study.[233] Three patients who were treated with hyoscine butlybromide and four patients who were treated with OCT-SA experienced a minor skin reaction.

4.2.7 Diarrhea related to chemotherapy, HIV-AIDS, Crohn's disease, or ileostomy

a) Study characteristics
Thirteen reports assessed the effects of octreotide in patients with diarrhea related to chemotherapy, HIV-AIDS Crohn's disease, or ileostomy. Two RCTs (four papers) studied patients with HIV-AIDS-related diarrhea.[234-237] Seven articles (five RCTs) reported on patients with diarrhea related to chemotherapy.[31,32,238-242]

Chemotherapy-related diarrhea
Of the five studies on patients undergoing chemotherapy, four compared OCT-SA with loperamide[31,238-240] and one compared OCT-SA with a placebo.[32] All studies were parallel RCTs. Three scored three or more on the Jadad scale,[31,32,239] which indicates a higher methodological quality. The allocation concealment was unclear in all five studies. One study reported double-blinding as a study design.[32] The sample size ranged between 16 and 43 patients, and the study duration ranged between one day and four days. No dropouts were reported in four studies. One study[239] reported that five patients did not receive treatment during the study, but their outcomes were included in the intention-to-treat analysis.

HIV-AIDS-related diarrhea
Two parallel design RCTs enrolled 129[236] and 20[234] patients with HIV-AIDS. One trial compared OCT-SA with placebo[236] and the other compared OCT-SA with placebo plus antidiarrheal agents.[234] One RCT reported having a double-blind design and scored five[236] on the Jadad scale. The other was open label and scored two.[234] We could not determine if either study had adequate allocation concealment. The treatment duration was 21 days[236] and 10 days.[234] In the Simon et al. study, 21 patients withdrew or were excluded from the analysis (Appendix 4, Table A20).[236] The other study did not have any withdrawals.[234]

Two additional studies with a cross-over design could not be analyzed. One study included patients with HIV-AIDS.[119] The other study included patients with ileostomy.[57] These studies did not report results before the cross over and were excluded. An attempt was made to contact the authors for pre cross-over data, but no data were provided. No data were extracted from these studies.

No reports assessed the efficacy of octreotide for patients with refractory diarrhea due to Crohn's disease, and no CCTs met the inclusion criteria for any of the refractory diarrhea indications.

Study characteristics, withdrawals, outcomes, and harms are summarized in Appendix 4, Tables A18 and A21.

b) Data analysis and synthesis

Death

Chemotherapy-related diarrhea: There were no deaths reported in the Cascinu et al.[32] trial, which compared OCT-SA with placebo.

None of the four trials[31,238-240] that compared OCT-SA with loperamide reported on death as an outcome. All patients were accounted for at the end of the studies and were assumed to have survived.

HIV-AIDS-related diarrhea: In one trial[236] that compared OCT-SA with placebo, one patient out of 76 who were treated with OCT-SA died. No reason was provided.

No deaths were reported in Garcia Compean *et al.*'s[234] trial.

Diarrhea control

For this analysis, patients showing a complete or major response to treatment were combined.

Chemotherapy-related diarrhea:

OCT-SA versus placebo: The Cascinu et al. (1994)[32] study reported that OCT-SA-treated patients were statistically significantly more likely to experience a complete or major response than patients who received placebo [RR=3.83 (95% CI 1.78, 8.21)] (Table 20).

OCT-SA versus loperamide: The results of the four trials[31,238-240] that included chemotherapy patients who were treated with OCT-SA or loperamide could not be pooled because of high heterogeneity (I^2=89.0%) (Table 20). The sample sizes ranged between 16 and 41 patients.

Two studies[31,240] found that OCT-SA patients experienced a statistically significantly greater chance of complete or major response to treatment [RR=6.03 (95% CI 2.11, 17.28); RR= 3.40 (95% CI 1.17, 9.87), respectively]. One study[239] reported that patients in the loperamide group were significantly more likely to experience complete or major response [RR= 0.53 (95% CI 0.32, 0.88)]. One study[238] did not report statistically significant results [RR=1.27 (0.96, 1.66)]. The event rates and relative risks appear in Table 20.

Table 20: Diarrhea control in chemotherapy patients			
Study	**Number of Patients with Complete or Major Response**		**RR (95% CI)**
	OCT-SA	**Control**	
OCT-SA versus placebo			
Cascinu, 1994[32]	22/23	5/20	3.83 (1.78, 8.21)
OCT-SA versus loperamide			
Cascinu 1993[31]	19/21	3/20	6.03 (2.11, 17.28)
Gebbia, 1993[238]	19/20	15/20	1.27 (0.96, 1.66)
Geller 1995[239]	10/22	12/14	0.53 (0.32, 0.88)
Nikou 1994[240]	8/8	2/8	3.40 (1.17, 9.87)

CI=confidence interval; OCT-SA=octreotide short-acting; RR=relative risk

HIV-AIDS-related diarrhea:

OCT-SA versus placebo: Simon et al. compared OCT-SA with placebo in patients with diarrhea related to HIV-AIDS.[236] No significant difference was detected between groups. [RR=1.28 (95% CI 0.82, 1.99)] (Table 21). Best- and worst-case analyses confirm these findings (data not shown).

Table 21: Diarrhea control in patients with HIV-AIDS			
Study	**Number of Patients with Complete or Major Response**		**RR (95% CI)**
	OCT-SA	**Control**	
OCT-SA versus placebo			
Simon, 1995[236]	34/74*	18/50*	1.28 (0.82, 1.99)
OCT-SA versus placebo with anti-diarrheal agents			
Garcia Compean, 1994[234]	2/10	0/10	NE

CI=confidence interval; NE=not estimable; OCT-SA=octreotide short-acting; RR=relative risk
*Results are based on available case analysis

OCT-SA versus placebo with anti-diarrheal agents: Garcia Compean *et al*. studied patients with HIV-AIDS who were randomly assigned to receive OCT-SA or placebo plus loperamide and diphenoxylate.[234] Two patients who received OCT-SA had a complete resolution of symptoms, whereas none in the control group did (Table 21).

Other outcomes

Other outcomes of interest, such as health-related quality of life, length of stay in hospital, return to work, hospital admittance, and need for intravenous fluid therapy were not reported in any of the included studies.

Optimal length of therapy

The treatment duration ranged between one day and 21 days. The three studies that reported statistically significant results in favour of OCT-SA did not surpass three days of therapy. The studies of longer duration did not find statistically significant results in favour of or against OCT-SA. As a result, longer treatment may not increase the patient's success with OCT-SA. Because of the limited number of trials in this review, a conclusion cannot be drawn about the optimal length of therapy for refractory diarrhea.

Harms data
The reported adverse events for refractory diarrhea appear in Appendix 4, Table A21.

Chemotherapy-related diarrhea:
OCT-SA versus placebo: The authors of one study that compared OCT-SA with placebo[32] reported that there were no differences in the incidence or severity of vomiting and nausea, that octreotide was well-tolerated by all patients, and that there were no treatment-related side effects. No other data were provided.

OCT-SA versus loperamide: Three trials that compared OCT-SA with loperamide reported data on adverse events,[31,238,239]and one[240] did not. One trial[31] reported that there were no adverse events in either treatment arm. Gebbia et al.[238] reported that 15% of the OCT-SA patients experienced adverse events related to the gastrointestinal tract and 15% experienced pain at the injection site. The study failed to report adverse events for the placebo arm. The third trial[239] reported that three patients who were treated with OCT-SA experienced minor adverse events. One had abdominal cramping and flatulence, and two had mildly elevated bilirubin. No adverse events were reported for patients in the placebo arm. The authors reported no major adverse events in either treatment arm.

HIV-AIDS-related diarrhea:
OCT-SA versus placebo: In the trial that compared OCT-SA with placebo,[236]129 patients were included in the safety analysis, which showed that 51% of patients taking OCT-SA (39/76) experienced adverse events compared with 38% in the placebo group (20/53) (p=0.01). Three patients taking OCT-SA and four patients taking placebo dropped out of the trial because of adverse events. The most commonly reported adverse event was abdominal discomfort (OCT-SA:13 events, placebo:1 event, p<0.01). There was no statistically significant difference between treatment groups for the other adverse events that occurred.

OCT-SA versus placebo with anti-diarrheal agents: One trial of patients with HIV-AIDS[234] compared OCT-SA versus placebo with loperamide and diphenoxylate. There were 20 patients in the safety analysis. Eight OCT-SA and three control group patients experienced adverse events (p<0.05). The most commonly reported adverse event was related to the gastrointestinal tract. Two patients in the OCT-SA group and one in the control group reported abdominal pain (p value not significant). Two patients in each group reported nausea and vomiting (not significant). Five patients taking OCT-SA reported pain at the injection site compared with none in the placebo group (p=0.05), and one patient taking OCT-SA reported paresthesia compared with none in the placebo group.

4.2.8 Hepatocellular carcinoma

a) Study characteristics
Eleven reports on seven RCTs compared octreotide with another treatment for patients with hepatocellular carcinoma. Of these, two studies compared OCT-LA with placebo[243,244] and one study compared OCT-LA with no treatment.[245] Two studies compared OCT-SA with no treatment,[246,247] one study compared OCT-LA and tamoxifen with tamoxifen alone,[248] and one study compared OCT-SA followed by OCT-LA with placebo.[249]

We identified one additional RCT that could not be included in the analysis. It randomized patients to be in three groups: OCT-LA, rofecoxib, and OCT-LA plus rofecoxib. At the interim analysis, the rofecoxib group was stopped and no outcomes for this group were reported. As a result, the study was excluded from our analysis because of an improper comparator group.[130,131]

All the included studies were randomized and open label, except two that were double-blinded.[243,249] The sample size varied from 13 to 266 participants. The study duration ranged from six weeks to three years. One study did not report the treatment duration.[244] Five trials obtained a Jadad score of three or greater[243,245,246,248,249] and the other two received a score of one, indicating poorer quality. The allocation concealment was adequate for one study.[243]

One study had no drop-outs or withdrawals.[247] It had a sample size of 13. Although we included this study in our review, the results must be interpreted with caution. Four studies reported that between one and ten patients had not completed the study[243,246,248,249] and all four used intention-to-treat analysis (Appendix 4, Table A24). The remainder of the studies did not report on withdrawals during the study period of interest, although one study reported using intention-to-treat.[245]

The trial characteristics and outcomes appear in Appendix 4, Tables A22 and A23.
Two non-randomized trials reported data on harms.[250,251] In both trials, patients were assigned to treatment or control without randomization or blinding. In one study, the allocation of patients to groups was based on the ability to afford treatment.[251] This would put into question the comparability of patients.

b) Data analysis and synthesis

A meta-analysis of the data and comparisons between studies were not possible because the treatment duration and length of follow-up were too different; or outcome data, such as variance or end-point values, were not reported. Attempts to contact the authors to obtain missing data were unsuccessful. Sub-group analyses were not possible because of the small number of trials.

Death

Five studies reported the number of deaths that occurred during the trial.

OCT-LA versus placebo or no treatment: Two studies reported the number of deaths.[243,245] The results were not pooled because the follow-up times were too different (26 weeks versus 30 months). Despite this dissimilarity in study design, the results were similar. Table 22 shows that the risk of dying was the same, whether the patient received OCT-LA, placebo, or no treatment.

Table 22: Death				
Study	Timing of End-point	Number of Deaths		RR (95% CI)
		OCT-LA	Control	
OCT-LA versus placebo or no treatment				
Yuen, 2002[245]	26 weeks	32/35	33/35	1.0 (0.9, 1.1)
Becker, 2007[243]	30 months	54/60	52/59	1.0 (0.9, 1.2)
OCT-LA with tamoxifen versus tamoxifen				
Verset, 2007[248]	Median 3 months	55/56	52/53	1.0 (0.95, 1.05)
OCT-SA versus no treatment				
Kouroumalis, 1998[246]	6 months	7/28	19/30	0.4 (0.2, 0.8)
	12 months	12/28	26/30	0.5 (0.3, 0.8)

CI=confidence interval; OCT-LA=octreotide long-acting; OCT-SA=octreotide short-acting; RR=relative risk

OCT-LA with tamoxifen versus tamoxifen: Out of 109 patients in the Verset et al study,[248] all but two had died at the last follow-up (median three months, range 0.1 to 31 months). There was no significant difference between groups (Table 22).

OCT-SA versus no treatment: One study[246] reported that at six and 12 months, the OCT-SA group had significantly fewer deaths than the group not receiving treatment (Table 22).

OCT-SA and OCT-LA versus placebo: In the Dimitroulopoulos et al. study, all patients died at the end of the follow-up period, except for one in the octreotide group who died four weeks later.[249]

Survival

Six studies measured survival (Table 23). It was not possible to compute the differences between treatment and control groups for all reported values because of missing variance data.

Two studies showed that octreotide was significantly better than no treatment or placebo at increasing survival time.[246,249] Two other studies showed no statistical difference between treated and control patients.[245,248] The results of two studies could not be interpreted because of missing variance data.[243,244]

Health-related quality of life

Six of the seven studies measured the impact of octreotide on health-related quality of life using indicators such as appetite and body weight.

OCT-LA versus placebo or no treatment: To measure quality of life, one study used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[243] and one study used the Karnofsky Performance Status.[245] Neither study showed an improvement in quality of life compared with baseline.

Table 23: Survival time					
Study	Treatment (Sample Size)	Control (Sample Size)	Median Survival in Months*		Survival Time Difference (95% CI)
			Treatment	Control	
OCT-LA versus placebo					
Barbare, 2005[244]	OCT-LA (134)	Placebo (132)	6.5 (range 4.7 to 7.0)	7.3 (range 5.5 to 8.6)	−0.8
Becker, 2007[243]	OCT-LA (60)	Placebo (59)	4.7	5.3	−0.6
OCT-LA versus no treatment					
Yuen, 2002[245]	OCT-LA (35)	No treatment (35)	1.93	1.97	−0.04 p=NS
OCT-LA with tamoxifen versus tamoxifen					
Verset, 2007[248]	OCT-LA + tamoxifen (56)	Tamoxifen (53)	3.0 (95%CI: 1.4, 4.6)	6.0 (95% CI: 2, 10)	−3.0 p=0.609
OCT-SA versus no treatment					
Kouroumalis, 1998[246]	OCT-SA (28)	No treatment (30)	13.0±1.9 (SE)	4.0±1.1 (SE)	9 (4.7, 13.3), p=0.002
OCT-SA and OCT-LA versus placebo					
Dimitroulopoulos, 2007[249]	Octreotide (31)	Placebo (30)	12.3 (IQ range 7.0 to 18)	7.0 (IQ range 4.8 to 8.5)	5.3 (2.3, 8.3)

CI=confidence interval; IQ=interquartile range; NS=not significant; OCT-LA=octreotide long-acting; OCT-SA=octreotide short-acting; SE=standard error
*Median survival is the time at which half the subjects have died

OCT-LA with tamoxifen versus tamoxifen: Verset et al.[248] found no difference in quality of life between patients receiving OCT-LA with tamoxifen and those receiving tamoxifen only. The authors used the Karnofsky Performance Status scale.

OCT-SA versus no treatment: Two studies[246,247] measured various domains, but they did not specify the instruments that were used. We did not pool the data because the treatment follow-up was 12 weeks for one study[247] and 14 months for the other.[246] No conclusion can be made given the small sample size for one study and missing variance data for the other (Table 24).

OCT-SA and OCT-LA versus placebo: Using the EORTC QLQ-C30, Dimitroulopoulos et al.[249] showed a 21% decrease in score with octreotide and a 39% decrease with placebo at one year. Absolute values and statistical significance were not reported.

Change in tumour size and response rates

Five studies provided information on response rates (tumour regression or progression).

OCT-LA versus placebo or no treatment: Becker et al.[243] reported no tumour regression in any patient. For stable or progressive disease, there was no statistically significant difference between groups.

Table 24: Number of patients who improved in various domains of health-related quality of life			
Study	**OCT-SA**	**No Treatment**	**RR (95% CI)**
Increase in appetite			
Farooqi, 2000[247]	5/6	0/7	p<0.05
Kouroumalis, 1998[246]	24/28	0/30	NE
Increase in body weight			
Farooqi, 2000[247]	NR	NR	NE
Kouroumalis, 1998[246]	12/28	0/30	NE
Improvement in feeling of well-being			
Farooqi, 2000[247]	4/6	0/7	p<0.05
Kouroumalis, 1998[246]	15/28	0/30	NE
Decrease in pain in right hypochondrium			
Farooqi, 2000[247]	4/6	1/7	4.7 (0.7, 31.2)
Kouroumalis, 1998[246]	NR	NR	NE

CI=confidence interval; NE=not estimable; NR=not reported; RR=relative risk

Tumour progression occurred in six of 35 patients who were receiving OCT-LA and in five of 35 patients with no treatment in the Yuen et al. study [RR=1.2 (95% CI: 0.4, 3.6)].[245]

OCT-LA with tamoxifen versus tamoxifen: Patients in either group who were still alive after three months showed no significant difference in tumour progression in the Verset et al. study.[248]

OCT-SA versus no treatment: In the Farooqi et al. study,[247] there was a statistically significant difference in tumour size between patients taking OCT-SA and patients receiving no treatment at end-point [mean difference= −7.6 cm (95% CI: −9.0, −6.2)]. Additional studies with larger sample sizes are needed to support or refute this finding.
Kouroumalis et al.[246] showed that the number of patients with tumour progression was statistically less with OCT-SA (19/35) compared with no treatment (30/30) [RR=0.68 (95% CI 0.53, 0.88)].

α-fetoprotein levels
Five studies measured α-fetoprotein levels.

OCT-LA versus placebo or no treatment: One study measured baseline values only.[243] Another study[245] reported no significant difference in α-fetoprotein reduction between OCT-LA and the no treatment group.

OCT-LA with tamoxifen versus tamoxifen: One study[248] reported no significant difference in α-fetoprotein reduction between OCT-LA with tamoxifen, and tamoxifen alone.

OCT-SA versus no treatment: Patients receiving OCT-SA had a decrease in α-fetoprotein levels compared with baseline, whereas the patients without treatment showed an increase in these levels.[247] The mean difference at three months [−994 ng/mL (95% CI: −1017, −971)] was statistically significant. This study, however, had a small sample size, and no conclusions can be drawn.

OCT-SA and OCT-LA versus placebo: One study measured baseline values only.[249]

Optimal length of therapy
The study duration ranged from six weeks to three years in six studies,[243,245-249] and one study did not report the duration.[244]

We cannot comment on the optimal length of therapy for this indication.

Harms data
All but one[249] of the seven RCTs that were included in the systematic review described adverse events (Appendix 4, Table A25).

In one study, 16 of the 60 patients in the OCT-LA group developed a serious adverse event compared with 25 out of 59 patients in the placebo group. The p value was not significant.[243]

Five studies reported on diarrhea. In one study, 13 of the 60 participants in the octreotide group developed diarrhea, compared with 7 of 59 in the control group. The p value was not significant.[243] In one study, one patient had to discontinue octreotide treatment because of diarrhea. Three of 53 patients in the control group had to discontinue treatment because of adverse events (digestive complaint, flushing, and gynecomastia).[248] Another study reported no serious adverse events with octreotide, and mainly diarrhea.[130] Two studies reported that 33% (2/6) and 40% (11/28) of patients on octreotide had diarrhea.[246,247]

One study reported one case of hypoglycemia in the octreotide group.[244]

One study stated that no serious adverse events were observed during the trial.[245]
In one non-randomized trial[251] of 42 patients (six months of octreotide in 22 patients versus 20 controls), three patients discontinued octreotide because of adverse events, two of them due to diarrhea. No serious adverse events were seen in patients who continued treatment with octreotide. The treated versus control patients may not be comparable. The untreated patients were selected as controls because of their inability to pay for treatment.

Another non-randomized trial compared 20 patients on pravastatin versus 30 patients on octreotide, versus eight patients on gemcitabine, who were followed until death.[250] Two pravastatin patients developed rhabdomyolysis. Seven patients in the octreotide group had diarrhea and abdominal cramps. Three and seven patients in the gemcitabine group had leucopenia and ascites respectively.

4.2.9 Pancreatic cancer

a) Study characteristics
Four RCTs were reported in seven citations (two full reports[45,48] and three abstracts[252-256]) that met the inclusion criteria. A total of 602 patients with pancreatic cancer participated in the trials. All participants had advanced cancer and inoperable tumours.

All studies had randomized, controlled, parallel designs, two were double-blinded[252,254] and the remaining two did not report blinding.[45,48] Except for the Cascinu et al.[48] report, which was given

a Jadad score of three, the studies were of poorer quality (Jadad score of two). The allocation concealment was inadequate in the Cascinu et al. study and was unclear in the other three.

In two studies,[252,254] participants were assigned to receive 160 mg of OCT-LA or placebo. The first study enrolled participants with stage II, III, and IV pancreatic cancer[252] and the second enrolled participants with stage III and IV cancer. All patients in the Schlag et al. study also received 5-fluorouracil.[254] In both studies, only patients who received one dose of study medication were analyzed (five and three patients were withdrawn from the Maurer et al.[252] and the Schlag et al.[254] studies, respectively).

In the Cascinu et al. study,[48] participants were randomized to receive OCT-SA 600 µg daily subcutaneously or best supportive care. A total of 107 patients with gastrointestinal cancer were enrolled, 32 of whom had a primary diagnosis of pancreatic cancer. Of these 32, none withdrew from the study.

Burch et al. compared the effects of OCT-SA with that of 5-fluorouracil, or 5-fluorouracil plus leucovorin, on pancreatic tumours.[45] In the trial, 42 patients were randomized to receive OCT-SA, originally at a dosage of 200 µg subcutaneously three times daily. After 12 participants were randomized, the OCT-SA dosage increased to 500 µg three times daily for 30 patients. Two patients were withdrawn because of protocol violations (OCT-SA: 1, 5-fluorouracil: 1). Another 10 patients from the two chemotherapy groups were excluded from the analysis.[45]

Appendix 4, Table A26 shows trial characteristics. Table A27 lists the outcomes.

b) Data analysis and synthesis

For the comparison of OCT-SA versus no treatment and that of OCT-SA versus chemotherapy, there was one included citation. Thus, there were no data to pool. For the OCT-LA versus placebo comparison, there was insufficient information on the sizes of the treatment and control groups.

Death

All patients died in the Cascinu et al. trial (OCT-SA versus no treatment) and in the Burch et al. trial (OCT-SA versus 5-fluorouracil).[45,48] The other two trials did not report the number of patients who died.[252,254]

Survival

OCT-LA versus placebo: Among the total of 474 patients who were enrolled in two RCTs, 466 patients received a dose of the study medication. No significant difference in survival time was reported in either study (Table 25).[252,254]

Table 25: Survival time					
Study	Treatment (Sample Size)	Control (Sample Size)	Median Survival in Weeks		Survival Time Difference
			Treatment	Control	
OCT-LA versus placebo					
Maurer, 1998[252]	OCT-LA (93)	Placebo (92)	16.0	16.9	−0.9 p=0.744
Schlag, 1998[254]	OCT-LA	Placebo	22.6	21.6	1.0 p=0.649
	(Total 284, number of patients per group NR)				

OCT-LA=octreotide long-acting; NR=not reported

OCT-SA versus no treatment: In the Cascinu et al. study,[48] all patients died. There was a statistically significant advantage in survival for the OCT-SA group compared with the control group (p=0.001). The last patient in the control group died at 17 weeks compared with 24 weeks in the OCT-SA group (median survival eight and 16 weeks, respectively).[48]

OCT-SA versus 5-fluorouracil: Of the 84 patients who were evaluated in the Burch et al. trial, 81 patients developed progressive disease and died.[45] The remaining three died before disease progression. The difference in the overall survival between the octreotide group and the chemotherapy group was not significant (p=0.80).

Tumour response rates

OCT-LA versus placebo: No objective responses were reported in one study that compared OCT-LA with placebo.[252] In the Schlag et al. trial,[254] one complete and one partial remission were reported in the octreotide group and one partial remission was reported in the placebo group.

OCT-SA versus no treatment: No objective responses were reported in patients who were enrolled in the trial that compared OCT-SA with best supportive care.[48]

OCT-SA versus 5-fluorouracil: The time to progression (the appearance of new areas of disease, decrease of more than one level on the Eastern Cooperative Oncology Group performance scale, development of new jaundice or ascites, definite increase in areas of existing disease, or more than 25% increase in measurements of indicator lesions) was measured in the trial that compared OCT-SA with 5-fluorouracil chemotherapy regimens.[45] The median time to disease progression was 42 days for the octreotide arm and 105 days for the chemotherapy arms combined. This difference was statistically significant (p=0.01).

Optimal length of therapy

Two trials reported the duration of octreotide therapy. The mean duration was 12 weeks (range from six to 32) for all patients in the OCT-SA versus no treatment trial.[48] The treatment duration in the OCT-SA versus 5-fluorouracil trial was eight weeks.[45] No conclusion can be drawn about the optimal length of therapy.

Health-related quality of life
None of the studies measured health-related quality of life.

Harms data
The two studies that compared OCT-LA with placebo did not report specific adverse events. They stated that octreotide was safe and well-tolerated.[252,254]

The trial comparing OCT-SA with 5-fluorouracil chemotherapy regimes reported adverse events that met the National Cancer Institute Common Toxicity Criteria of three or more. Patients in the chemotherapy arms experienced more severe adverse events than those in the OCT-SA arm (statistical significance not reported). In the OCT-SA arm, the most common adverse events were nausea, vomiting, and diarrhea (Appendix 4, Table A28).[45]

Specific adverse events were reported in the trial that compared OCT-SA with no treatment.[48] This trial included patients with many types of gastrointestinal cancers, and the adverse events were not specific to those with pancreatic cancer. The number of adverse events that were reported in the control group was missing. None of the patients in the OCT-SA group discontinued therapy because of adverse events (Appendix 4, Table A28).

4.2.10 Pediatric idiopathic or persistent hyperinsulinism

No RCTs or CCTs met the inclusion criteria for pediatric hyperinsulinism.

4.2.11 Short bowel syndrome

Five RCTs compared OCT-LA with placebo[57,58,120,121] or with loperamide, codeine, or soy polysaccharide in patients with short bowel syndrome.[122] All were cross-over studies. Data analysis was not possible because the results were not provided for the first study period, before the cross-over to the other treatment arm. Attempts to contact the authors to obtain the results were unsuccessful. As a result, these studies were excluded.

5 ECONOMIC ANALYSIS

5.1 Review of Economic Studies: Methods

A protocol for the review was written a priori and followed throughout the review process.

5.1.1 Literature search strategy

We conducted a literature review to gather economic information.

Published literature was identified by searching MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE and BIOSIS Previews on Ovid (Appendix 1). Parallel searches were performed on The Cochrane Library. The Health Economic Evaluations Database (HEED) was searched for the economic literature. No language or date restrictions were placed on any of

the searches. The economic information was restricted to human subjects. All searches were updated regularly from May 2006 to the first week of February 2008.
Grey literature was identified from the websites of health technology assessment and related agencies and their associated databases. Google™ and other Internet search engines were used to search for additional web-based materials and information. These searches were supplemented by hand searching the bibliographies and abstracts of selected papers and appropriate conference proceedings and by contacting appropriate experts and agencies.

5.1.2 Selection criteria

The same criteria for the population, intervention, and comparator used in the clinical review were used in the selection of the economic articles. Health outcomes (for example, quality-adjusted life-years, life-years), costs, and incremental cost-effectiveness ratios were the primary outcomes of interest. Study designs included cost minimization analysis, cost-effectiveness analysis, cost utility analysis, cost benefit analysis, and cost comparison analysis. Economic evaluations published as abstracts or conference proceedings were included.

5.1.3 Selection method

Potentially relevant articles were selected independently by two reviewers (BD and SC). First, the reviewers applied the eligibility criteria to the search results. If the title or abstract met all the criteria, the full text was obtained. When there was uncertainty or disagreement between reviewers regarding an abstract, the full text paper was requested. In the second step, the inclusion criteria were applied to the full text papers. The selected articles satisfied all criteria. Disagreements were resolved through discussion.

5.1.4 Data extraction strategy

Data extraction forms were presented in the study protocol. The following elements were extracted from all the selected articles: authors, year of publication, country, type of economic evaluation, principal participant characteristics, intervention and comparators, perspective, time horizon, health-related economic outcome indices, relevant cost indices, incremental economic outcome indices, and relevant notes or comments.

One reviewer (BD or CP) extracted the data from the selected papers. A second reviewer (KM, CP or GM) verified data extraction. If there was inconsistency, the paper was reviewed again.

5.1.5 Strategy for assessing validity of included studies

One reviewer (BD or GM) assessed the quality of the included economic papers using the BMJ 35-question checklist.[257] Each economic article was then reviewed and discussed with another reviewer (KM or CP) to clarify its validity and quality. Disagreements were resolved through discussion.

Section 3 of the Drummond et al. checklist for assessing economic evaluations[258] was used. This enables economic reviewers to assess the study design of the efficacy or effectiveness trials. The BMJ checklist is used by authors as a reference standard to guide the conduct of economic

studies. A perfect score on the BMJ-35 checklist (35 "yes" answers) indicates a high quality analysis. A paper that fails on every item would be a low quality analysis (35 "no" or "can't tell" answers). While the sum of the "no" and "can't tell" answers indicates the extent to which issues were not dealt with, there is no cut-off point to define high or low quality studies. Instead, the reviewer subjectively assesses the quality of the analysis by evaluating the reasons given for not complying with a guideline.

5.1.6 Data analysis methods

The low number of health economic studies that met the inclusion criteria only permitted a narrative synthesis.

5.2 Review of Economic Studies: Results

Of 671 articles, 576 papers were excluded because they did not meet our selection criteria (Appendix 3, Figure A30). The remaining 95 papers were assessed with three unpublished reports that we obtained through personal communication. Of the 98 reports that were submitted for further evaluation, nine were included. Articles were excluded because of inappropriate study design (62), inappropriate population (14), inappropriate comparators and interventions (11), and language issues (2) (Appendix 2). The translation of articles written in a foreign language was unnecessary.

Eight of the nine included reports (Appendix 4, Tables A29 and A30) were unique economic evaluations of acromegaly (3), esophageal variceal bleeding (1), GEPNET (2), and prevention of complications after pancreatic surgery (2) (L. Wilson, University of California, San Francisco: unpublished data, 1999; Novartis Pharmaceuticals Canada Inc, Dorval: unpublished data, January 1999 and May 1999).[24,25,83,259-261] One report was an abstract[25] of a study that was available in full text.[24]

No economic evaluations were retrieved for the unapproved indications.

Most of the studies were cost-effectiveness or cost-efficacy analyses that used a variety of measures of cost per unit of health effect, such as cost per patient achieving a target growth hormone level, cost per bleed prevented, or cost per year of remission gained (Novartis Pharmaceuticals Canada Inc, Dorval: unpublished data, January 1999; L. Wilson, University of California, San Francisco: unpublished data, 1999).[24,83,260,261] One study conducted a cost-utility analysis.[83] There was one cost-minimization and one cost-benefit analysis (Novartis Pharmaceuticals Canada Inc, Dorval: unpublished data, May 1999).[259] The perspective of the analyses was mainly the health care system or drug plan payer. None of the studies took the societal perspective. The time horizon was not reported in three studies (L. Wilson, University of California, San Francisco: unpublished data, 1999).[83,261] One study took a lifetime perspective.[260] The remaining studies used a short-term time horizon (one to 19 months).

Four studies were Canadian, three were from the US, and one was from the UK. Six studies received all or part of their funding from the pharmaceutical industry, including three unpublished reports supplied by Novartis Pharmaceuticals Canada Inc.[24,260,261] One study

received funding from a non-industry source,[83] and one study did not report the source of funding.[259]

The results of the economic analyses appear in Appendix 4, Table A30. The quality assessment of the studies appears in Appendix 4, Table A31.

5.2.1 Acromegaly

Novartis provided an unpublished report that contained two analyses: a Canadian cost-efficacy analysis (Novartis Pharmaceuticals Canada Inc, Dorval: unpublished data, January 1999) and a cost-effectiveness analysis (L. Wilson, University of California, San Francisco: unpublished data, 1999). Both evaluations compared OCT-LA to OCT-SA. Observational studies were used for efficacy data and the doses of OCT-SA. The doses of OCT-LA that were used in the models were assumed. The achievement of a growth hormone level of less than 2 μg/L was used as the marker for treatment success. Limited or no sensitivity analyses were conducted.

The cost-efficacy analysis reported that OCT-LA was more costly and more effective than OCT-SA. The incremental cost-efficacy ratio over the 19 months was C$43,031 (Novartis Pharmaceuticals Canada Inc, Dorval: unpublished data, January 1999). The cost-effectiveness study was missing the appendix that described the model and data parameters. Thus, it was not possible to assess the validity of the study. An incremental annual cost of C$3,000 to C$7,000 per additional patient being "cured" was reported for OCT-LA versus OCT-SA, depending on whether patients had macroadenomas or microadenomas (L. Wilson, University of California, San Francisco: unpublished data, 1999).

A cost-effectiveness analysis conducted in the UK compared somatostatin analogues (OCT-LA and lanreotide) with bromocriptine, cabergoline and with no treatment.[83] A decision analytic model was used to translate treatment effects (based on growth hormone levels) to life-year saved and quality-adjusted life-years. Efficacy parameters were based on observational studies and health-related quality of life values were assumed. The incremental cost per life-year saved was UK£64.5 million for somatostatin analogues compared to cabergoline and UK£18.6 million compared to bromocriptine. The incremental cost per quality-adjusted life-year was UK£531,000 and UK£126,000 for cabergoline and bromocriptine, respectively.[83]

5.2.2 Esophageal variceal bleeding

Arcona and Zacker produced a cost-effectiveness model to evaluate the economic impact of propranolol and OCT-LA combined with esophageal ligation for the primary and secondary prevention of esophageal variceal bleeding. The study reported that treatment was cost saving or had a cost per bleed prevented of up to US$5,836. The abstract provided insufficient details to assess the validity of the study and its relevance to our report. No conclusions could be drawn from the available data.[261]

5.2.3 GEPNET

A cost-effectiveness analysis was performed in the US in patients with carcinoid syndrome or vasoactive intestinal polypeptide-secreting tumour (VIPomas).[260] The study used a Markov

model to evaluate OCT-SA versus usual care. The study was limited by the use of an expert panel to estimate health state values and quantities of resources. The study reported that OCT-SA was cost saving for VIPomas and cost-effective for treating carcinoid tumours at US$752 per additional year of life.

Novartis provided an unpublished cost-minimization study comparing OCT-SA with OCT-LA for the treatment of carcinoid tumours and VIPomas. The clinical efficacy of OCT-SA and OCT-LA was stated to be equivalent based on the results of one RCT of 24 weeks' duration. The authors reported that the monthly cost of OCT-SA may range between C$270 and C$4,077, depending on the required treatment. Monthly costs of OCT-LA range from C$1,100 to $1,840. OCT-LA was associated with fewer injections per month (Novartis Pharmaceuticals Canada Inc, Dorval: unpublished data, May 1999).

5.2.4 Prevention of complications after pancreatic surgery

In 1999, Rosenberg et al. published a Canadian cost-effectiveness analysis that compared OCT-SA to placebo for the prevention of complications after pancreatic resection.[24] The complication rates were taken from a meta-analysis of RCTs. Model 1 was based on Canadian per diem costs. On average, the model predicted that OCT-SA saved C$853 per patient. Model 2 used the costs of hospitalization for patients who were undergoing pancreatic surgery. The incremental outcome was a saving of C$1,642 per patient. In both models, 16 additional patients out of a theoretical cohort of 100 avoided complications when they were treated with OCT-SA. Both models were robust to one-way and two-way sensitivity analyses. This good quality analysis showed that OCT-SA, when compared with placebo, was cost-saving in preventing complications after pancreatic surgery.[24,25]

In the US, Vanounou et al.[259] conducted a cost-benefit analysis that compared OCT-SA to usual care for the prevention of fistulas after pancreaticoduodenectomy. In a typical cost-benefit analysis, the change in clinical outcomes is expressed in monetary terms and compared with the dollar value of the change in costs. In this analysis, there was no attempt to put a monetary value on clinical outcomes. The analysis only involved the cost, so it cannot be a true cost-benefit analysis.

Cost data were collected from a retrospective observational study. Although the incidence of fistulas was not significantly different between the groups, the cost of care was higher in the patients who received usual care. Subgroup analyses were also conducted according to the patient's risk of fistulas. These results, however, must be interpreted with caution because of the small number of patients who developed fistulas. The authors reported that the use of OCT-SA resulted in cost savings of US$4,249 per patient, with a cost benefit ratio of 5.8. OCT-SA showed the most clinical value and cost benefit for the subgroup of patients who were at a high risk of developing fistulas.[259]

6 HEALTH SERVICES IMPACT

6.1 Population Impact

Prevalence data for the approved and unapproved indications in 2006 to 2010 for all Canadian provinces and territories were based on the rates and sources listed in Appendix 4, Table A32 and Statistics Canada's population projections by province.[262]

Table 26 provides estimates of the prevalence of each condition in Canada. We were unable to find prevalence data for ileostomy-related diarrhea. The prevention of complications after pancreatic surgery was determined by estimating the number of patients who were undergoing pancreatic surgery. We assumed that all patients who had surgery would be treated with octreotide. No data were found on the proportion of patients who were surgically treated for pancreatitis. Therefore, the number of patients who were undergoing pancreatic surgery was based on that for pancreatic cancer only.

The indication-specific prevalence rates were applied to the Canadian population. The results show that there are fewer than 8,500 potential beneficiaries for the approved indications in Canada (Table 26). The number of potential beneficiaries was greater in groups that required octreotide for unapproved indications.

We included additional prevalence data in Appendix 4, Tables A33 to A35; prevalence data from the five provinces that were included in the budget impact analysis (British Columbia, Saskatchewan, Manitoba, New Brunswick, and Nova Scotia) appear in Appendix 4, Tables A36 to A40. The prevalence estimates for other jurisdictions are available upon request.

6.2 Budget Impact

We estimated the budget impact if changes were made to the listing criteria of approved and unapproved indications of OCT-SA and OCT-LA by publicly funded drug plans in Canada. These analyses were performed over four years for the five publicly funded drug plans that provided historical drug use data: British Columbia, Saskatchewan, Manitoba, New Brunswick, and Nova Scotia. We were unable to assess the budget impact of other publicly funded drug plans because no drug use data were provided or the data were insufficiently detailed for our analysis. It was not possible to estimate a budget impact for Canada, because of the many different listings criteria among drug plans and insufficient data. Health services impact analyses were not performed because of the many indications and because this project focuses on the reimbursement of costs for OCT-SA and OCT-LA by publicly funded drug plans.

The net incremental cost impact of changing the listing criteria through different scenarios of reimbursement was compared to that of the base case scenario (no change in listing criteria). The listing criteria and the budget impact results appear in Tables 27 and 28. Partial budget impact models appear in Appendix 4, Tables A41 to A45. Complete budget impact models by province are available upon request.

Table 26: Prevalence by indication per year in Canada (all age groups)					
	2006	**2007**	**2008**	**2009**	**2010**
GEPNET	1,106	1,114	1,122	1,129	1,136
Acromegaly	1,952	1,967	1,980	1,993	2,005
Pancreatic surgery*	651	656	660	664	668
Bleeding esophageal varices	4,554	4,589	4,620	4,650	4,678
Hepatocellular carcinoma	1,903	1,917	1,931	1,943	1,955
Pancreatic cancer	3,253	3,278	3,300	3,321	3,341
Chemotherapy-related diarrhea	81,329	81,938	82,507	83,037	83,528
Ileostomy-related diarrhea†	NE	NE	NE	NE	NE
HIV-AIDS-related diarrhea	29,278	29,498	29,703	29,893	30,070
Crohn's-related diarrhea‡	49,723	50,095	50,443	50,767	51,067
Short bowel syndrome	98	98	99	100	100
Bowel obstruction (inoperable)	18,218	18,354	18,482	18,600	18,710
Pediatric hyperinsulinism**	11	12	12	12	12
Approved indications total	8,263	8,326	8,382	8,436	8,487
Unapproved indications total	183,813	185,190	186,477	187,673	188,783
All indications	192,076	193,516	194,859	196,109	197,270

GEPNET=gastroenteropancreatic neuroendocrine tumour; HIV-AIDS=human immunodeficiency virus-acquired immune deficiency syndrome; NE=not estimable
*Based on number of patients with operable pancreatic cancer
†Unable to find prevalence data
‡Low confidence data
**Data based on incidence rate of 1 per 30,000 live births. Average growth rate in Canadian population of 1.1% applied

6.2.1 Methods

a) Sales projections

Based on the 1996 to 2006 drug use data from the five publicly funded drug plans (British Columbia, Saskatchewan, Manitoba, New Brunswick, and Nova Scotia), we made projections for the fiscal years of 2006-2007 to 2009-2010 using Vanguard Studio software.[263]

The projections were made from historical sales, historical number of beneficiaries, and historical number of prescriptions per fiscal year. The projections were performed for OCT-SA and OCT-LA and some comparators (bromocriptine 2.5 mg and 5 mg, cabergoline, diphenoxylate, and loperamide). These comparators were selected because of their availability throughout Canada, their status as gold standard or first-line treatment agents, and their use as direct comparators in health economic analyses of octreotide.

The average costs per prescription, average prescriptions per drug, average units per prescription, and average cost per unit were calculated based on the drug use data for each drug plan that was evaluated.

For each province, we calculated the annual total cost of each drug by multiplying the projected prescriptions per drug, per fiscal year, by the average cost per prescription, per drug, and compared it with our projections for the annual total sales of each drug. The results confirmed that the model we used for our projections was robust.

b) Budget impact analysis

The provincial drug plans' listing criteria for OCT-SA, OCT-LA, and the comparators were collected for the budget impact analysis. Descriptions of the different plans offered by each drug plan program (British Columbia, Saskatchewan, Manitoba, New Brunswick, and Nova Scotia)[264-270] were collected for a better understanding of the coverage of OCT-SA and OCT-LA.

We followed five steps to estimate the budget impact for each provincial drug plan:

- After looking at the current listing criteria (base case), we determined scenario 1 and scenario 2, which expanded or restricted the coverage of OCT-SA and OCT-LA (Table 27).
- For the base-case scenario, we applied the population impact (an increase or decrease) to the projected prescription data. The population impact was calculated by using population projections by Statisics Canada, scenario 1, by province.[262]
- For scenarios 1 and 2, we applied the population impact (increase or decrease)[262] and the impact of changing the listing criteria (switching assumptions), which was calculated by using the provincial indication-specific prevalence data. The switching assumptions were applied to the projected prescriptions.
- The total drug costs for the base case, scenario 1, and scenario 2 were calculated by multiplying the projected prescriptions by the average cost per prescription.
- The incremental budget impact was calculated as the difference between the projected costs after the changes in listing criteria and the projected costs before the changes in listing criteria (base-case analysis).

The approved indications that were used in scenarios 1 and 2 were limited to acromegaly and GEPNET, assuming that these patients were treated in an ambulatory care setting. In some switching scenarios, a portion of the market share of the alternative agents (bromocriptine, cabergoline, diphenoxylate and loperamide) was shifted to octreotide. We used the indication-specific prevalence data to calculate the number of beneficiaries in scenarios 1 and 2 because of limitations in the data from the drug plans. In one case (British Columbia), the number of beneficiaries by plan was also used.

The budget impact models are available upon request for British Columbia, Saskatchewan, Manitoba, New Brunswick, and Nova Scotia. The projected costs before and after the changes in listing criteria, and the incremental budget impact results, appear in Appendix 4, Tables A41 to A45.

Table 27: Drug plan listing criteria used in budget impact analysis*

Province and Analysis	Listing Criteria
British Columbia	
Base-case analysis	OCT-SA is a benefit for palliative care programs (all indications) and a restricted benefit under Special Authority Process (case-by-case basis) for all other plans. OCT-LA is not a benefit in any plan.
Scenario 1	OCT-LA is listed as a benefit for palliative care (Plan P) and on a case-by-case basis for all other plans.
Scenario 2	OCT-SA and OCT-LA is listed as a benefit for all plans (except Plan I) for approved and unapproved indications, and only for approved indications for 56 beneficiaries in Plan I (all other British Columbians or Fair PharmaCare)
Saskatchewan	
Base-case analysis	OCT-SA and OCT-LA is reimbursed through EDS process for acromegaly (all patients) and terminal malignant bowel obstruction in palliative patients.

Table 27: Drug plan listing criteria used in budget impact analysis*	
Province and Analysis	**Listing Criteria**
Scenario 1	OCT-SA and OCT-LA is reimbursed through EDS for all approved indications and terminal malignant bowel obstruction in palliative care patients.
Scenario 2	OCT-SA and OCT-LA is listed as a benefit. Per cent of beneficiaries to be treated set up to be same as that of Nova Scotia.
Manitoba	
Base-case analysis	OCT-SA has open listing on interchangeability drug formulary. OCT-LA is available through EDS process.
Scenario 1	OCT-LA is available, restricted to approved indications only.
Scenario 2	OCT-LA has open listing on interchangeability drug formulary.
Nova Scotia	
Base-case analysis	OCT-SA and OCT-LA is a benefit for plans C, F, and S (Drug Assistance for Cancer Patients, Community Services Pharmacare, Seniors' Pharmacare).
Scenario 1	Double the proportion of patients treated (all indications).
Scenario 2	OCT-LA listing restricted to acromegaly and GEPNET.
New Brunswick	
Base-case analysis	OCT-SA is listed as restricted access for patients with metastatic carcinoid and VIPomas, GEPNET, and acromegaly. OCT-LA is restricted to access by patients with acromegaly. Plan W (extramural hospital patients).
Scenario 1	Same indications as base case, but expanded to plans A, E, F, and V (seniors, adults in licensed residential facilities, family and community services, and nursing home beneficiaries).
Scenario 2	Listing criteria changed to "open" for plans in scenario 1.

EDS=Exceptional Drug Status; GEPNET=gastroenteropancreatic neuroendocrine tumour; OCT-LA=octreotide long-acting; OCT-SA=octreotide short-acting; VIPoma=vasoactive intestinal polypeptide-secreting tumour
*Actual listing criteria obtained from each respective Provincial Drug Plan website or formulary[264-270]

Lanreotide (Somatuline Autogel®) is a long-acting somatostatin analogue that has been approved by Health Canada for use in acromegaly. We excluded lanreotide from the analysis, mainly because of insufficient data. If lanreotide was to be listed on publicly funded drug plan formularies for acromegaly, it would take some of OCT-LA's market share. Because the unit cost of lanreotide is similar to that of OCT-LA, we foresee an insignificant difference in the total annual costs.

6.2.2 Results

The results of the budget impact analyses appear in Table 28, which shows the per cent of variation. The results show that drug plan budgets are sensitive, to various degrees, to any expansion of their coverage for OCT-SA and OCT-LA. Any variation in coverage for OCT-LA entails the largest percentage change for any of the drug plan programs.

The prevalence data (Table 26) show that the potential population of beneficiaries for unapproved indications exceeds 180,000 patients. The results that were obtained for scenario 2 in Manitoba and Saskatchewan show a cost impact if access to OCT-SA and OCT-LA becomes open to unapproved indications. The reimbursement of OCT-SA and OCT-LA for the unapproved indications will have a large impact on the budgets of publicly funded drug plans.

The results that were obtained from the analysis in British Columbia show that the reimbursement of OCT-SA and OCT-LA for beneficiaries of the Palliative Care Program increases costs by 13% or C$122,714 in fiscal year 2006-2007, or by 54% or C$488,542 in fiscal year 2009-2010. For palliative care program beneficiaries, reimbursement for approved and unapproved indications resulted in a smaller budget increase.

Table 28: Drug budget impact for British Columbia, Saskatchewan, Manitoba, Nova Scotia, and New Brunswick (C$)

Province and Analysis*	2006-2007	2007-2008	2008-2009	2009-2010
British Columbia				
Base-case analysis	**$ 916,711**	**$ 905,446**	**$ 903,584**	**$ 897,270**
Scenario 1	$ 122,714 ↑ 13%	$ 245,050 ↑ 27%	$ 367,043 ↑ 41%	$ 488,542 ↑ 54%
Scenario 2	$ 437,720 ↑ 48%	$ 703,497 ↑ 78%	$ 968,131 ↑ 107%	$ 1,235,731 ↑ 137%
Saskatchewan				
Base-case analysis	**$ 700,760**	**$ 726,786**	**$ 750,144**	**$ 771,402**
Scenario 1	$ 22,003 ↑ 3%	$ 23,258 ↑ 3%	$ 24,399 ↑ 3%	$ 25,451 ↑ 3%
Scenario 2	$ 725,211 ↑ 103%	$ 767,349 ↑ 106%	$ 805,705 ↑ 107%	$ 841,045 ↑ 109%
Manitoba				
Base-case analysis	**$ 1,240,676**	**$ 1,299,447**	**$ 1,365,674**	**$ 1,425,764**
Scenario 1	$ 189,760 ↑ 15%	$ 201,660 ↑ 16%	$ 213,593 ↑ 16%	$ 225,563 ↑ 16%
Scenario 2	$ 909,011 ↑ 73%	$ 965,389 ↑ 74%	$ 1,021,492 ↑ 75%	$ 1,078,191 ↑ 76%
Nova Scotia				
Base-case analysis	**$ 605,166**	**$ 621,402**	**$ 656,534**	**$ 668,337**
Scenario 1	$ 77,192 ↑ 13%	$ 80,638 ↑ 13%	$ 87,897 ↑ 13%	$ 90,526 ↑ 14%
Scenario 2	$ −73,517 ↓ 12%	$ −79,155 ↓ 13%	$ −84,372 ↓ 13%	$ −89,242 ↓ 13%
New Brunswick				
Base-case analysis	**$ 293,560**	**$ 299,746**	**$ 306,292**	**$ 313,155**
Scenario 1	$ 180,335 ↑ 61%	$ 187,130 ↑ 62%	$ 194,163 ↑ 63%	$ 201,410 ↑ 64%
Scenario 2	$ 270,558 ↑ 92%	$ 280,749 ↑ 94%	$ 291,299 ↑ 95%	$ 302,170 ↑ 96%

C=Canadian; ↑=increase in drug budget; ↓=decrease in drug budget
*Base-case data represent total drug budget costs. Scenarios 1 and 2 represent incremental costs or savings and per cent change relative to base case

6.2.3 Analysis issues

During our analysis, many issues were noted. First, the budget impact analysis had to be tailored for each province because OCT-SA has been approved for use in Canada for more than 15 years, and OCT-LA since 1998.[63] During this time, provincial listings criteria for octreotide (both

formulations) have been revised by the drug plans, based on updated research and new submissions by the manufacturers. There are differences in the listings of octreotide in the publicly funded drug plans in Canada. We have tried to be consistent in our analyses for provinces with available drug use data that were sufficient for the budget impact analysis.

Another issue is the low number of beneficiaries who are prescribed octreotide in some provinces. This poses a problem of confidentiality for the drug plans that provided drug use data. In many cases, we had to assume that the number of beneficiaries was 2.5 when the data were supplied as "less than five beneficiaries." This may have affected our results and the tabulation of data by indication. Because of the low number of patients, the confidence level of some indications is low. For this reason, indication-specific prevalence rates were used to calculate the number of beneficiaries who would receive octreotide in scenarios 1 and 2.

6.3 Planning, Implementation, Utilization, and Legal or Regulatory Considerations

A review of formulary listings of OCT-SA and OCT-LA revealed no consensus on reimbursement policies for octreotide among publicly funded drug programs. OCT-SA and OCT-LA were found to be a benefit in about half of the publicly funded drug programs. In others, they were restricted under "Limited Use," "Exception Drug Status," or "Special Authorization."[264-278] The listing criteria determine the number of beneficiaries who are entitled to coverage for octreotide, thus increasing or decreasing expenses.
Lanreotide is anticipated to compete for a share of the market in the treatment of acromegaly. Although some patients taking octreotide may be switched to take lanreotide, the total number of beneficiaries is not expected to grow. Based on available information, the budget impact for the publicly funded drug plans is expected to be insignificant.

There are concerns about octreotide's unapproved use. This costly medication may be used chronically. Its use in pediatric hyperinsulinism, short bowel syndrome, refractory diarrhea, pancreatic cancer, and bowel obstruction has been inadequately studied. Based on our analysis, there was no good evidence from meta-analyses or RCTs that confirmed the clinical benefit of octreotide for these conditions.

6.4 Ethical and Psychosocial Considerations

Octreotide is approved for use in Canada for four indications. Physicians also use it for unapproved indications (off-label use), some of which were examined for evidence of benefit in this report. Off-label use is common in medicine, especially in pediatrics, oncology, and HIV-AIDS, because of the paucity of drug studies in these populations.

When prescribing a treatment, the physician's primary responsibility is to the patient. A physician who is prescribing a drug would be guided by what is deemed to be best for the patient and what is accepted medical practice, not necessarily by what is the most cost-effective treatment from a population perspective (i.e., provides the most health for the largest number of people given the limited resources available). This may place a physician's decision in conflict with those of health care sponsors such as publicly funded drug plan insurers. Policy makers face

decisions about the optimal allocation of limited resources and the establishment of policies that consider the greater good of society.

The advent of octreotide therapy has resulted in questions about physicians' prescribing treatments for which there is no evidence of benefit and no assurance of freedom from harm. As part of the process of informed consent regarding health care technologies, the physician has a responsibility to discuss, with every patient, the advantages and disadvantages of octreotide therapy, including the off-label indications. To give valid informed consent to treatment, patients should be adequately informed about the benefits and harms of therapy. Patients have become knowledgeable about their disease and treatments, partly because of the fiduciary duty of physicians to disclose all possible treatments, including the off-label ones, and partly because of access to information such as that on the Internet. Patients increasingly expect (and demand) treatment, even if it has not been proven to be beneficial or to cause no harm.

The benefits of octreotide therapy are unproven for the off-label indications under study. Some of these conditions result in high mortality (pancreatic cancer) or high morbidity (pediatric hyperinsulinism) for which octreotide may be a drug of last resort. Thus, the physician faces the decision of whether to prescribe a drug that has not been proven to be effective (because of a lack of trials or because of poor quality trials) and for which approval has not been granted by Health Canada for that use. Furthermore, in most of the publicly funded drug plans, octreotide is only reimbursed provided specific medical criteria are met through special authorization. Because of the lack of regulatory approval for off-label indications, drug plan insurers may be reluctant to provide reimbursement for octreotide or they may have policies that prevent them from doing so.

Any consideration of the benefits and risks of therapy for the indications under study must include the psychosocial dimensions and the clinical and economic outcomes. Physicians and other caregivers should discuss the impact of octreotide therapy on a patient's quality of life or well-being. Patients' attitudes are influenced by cultural differences, beliefs, and previous experiences with the health system.

7 DISCUSSION

7.1 Summary of Results

7.1.1 Clinical review

The goal of the clinical review on octreotide was to examine its clinical effectiveness, specifically efficacy and harm for four approved and six unapproved indications. In a search for systematic reviews that addressed the research questions, we failed to find a report that met pre-determined standards. As a result, we conducted a systematic review.

A total of 82 parallel or cross-over randomized controlled trials (RCTs) were included in our analysis. Data from nine non-randomized controlled clinical trials (CCTs) supplemented the harms data. The outcomes that were measured in the RCTs included adverse events, serious

adverse events, death, survival, rate of complications, symptom control, quality of life, length of hospital stay, and other outcomes that were more specific to each condition. The trials compared OCT-SA and OCT-LA with each other, or to placebo, no treatment, lanreotide, somatostatin, or to other appropriate active controls, depending on the conditions under review.

High quality RCTs are lacking. Of the 82 RCTs, seven (9%) studies had adequate allocation concealment and 31 (38%) met the Jadad criteria for higher methodological quality. Many RCTs had a small sample size. Octreotide showed benefit in improving surrogate markers of efficacy or short-term symptom control. Most studies did not measure health-related quality of life.

The reporting of harms in the randomized and non-randomized clinical trials was limited and the data were sparse. For example, not all studies reported the absolute number of patients with a given adverse event. Furthermore, the methods that were used in non-randomized trials were poorly described and the populations studied were not always comparable. For these reasons, we could only provide a narrative review and the results must be interpreted with caution. They provide an overview of the potential harm that is associated with the use of octreotide, but they do not clarify the prevalence or incidence of any adverse event.

Given these limitations, the analysis of the adverse events data suggests that octreotide did not cause substantial harm in the short term. Adverse events were mainly gastrointestinal symptoms and pain at the injection site. Few patients withdrew from treatment because of an adverse event. More serious adverse events that were reported in a few patients taking octreotide were throat spasms, flushing and shallow breathing; hypoglycemia; hyperglycemia; paralytic ileus; pulmonary edema; renal failure; bradycardia; tachycardia; and febrile rash. A causal relationship cannot be determined given the quality of the data.

Conclusions about the optimal length of therapy could not be drawn.

a) Acromegaly

Ten RCTs compared OCT-SA and OCT-LA to each other or to a control treatment (placebo or no treatment, lanreotide, bromocriptine, or surgery). Four CCTs provided additional harms data.

Results could only be pooled in two instances. It was difficult to draw conclusions for most of the outcomes because the studies did not measure an outcome of interest or did not provide results that could be interpreted easily. Furthermore, most of the studies had small sample sizes. Five RCTs obtained a Jadad score that indicated poorer quality. Allocation concealment could not be determined for all ten studies.

With these limitations, this systematic review could not detect differences between OCT-LA and lanreotide in patients with acromegaly in reducing growth hormone and insulin-like growth factor-1 levels.

OCT-SA significantly decreased growth hormone and insulin-like growth factor levels when it was compared with placebo or no treatment. One study showed that more patients in the OCT-SA group obtained normal growth hormone levels compared with those in the no treatment group.

No conclusion can be drawn when OCT-LA is compared to surgery or when OCT-SA is compared to bromocriptine. Furthermore, no conclusions can be drawn for the outcomes of death, symptom control, and reduction in pituitary tumour size.

b) Emergency management of acute variceal bleeding

We analyzed 36 RCTs that compared OCT-SA with placebo, no treatment, or active comparators (sclerotherapy, balloon tamponade, somatostatin, terlipressin, or vasopressin). Overall, 4,025 patients were evaluated. Of these patients, 74% were enrolled in trials that compared octreotide to placebo or no treatment. Three (8%) trials had adequate allocation concealment. Eight (22%) trials were considered to be of a higher methodological quality.

No significant difference was detected between OCT-SA and any comparator when the number of deaths was considered.

OCT-SA reduced the risk of failing initial hemostasis when it was compared with placebo or no treatment, terlipressin, or vasopressin. No significant difference was detected when OCT-SA was compared with sclerotherapy, balloon tamponade, or somatostatin.

OCT-SA reduced the risk of rebleeding when it was compared with placebo or no treatment. No significant difference was detected when OCT-SA was compared to the other comparators. Moderate heterogeneity, which was detected in most analyses, was partly due to differences in how rebleeding was defined or when it was measured.
When data on the number of patients with uncontrolled bleeding requiring treatment were pooled, we detected no significant difference between OCT-SA and sclerotherapy. Among the other eight trials reporting on this outcome, one reported a significant result (OCT-SA reduced the risk of uncontrolled bleeding requiring treatment compared with placebo).

We produced a narrative synthesis of the blood transfusion and hospital length of stay data. Seven of 27 RCTs reported that patients who were treated with OCT-SA required significantly fewer blood transfusions. Three RCTs reported a significant increase in the number of transfusions. In most RCTs, the absolute difference between groups was less than one unit of blood.

Two RCTs reported that patients who were treated with OCT-SA had a significantly shorter length of hospital stay compared with those who received placebo or no treatment. Three trials reported that the length of hospitalization was significantly longer in the OCT-SA group than in the control group (placebo, sclerotherapy, or terlipressin). No difference was detected in the other four RCTs.

c) GEPNET

Four RCTs compared OCT-SA with OCT-LA, lanreotide, or placebo. Two RCTs had a Jadad score that indicated higher methodological quality, and one had adequate allocation concealment. Two CCTs provided additional harms data. The results could not be pooled.

Limited data suggest that OCT-SA may be similar to lanreotide or to OCT-LA in relieving the symptoms of flushing and diarrhea. One small study showed a statistically significant reduction in the symptom of flushing, but not abdominal pain when OCT-SA was compared with placebo. The results, which should be interpreted with caution, need to be confirmed in larger trials.

One study with 93 participants showed no difference in treatment success (the need for rescue therapy) when the two formulations of octreotide were compared.

No conclusion can be reached on whether octreotide affects death, health-related quality of life, or 5-HIAA levels in patients with GEPNET because the studies did not measure the outcome or did not provide results that could be interpreted easily.

d) Prevention of complications after pancreatic surgery

Twelve RCTs compared OCT-SA with placebo or no treatment. Patients had pancreatitis, had malignant or benign tumour, had undergone transplantation, or had a combination of these conditions. Seven RCTs had a Jadad score that indicated higher methodological quality, and two had adequate allocation concealment. One quasi-randomized trial provided additional harms data.

Patients who were taking OCT-SA experienced a lower incidence of fluid collection, fewer pancreatic fistulas, and an overall lower complication rate than patients who were taking placebo or no treatment. When only the two trials with adequate allocation concealment were analyzed, there was no statistically significant difference for these outcomes.

There was no statistically significant overall effect for OCT-SA regarding hospital stay, post-surgical abscess, bleeding, infection, death, or pancreatitis. Data on quality of life, survival, and intensive care unit length of stay were not reported.

e) Bowel obstruction

Two RCTs compared OCT-SA to hyoscine butylbromide in patients with cancer and inoperable bowel obstruction. Both RCTs were of lower quality and had unclear allocation concealment. OCT-SA significantly reduced vomiting and nausea when it was compared with hyoscine butylbromide. Patients who were treated with OCT-SA for three days vomited one fewer time per day than those treated with hyoscine butylbromide. OCT-SA also reduced the severity of nausea when it was compared with hyoscine butylbromide.

No significant differences were detected between treatments for other symptoms of bowel obstruction (pain, drowsiness, or dry mouth). Data on quality of life, hospital length of stay, and need for nasogastric tube insertion were not reported in either RCT.

f) Diarrhea related to chemotherapy, HIV-AIDS, Crohn's disease, or ileostomy

No studies met the inclusion criteria for diarrhea related to Crohn's disease or ileostomy.
Of the seven RCTs, five assessed the efficacy of OCT-SA in patients with chemotherapy-related diarrhea, and two assessed the efficacy of OCT-SA in patients with HIV-AIDS. The RCTs compared OCT-SA with placebo, loperamide, or placebo plus loperamide and diphenoxylate. Two outcomes were measured (death and diarrhea control). Other outcomes such as health-related quality of life, admittance to hospital, hospital length-of-stay, return to work, and need for intravenous fluid therapy were not reported. Four studies had a Jadad score that indicated higher quality, and allocation concealment was unclear in all trials.

Chemotherapy patients with diarrhea
One study found that chemotherapy patients who were taking OCT-SA were more likely to experience major or complete resolution of diarrhea compared with those who were receiving placebo.

The results of the four studies that compared OCT-SA with loperamide could not be pooled because of high levels of heterogeneity. These could be due to inherent differences between chemotherapy patients who are taking different medications and who have different types of cancer. Another factor that could have contributed to the high heterogeneity was the variation in dose of OCT-SA from 200 μg to 1500 μg per day. The dosing regimen of loperamide varied between 8 mg and 16 mg per day. In two trials, patients who were treated with OCT-SA were significantly more likely to respond to treatment. One trial reported that significantly more patients who were treated with loperamide had a complete or major response to treatment. A fourth trial found no difference between treatments.

HIV-AIDS patients with refractory diarrhea
In the HIV-AIDS population, no significant difference was detected between OCT-SA and placebo or placebo plus antidiarrheal agents.

g) Hepatocellular carcinoma
Seven RCTs compared OCT-SA or OCT-LA with a control treatment (placebo or no treatment, or tamoxifen). Five studies were of higher quality, based on the Jadad score, and allocation concealment was unclear in all but one trial. Two CCTs provided additional harms data.

The results could not be pooled. Studies did not measure a particular outcome or did not provide results that could be interpreted easily. The statistically significant results that were obtained for this indication are based on single studies.

Two studies showed that survival was significantly greater with octreotide compared with placebo or no treatment. Four other studies found no difference between treatment groups.

In one small study, OCT-SA significantly reduced the number of deaths at six and 12 months and slowed tumour progression compared with no treatment. No other conclusions can be drawn regarding OCT-SA.

OCT-LA did not affect death, quality of life, tumour response rates, and α-fetoprotein levels compared with various control groups.

h) Pancreatic cancer
Four RCTs enrolled patients with advanced stage pancreatic cancer and inoperable tumours. They compared OCT-SA with no treatment or with chemotherapy, and OCT-LA with placebo. The three outcomes measured were death, survival, and tumour response rates. Health-related quality of life was not measured in any of the included studies. All the trials had unclear or inadequate allocation concealment, and three were of poorer quality according to the Jadad scale. The data could not be pooled.

One RCT showed a significant increase of eight weeks in the median survival time when OCT-SA was compared to no treatment. No significant difference in survival time was detected in the other three RCTs.

No effect on the pancreatic tomour was detected with OCT-SA or OCT-LA compared with placebo, no treatment, or 5-fluorouracil.

i) Pediatric hyperinsulinism

No RCTs or CCTs were identified in the literature search that assessed octreotide for pediatric hyperinsulinism. Other studies have shown that octreotide is effective in elevating blood glucose, which is the aim of this therapy for patients with hyperinsulinism, and since there are no other comparator drugs available, an RCT with a placebo control would likely be considered unethical. In clinical practice, octreotide is considered to be second-line therapy in infants with hyperinsulinism. It is the only medical treatment available for patients with an abnormality of the beta cell potassium-adenosine triphosphate channel.

j) Short bowel syndrome

None of the five cross-over RCTs that met the inclusion criteria could be analyzed because the data were not reported before cross-over.

7.1.2 Economic review

Few health economic analyses have been conducted on octreotide in the populations of interest. Eight studies assessed the cost-effectiveness of octreotide for the Health Canada-approved indications. No studies were identified for any of the unapproved indications.

High quality RCTs are lacking for many of these disease states. This lack of data had an impact on the evaluation of cost-effectiveness. Most studies used observational studies as the source of effectiveness data and, in several cases, key data parameters were assumed. This was of particular concern for the studies in acromegaly and GEPNET.

Most studies conducted a cost-effectiveness analysis that limited our ability to compare results between studies. Considering the morbidity associated with acromegaly and GEPNETs, a cost-utility analysis may have been more informative. Using a societal perspective would have captured other costs that may be affected by treatment.

Incomplete information in some studies was also an issue. One of the acromegaly studies was missing the appendix with the details of the data parameters and the model. Without this information, it is difficult to draw any conclusions from the study (L. Wilson; unpublished data, 1999). The same is true for Arcona et al. abstract.[261]

We can be most confident about the studies of patients who were undergoing pancreatic surgery. The Canadian cost-effectiveness study was of high quality and met most of the criteria in the BMJ checklist. Efficacy data were taken from a meta-analysis of RCTs, and two simple models were used to calculate the cost-effectiveness. In both models, OCT-SA was the dominant strategy (more effective and less costly than placebo). The cost-benefit analysis that was conducted in the US also concluded that OCT-SA was cost saving in patients who were

undergoing pancreaticoduodenectomy, particularly if use was limited to patients considered to be at high risk of developing fistulas.[259]

7.2 Strengths and Weaknesses of this Assessment

7.2.1 Clinical review

This clinical review presents a comprehensive examination of all RCTs on octreotide that met the inclusion criteria. The review was challenging given its broad scope, which included 10 indications and many interventions, comparators, and study outcomes. The methods were robust and followed CADTH's guidelines. The meta-analysis was conducted according to the *Cochrane Handbook for Systematic Reviews of Interventions*.[76] The review, however, only included English and French papers. Of 17 relevant non-English papers, three abstracts could be used.

The strength of the conclusions of a systematic review depends on the quality of the primary literature. Of the RCTs, 61% were given a Jadad score that indicated lower methodolgical quality. Allocation concealment was unclear in more than 90% of the studies. Data such as variance, number of participants in each group, or endpoint values were not always reported, particularly in studies that were only available as abstracts. Most of the cross-over studies did not give results from the first treatment group before patients crossed over to the other group. Attempts were made to contact authors to obtain missing variables, but in most cases we were unsuccessful.

The data for acromegaly, GEPNET, bowel obstruction, hepatocellular carcinoma, pancreatic cancer, and refractory diarrhea related to HIV-AIDS or chemotherapy were sparse, with a limited number of RCTs in small numbers of patients. Additional studies are needed to confirm the reported findings. Except for the indications of variceal bleeding and the prevention of complications after pancreatic surgery, data were rarely pooled because the duration of treatment or the comparators were too dissimilar or – in most instances – data were missing. Adverse events were poorly reported and harms could not be quantified systematically.

The results of the systematic review must be interpreted in light of these limitations.

7.2.2 Economic review

The economic review was conducted according to a protocol that was developed a priori and based on CADTH's guidelines. A literature search that included published and unpublished data was undertaken. The number of studies that met the inclusion criteria was small. No studies for the unapproved indications were retrieved.

Although each study was assessed for methodological quality using the BMJ checklist[257] and the Drummond partial checklist,[258] these tools have their limitations. A study may meet many of the items on the checklists and still be subject to bias. Reporting often lacks sufficient details to thoroughly assess a study against the checklist. We could not draw any conclusions for the cost-effectiveness of octreotide in bleeding esophageal varices, acromegaly, or GEPNETs because of the lack of studies or because of the methodological limitations in the available studies.

Each economic evaluation must be interpreted in the context where it was conducted, thus making the extrapolation of results from one jurisdiction to another problematic. Studies conducted in different jurisdictions may report contradictory findings. No direct comparison could be made between economic analyses for acromegaly, partly because of differences in study designs, cost-effectiveness outcomes (cost per quality-adjusted life-year and cost per year of life saved versus cost per patient being "cured"), and geographical location.

The results of the economic review must be interpreted in light of these limitations.

7.3 Generalizability of Findings

7.3.1 Clinical review

To be inclusive, we conducted a broad search for clinical trials that was not limited by publication date or by treatment comparator. Some of the comparators that were included in the review are unavailable in Canada (for example, terlipressin). Of the 82 included RCTs, 39 were published in 1997 or earlier. As clinical practice evolves, some treatments may be phased out (for example, somatostatin, vasopressin). Surgical and other procedures also vary as techniques evolve. Thus, some comparators may be less relevant to current Canadian clinical practice.

The results of our study, in general, were consistent with those of the 17 systematic reviews that we identified.[81-89,91-98] The most controversy exists for the use of octreotide in patients who are undergoing pancreatic surgery. Two systematic reviews concluded that there is disagreement among studies about the value of octreotide in preventing post-operative complications.[93,95] A third review that focused on patients who were undergoing pancreaticoduodenectomy found no benefit with somatostatin and its analogues in reducing morbidity or mortality.[97] Because our inclusion criteria were broad, our analysis included any patient who was undergoing pancreatic resection, regardless of the underlying disease state or surgical technique used. This must be considered when our results are applied to the Canadian population, because there may be populations where octreotide is most effective or, conversely, of little benefit.

7.3.2 Economic review

Economic evaluations that are conducted in other countries may shed light on a technology's "value for money," but generalizability to the Canadian context is limited. Differences in approved comparators, methods of care, and health care systems can affect the results. For this reason, the US and UK studies that were included in this review cannot be generalized to Canada.[83,259-261]

The findings of the Canadian economic evaluation in patients who are undergoing pancreatic surgery[24] can be applied to all provincial or territorial ministries of health. Economic evaluations that apply to Canada for other indications is lacking. With the available resources and the number of indications that are covered in this report, we were unable to conduct a new economic evaluation. A follow-up study could be considered, now that the limitations of the existing data are known. Careful evaluation of the effectiveness data would be required, because the data may be insufficiently robust for a cost-effectiveness study

7.4 Knowledge Gaps

Research is still required to address several clinical questions:

- What is the clinical effectiveness of OCT-LA in the selected indications when it is compared with OCT-SA?
- What is the optimal length of octreotide therapy in the selected indications?
- What are the benefits and harms of octreotide in pediatric hyperinsulinism, short bowel syndrome, and refractory diarrhea related to Crohn's disease or ileostomy?
- How do the benefits of octreotide compare with those of the lanreotide long-acting formulation that is available in Canada?
- Does octreotide affect the long-term morbidity and mortality in acromegaly and GEPNET patients?
- Do the short-term benefits observed in some octreotide trials translate into better mid-range outcomes for patients with liver disease and acute variceal bleeding?
- Does octreotide improve health-related quality of life in patients where symptom management is the main treatment goal?
- What is the incidence of adverse events and serious adverse events with octreotide? How many patients discontinue treatment because of adverse events, and why?
- What is the long-term safety of octreotide for patients on chronic therapy?
- What is the cost-effectiveness of OCT-SA or OCT-LA in Canada in patients with acromegaly, GEPNETs, esophageal variceal bleeding, and all the selected unapproved indications?
- What is the cost-effectiveness of lanreotide compared with OCT-LA in all approved and unapproved indications?
- Is there a difference in quality-adjusted life-years between patients who are taking OCT-SA and patients who are taking OCT-LA in Canada?

8 CONCLUSIONS

Octreotide showed a benefit in improving surrogate markers of efficacy or short-term symptom control in patients with acromegaly, GEPNETs, esophageal bleeding, and bowel obstruction. Octreotide reduced the risk of some complications after pancreatic surgery. No overall benefit was detected in death rate or survival time for variceal bleeding, pancreatic surgery, or pancreatic cancer. No conclusions could be drawn regarding the impact of octreotide on health-related quality of life, the relative efficacy of OCT-SA compared to OCT-LA, or the optimal length of octreotide therapy. A descriptive review of adverse events suggested that octreotide was not associated with substantial harm in the short term.

We were unable to assess four indications (pediatric hyperinsulinism, short bowel syndrome, diarrhea related to ileostomy or Crohn's disease) because of a lack of RCTs. Conclusions on the efficacy of octreotide for hepatocellular carcinoma or refractory diarrhea related to chemotherapy or HIV-AIDs could not be drawn.

In our review of economic evaluations, there were sufficient data to draw conclusions for one indication. For patients undergoing pancreatic surgery, OCT-SA was more effective and less

costly than placebo. For publicly funded drug plans, the expansion of listing criteria to include the unapproved indications could double the expenditures on octreotide.

9 REFERENCES

1. Canadian Pharmacists Association. Sandostatin®, Sandostatin LAR®. In: *Compendium of pharmaceuticals and specialties* [database online]. Ottawa: The Association; 2007.

2. Sandostatin. In: *Notice of compliance database* [database online]. Ottawa: Therapeutic Products Directorate, Health Canada; 2006. Available: http://www.nocdatabase.ca (accessed 2008 Jan 31).

3. Sandostatin LAR. In: *Notice of compliance database* [database online]. Ottawa: Therapeutic Products Directorate, Health Canada; 2006. Available: http://www.nocdatabase.ca (accessed 2008 Jan 31).

4. Ezzat S, Forster MJ, Berchtold P, Redelmeier DA, Boerlin V, Harris AG. Acromegaly. Clinical and biochemical features in 500 patients. *Medicine (Baltimore)* 1994;73(5):233-40.

5. Ezzat S, Serri O, Chik CL, Johnson MD, Beauregard H, Marcovitz S, et al. Canadian consensus guidelines for the diagnosis and management of acromegaly. *Clin Invest Med* 2006;29(1):29-39.

6. Ezzat S. Pharmacological options in the treatment of acromegaly. *Curr Opin Investig Drugs* 2005;6(10):1023-7.

7. Wilson LS, Shin JL, Ezzat S. Longitudinal assessment of economic burden and clinical outcomes in acromegaly. *Endocr Pract* 2001;7(3):170-80.

8. Feenstra J, de Herder WW, ten Have SM, van den Beld AW, Feelders RA, Janssen JA, et al. Combined therapy with somatostatin analogues and weekly pegvisomant in active acromegaly. *Lancet* 2005;365(9471):1644-6.

9. Cheung J, Wong W, Zandieh I, Leung Y, Lee SS, Ramji A, et al. Acute management and secondary prophylaxis of esophageal variceal bleeding: a western Canadian survey. *Can J Gastroenterol* 2006;20(8):531-4.

10. Morris JM, Forrest EH. Managing variceal haemorrhage. *Br J Intensive Care* 2007;17(1):23, 25-6, 28,-30.

11. D'Amico G, De Franchis R, Cooperative Study Group. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology* 2003;38(3):599-612.

12. Zaman A, Arnold RJG, Pettit KG, Kaniecki DJ, Benner K, Zacker C, et al. Cost of treating an episode of variceal bleeding in a VA setting. *Am J Gastroenterol* 2000;95(5):1323-30.

13. Taal BG, Visser O. Epidemiology of neuroendocrine tumours. *Neuroendocrinology* 2004;80(Suppl 1):3-7.

14. Ramage JK, Davies AH, Ardill J, Bax N, Caplin M, Grossman A, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. *Gut* 2005;54(Suppl 4):iv1-16.

15. Modlin IM, Sandor A. An analysis of 8305 cases of carcinoid tumors. *Cancer* 1997;79(4):813-29.

16. Perez EA, Koniaris LG, Snell SE, Gutierrez JC, Sumner WE, Lee DJ, et al. 7201 carcinoids: increasing incidence overall and disproportionate mortality in the elderly. *World J Surg* 2007;31(5):1022-30.

17. Maggard MA, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. *Ann Surg* 2004;240(1):117-22.

18. Arnold R. Endocrine tumours of the gastrointestinal tract. Introduction: definition, historical aspects, classification, staging, prognosis and therapeutic options. *Best Pract Res Clin Gastroenterol* 2005;19(4):491-505.

19. Teunissen JJ, Kwekkeboom DJ, de JM, Esser JP, Valkema R, Krenning EP. Endocrine tumours of the gastrointestinal tract. Peptide receptor radionuclide therapy. *Best Pract Res Clin Gastroenterol* 2005;19(4):595-616.

20. Shah T, Caplin M. Endocrine tumours of the gastrointestinal tract. Biotherapy for metastatic endocrine tumours. *Best Pract Res Clin Gastroenterol* 2005;19(4):617-36.

21. Halloran CM, Ghaneh P, Bosonnet L, Hartley MN, Sutton R, Neoptolemos JP. Complications of pancreatic cancer resection. *Dig Surg* 2002;19(2):138-46. Available: http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowPDF&ProduktNr=223996&Ausgabe=227627&ArtikelNr=52029 (accessed 2008 Jan 31).

22. Poon RT, Lo SH, Fong D, Fan ST, Wong J. Prevention of pancreatic anastomotic leakage after pancreaticoduodenectomy. *Am J Surg* 2002;183(1):42-52.

23. Topal B, Aerts R, Hendrickx T, Fieuws S, Penninckx F. Determinants of complications in pancreaticoduodenectomy. *Eur J Surg Oncol* 2007;33(4):488-92.

24. Rosenberg L, MacNeil P, Turcotte L. Economic evaluation of the use of octreotide for prevention of complications following pancreatic resection. *J Gastrointest Surg* 1999;3(3):225-32.

25. Rosenberg L, Mac Neil Pierre, Turcotte L. Cost-effectiveness analysis of octreotide in prevention of complications following pancreatic resection [abstract]. *Gastroenterology* 1997;112(4 Suppl):A1470.

26. Friess H, Beger HG, Sulkowski U, Becker H, Hofbauer B, Dennler HJ, et al. Randomized controlled multicentre study of the prevention of complications by octreotide in patients undergoing surgery for chronic pancreatitis. *Br J Surg* 1995;82(9):1270-3.

27. Quickel R, Hodin RA. Clinical manifestations and diagnosis of small bowel obstruction. In: *UpToDate* [database online]. Version 15.2. Waltham (MA): UpToDate; 2007.

28. McCowan C. Obstruction, large bowel. In: *Emergency Medicine - Gastrointestinal Articles* [eMedicine Specialties]. Omaha (NE): WebMD Health; 2007. Available: http://www.emedicine.com/emerg/topic65.htm (accessed 2008 Jan 31).

29. Foster NM, McGory ML, Zingmond DS, Ko CY. Small bowel obstruction: a population-based appraisal. *J Am Coll Surg* 2006;203(2):170-6.

30. Ripamonti C, Mercadante S. How to use octreotide for malignant bowel obstruction. *J Support Oncol* 2004;2(4):357-64.

31. Cascinu S, Fedeli A, Fedeli SL, Catalano G. Octreotide versus loperamide in the treatment of fluorouracil-induced diarrhea: a randomized trial. *J Clin Oncol* 1993;11(1):148-51.

32. Cascinu S, Fedeli A, Fedeli SL, Catalano G. Control of chemotherapy-induced diarrhea with octreotide. A randomized trial with placebo in patients receiving cisplatin. *Oncology* 1994;51(1):70-3.

33. Benson AB, III, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA, Jr., et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol* 2004;22(14):2918-26.

34. Katabira ET. Epidemiology and management of diarrheal disease in HIV-infected patients. *Int J Infect Dis* 1999;3(3):164-7.

35. Beal JA, Martin BM, Ballen K. The clinical management of wasting and malnutrition in HIV/AIDS. *AIDS Patient Care* 1995;9(2):66-74.

36. Inflammatory bowel disease. In: Kasper DL, editor. *Harrison's principles of internal medicine*. 16th ed. New York: McGraw-Hill, Medical Pub. Division; 2005. p.1776-89.

37. Cooper JC, Williams NS, King RF, Barker MC. Effects of a long-acting somatostatin analogue in patients with severe ileostomy diarrhoea. *Br J Surg* 1986;73(2):128-31.

38. Blum HE. Treatment of hepatocellular carcinoma. *Best Pract Res Clin Gastroenterol* 2005;19(1):129-45.

39. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42(5):1208-36.

40. Llovet JM. Updated treatment approach to hepatocellular carcinoma. *J Gastroenterol* 2005;40(3):225-35.

41. Stuart KE. Systemic treatment for advanced hepatocellular carcinoma. In: *UpToDate* [database online]. Version 16.1. Waltham (MA): UpToDate; 2008.

42. Llovet J, Ricci S, Mazzaferro V, Hilgard P, Raoul J, Zeuzem S, et al. Sorafenib improves survival in advanced Hepatocellular Carcinoma (HCC): results of a Phase III randomized placebo-controlled trial (SHARP trial) [abstract]. *J Clin Oncol* 2007;25(18 Suppl):LBA1. 2007 ASCO Annual Meeting Proceedings Part I. Available: http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=32716 (accessed 2008 Apr 23).

43. Rosenberg L. Pancreatic cancer: does octreotide offer any promise? *Chemotherapy* 2001;47(Suppl 2):134-49.

44. Pancreatic cancer. In: Kasper DL, editor. *Harrison's principles of internal medicine*. 16th ed. New York: McGraw-Hill, Medical Pub. Division; 2005. p.537-9.

45. Burch PA, Block M, Schroeder G, Kugler JW, Sargent DJ, Braich TA, et al. Phase III evaluation of octreotide versus chemotherapy with 5-fluorouracil or 5-fluorouracil plus leucovorin in advanced exocrine pancreatic cancer: a North Central Cancer Treatment Group study. *Clin Cancer Res* 2000;6(9):3486-92. Available: http://clincancerres.aacrjournals.org/cgi/reprint/6/9/3486?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&author1=burch&titleabstract=phase&searchid=1&FIRSTINDEX=0&volume=6&fdate=1/1/2000&tdate=12/31/2001&resourcetype=HWCIT (accessed 2008 Jan 31).

46. Burris HA, III, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15(6):2403-13.

47. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007;25(15):1960-6.

48. Cascinu S, Del Ferro E, Catalano G. A randomised trial of octreotide vs best supportive care only in advanced gastrointestinal cancer patients refractory to chemotherapy. *Br J Cancer* 1995;71(1):97-101.

49. Hussain K. Congenital hyperinsulinism. *Semin Fetal Neonatal Med* 2005;10(4):369-76.

50. Thornton PS. Congenital Hyperinsulinism. In: *Sur1.org: the website for families of children with hyperinsulinism*. Palm Springs (CA): Sur1.org; 2007. Available: http://www.sur1.org/hyperinsulism.htm (accessed 2008 Jan 31).

51. Nestorowicz A, Glaser B, Wilson BA, Shyng SL, Nichols CG, Stanley CA, et al. Genetic heterogeneity in familial hyperinsulinism. *Hum Mol Genet* 1998;7(7):1119-28. Available: http://hmg.oxfordjournals.org/cgi/reprint/7/7/1119 (accessed 2008 Jan 31).

52. Mathew PM, Young JM, bu-Osba YK, Mulhern BD, Hammoudi S, Hamdan JA, et al. Persistent neonatal hyperinsulinism. *Clin Pediatr (Phila)* 1988;27(3):148-51.

53. Menni F, de LP, Sevin C, Touati G, Peigne C, Barbier V, et al. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. *Pediatrics* 2001;107(3):476-9.

54. Meissner T, Wendel U, Burgard P, Schaetzle S, Mayatepek E. Long-term follow-up of 114 patients with congenital hyperinsulinism. *Eur J Endocrinol* 2003;149(1):43-51.

55. Kane C, Lindley KJ, Johnson PR, James RF, Milla PJ, ynsley-Green A, et al. Therapy for persistent hyperinsulinemic hypoglycemia of infancy. Understanding the responsiveness of β cells to diazoxide and somatostatin. *J Clin Invest* 1997;100(7):1888-93. Available: http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=508376&blobtype=pdf (accessed 2008 Jan 31).

56. Thornton PS, Alter CA, Katz LE, Baker L, Stanley CA. Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. *J Pediatr* 1993;123(4):637-43.

57. Kusuhara K, Kusunoki M, Okamoto T, Sakanoue Y, Utsunomiya J. Reduction of the effluent volume in high-output ileostomy patients by a somatostatin analogue, SMS 201-995. *Int J Colorectal Dis* 1992;7(4):202-5.

58. Ladefoged K, Christensen KC, Hegnhøj J, Jarnum S. Effect of a long acting somatostatin analogue SMS 201-995 on jejunostomy effluents in patients with severe short bowel syndrome. *Gut* 1989;30(7):943-9.

59. Short bowel syndrome. In: Kasper DL, editor. *Harrison's principles of internal medicine*. 16th ed. New York: McGraw-Hill, Medical Pub. Division; 2005. p.1773.

60. Octreotide acetate. In: McEvoy GK, editor. *AHFS drug information*. Bethesda (MD): American Society of Health-System Pharmacists; 2005. p.3741-4.

61. Arnold R, Simon B, Wied M. Treatment of neuroendocrine GEP tumours with somatostatin analogues: a review. *Digestion* 2000;62 Suppl 1:84-91.

62. Jenkins SA, Kynaston HG, Davies ND, Baxter JN, Nott DM. Somatostatin analogs in oncology: a look to the future. *Chemotherapy* 2001;47 Suppl 2:162-96.

63. Octreotide. In: *Notice of compliance database* [database online]. Ottawa: Therapeutic Products Directorate, Health Canada; 2007. Available: http://www.nocdatabase.ca (accessed 2008 Jan 31).

64. Alberta Health and Wellness. *Interactive drug benefit list* [database online]. Edmonton: Alberta Ministry of Health and Wellness; 2007. Available: http://www.ab.bluecross.ca/dbl/idbl_main1.html (accessed 2008 Jun 18).

65. Canadian Agency for Drugs and Technologies in Health. *CEDAC final recommendation and reasons for recommendation for lanreotide acetate (Somatuline® Autogel®)*. Ottawa: The Agency; 2007. Available: http://www.cadth.ca/media/cdr/complete/cdr_complete_Somatuline-Autogel_July-19_2007.pdf (accessed 2008 Jan 31).

66. Somatuline® Autogel®. In: *Notice of compliance database* [database online]. Ottawa: Therapeutic Products Directorate, Health Canada; 2007. Available: http://www.nocdatabase.ca (accessed 2008 Jan 31).

67. WHO Collaborating Centre for Drug Statistics Methodology. *ATC/DDD Index 2007* [database online]. Oslo: The Centre; 2007. Available: http://www.whocc.no/atcddd/ (accessed 2008 Jan 31).

68. *Summary basis of decision Somatuline® Autogel®: 60 mg, 90 mg, 120 mg lanreotide / unit (syringe) extended-release supersaturated solution*
Ipsen Limited submission control No. 098949. Ottawa: Therapeutic Products Directorate, Health Canada; 2007. Available: http://cpe0013211b4c6d-cm0014e88ee7a4.cpe.net.cable.rogers.com/NocWeb/viewdoce.jsp?doc=Sebifcgdllh (accessed 2008 Jan 31).

69. Stilamin®. In: *Notice of compliance database* [database online]. Ottawa: Therapeutic Products Directorate, Health Canada; 2007. Available: http://www.nocdatabase.ca/ (accessed 2008 Jan 31).

70. Khan KS, ter Riet G, Glanville J, owden AJ, Kleijnen J, editors. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews*. 2nd ed. York (UK): NHS Centre for Reviews and Dissemination, University of York; 2001. CRD report no 4. Available: http://www.york.ac.uk/inst/crd/report4.htm.

71. Shea B, Dubé C, Moher D. Assessing the quality of reports of systematic reviews: the QUOROM statement compared to other tools. In: Egger M, Smith GD, Altman DG, editors. *Systematic reviews in health care: meta-analysis in context*. 2nd ed. London: BMJ Publishing Group; 2001. p.122-39.

72. Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Clinical safety data management: definitions and standards for expedited reporting. *Fed Regist* 1995;60(40):11284-7.

73. *TrialStat! SRS* [computer program]. Version 4.0. Ottawa: TrialStat; 2001.

74. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17(1):1-12.

75. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273(5):408-12.

76. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions 4.2.6 [updated September 2006]*. Chichester (UK): John Wiley & Sons; 2006. Available: http://www.cochrane.org/resources/handbook/Handbook4.2.6Sep2006.pdf (accessed 2008 Jan 31).

77. *Review manager (RevMan)* [computer program]. Version 4.2.10 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2003.

78. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-60.

79. *Visual Rx* [computer program]. Version 2.0; 2004.

80. *SPSS* [computer program]. Version 16.0. Chicago: SPSS; 2007.

81. Freda PU, Katznelson L, van der Lely AJ, Reyes CM, Zhao S, Rabinowitz D. Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. *J Clin Endocrinol Metab* 2005;4465-73. Available: http://jcem.endojournals.org/cgi/reprint/90/8/4465 (accessed 2008 Jan 31).

82. Melmed S, Sternberg R, Cook D, Klibanski A, Chanson P, Bonert V, et al. Clinical review: a critical analysis of pituitary tumor shrinkage during primary medical therapy in acromegaly. *J Clin Endocrinol Metab* 2005;4405-10. Available: http://jcem.endojournals.org/cgi/reprint/90/7/4405 (accessed 2008 Jan 31).

83. Moore D, Meads C, Roberts L, Song F. *The effectiveness and cost-effectiveness of somatostatin analogues in the treatment of acromegaly*. Updated. Birmingham (UK): West Midlands Development and Evaluation Service, University of Birmingham; 2002. Available: http://www.rep.bham.ac.uk/2002/Acromegaly.pdf (accessed 2008 Jul 16).

84. D'Amico G, Pietrosi G, Tarantino I, Pagliaro L. Emergency sclerotherapy versus vasoactive drugs for variceal bleeding in cirrhosis: a Cochrane meta-analysis. *Gastroenterology* 2003;124(5):1277-91.

85. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. In: *Cochrane Database of Systematic Reviews 2008 Issue 2*. Chichester (UK): John Wiley & Sons; 2003. DOI: 10.1002/14651858.CD002147.

86. Banares R, Albillos A, Rincon D, Alonso S, Gonzalez M, Ruiz-del-Arbol L, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. *Hepatology* 2002;35(3):609-15.

87. Corley DA, Cello JP, Adkisson W, Ko WF, Kerlikowske K. Octreotide for acute esophageal variceal bleeding: a meta-analysis. *Gastroenterology* 2001;120(4):946-54.

88. Gøtzsche PC. Somatostatin analogues for acute bleeding oesophageal varices. In: *Cochrane Database of Systematic Reviews 2005 Issue 1*. Chichester (UK): John Wiley & Sons; 2005. DOI: 10.1002/14651858.CD000193.

89. Gross M, Schiemann U, Mühlhöfer A, Zoller WG. Meta-analysis: efficacy of therapeutic regimens in ongoing variceal bleeding. *Endoscopy* 2001;33(9):737-46.

90. D'Amico G, Pietrosi G, Tarantino I, Pagliaro L. Emergency sclerotherapy versus medical interventions for bleeding oesophageal varices in cirrhotic patients. In: *Cochrane Database of Systematic Reviews 2008 Issue 2*. Chichester (UK): John Wiley & Sons; 2002. DOI: 10.1002/14651858.CD002233.

91. Erstad BL. Octreotide for acute variceal bleeding. *Ann Pharmacother* 2001;35(5):618-26.

92. Szilagyi A, Shrier I. Systematic review: the use of somatostatin or octreotide in refractory diarrhoea. *Aliment Pharmacol Ther* 2001;15(12):1889-97.

93. Major P, Figueredo A, Tandan V, Bramwell V, Charette M, Oliver T. Role of octreotide in the management of patients with cancer. *Curr Oncol* 2003;10(3):161-79.

94. Connor S, Alexakis N, Garden OJ, Leandros E, Bramis J, Wigmore SJ. Meta-analysis of the value of somatostatin and its analogues in reducing complications associated with pancreatic surgery. *Br J Surg* 2005;92(9):1059-67.

95. Li-Ling J, Irving M. Somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of enterocutaneous pancreatic fistulas: a systematic review of randomized controlled trials. *Br J Surg* 2001;88(2):190-9.

96. Mercadante S, Casuccio A, Mangione S. Medical treatment for inoperable malignant bowel obstruction: a qualitative systematic review. *J Pain Symptom Manage* 2007;33(2):217-23.

97. Zeng Q, Zhang Q, Han S, Yu Z, Zheng M, Zhou M, et al. Efficacy of somatostatin and its analogues in prevention of postoperative complications after pancreaticoduodenectomy: a meta-analysis of randomized controlled trials. *Pancreas* 2008;36(1):18-25.

98. Alghamdi AA, Jawas AM, Hart RS. Use of octreotide for the prevention of pancreatic fistula after elective pancreatic surgery: a systematic review and meta-analysis. *Can J Surg* 2007;50(6):459-66.

99. Silva G, Quera R, Fluxá F, Sanhueza E, Segovia R, Brahm J, et al. Octreótido, tratamiento endoscópico o ambos en la hemorragia variceal activa en pacientes cirróticos: estudio multicéntrico [Octreotide administration and/or endoscopic treatment in cirrhotic patients with acute variceal bleeding: a multicentric study]. *Rev Med Chil* 2004;132(3):285-94. Available: http://www.scielo.cl/pdf/rmc/v132n3/art02.pdf (accessed 2008 Jan 31).

100. Cho SB, Park KJ, Lee JS, Lee WS, Park CH, Joo YE, et al. Comparison of terlipressin and octreotide with variceal ligation for controlling acute esophageal variceal bleeding--a randomized prospective study [in Korean]. *Korean J Hepatol* 2006;12(3):385-93. Available: http://www.kasl.org/JournalSearch_index.asp?year=2006&page=385&vol=12&iss=3 (accessed 2008 Jan 31).

101. Rao ZH. The clinical observation of treating the rupture and bleeding of vein varicose of esophagus and the bottom of stomach with Sandostatin [in Chinese]. *Hainan Medical Journal* 2004;15(3):3-4.

102. Besson I, Ingrand P, Person B, Boutroux D, Heresbach D, Bernard P, et al. Association sclerose endoscopique et octreotide dans le traitement d'urgence et al prevention de la recidive precoce de la rupture de varices œsocardiales: resultats d'une étude multicentrique en double aveugle. *Gastroenterol Clin Biol* 1995;19(2 bis):A9.

103. Li SL, Wang MC, Gong LB. A clinical study of octreotide in the treatment of bleeding of esophageal and gastric varices [in Chinese]. *Chin J Crit Care Med* 1996;16(2):10-2.

104. Liu XM, Song GP. Cure of esophageal gastro-varices bleeding by sandostatin shitaning and pitutrin.a control study [in Chinese]. *Chin J Pract Intern Med* 1998;18(1):29-30.

105. Ruan JJ. Therapeutic observation of Octreotide on bleeding of varices rupture of esophogus [in Chinese]. *Zhong Xi Yi Jie He Gan Bing Za Zhi* 2000;10(1):53-4.

106. Song Y, Wu KC, Fan DM, Hu JL, Zhang HB, Sun AH, et al. Octreotide in treatment of 12 patients with hemorrhage for esophageal varices [in Chinese]. *Chin J New Gastroenterol* 1996;4(12):716-7.

107. Xu LS, Zhang YL, Zhang JG, Chen MD, Wang C. Octreotide in treatment of 18 patients with hemorrhage of rupture of esophageal varices [in Chinese]. *Chin J New Gastroenterol* 1996;4(10):592.

108. Xu XY, Zhang SQ. Comparison of sandostatin with dual-bag and three cavity stomach catheter and pituitrin in management of esophageal varices bleeding [in Chinese]. *J Clin Intern Med* 1998;15(6):330-2.

109. Xu YC, Wang GL, Shen J, Wu XN. Clinical study on octreotide treatment of esophageal varices [in Chinese]. *Zhonghua xiao hua za zhi* 1993;13(5):302-3.

110. Yan J, Xu HP. Comparison of 3 treatment effects for esophageal and gastric varices [in Chinese]. *Acta Acad Med Suzhou* 1997;17(5):944-5.

111. Zheng GA, Ye XY. Clinical observation of Sandostatin curing bleeding with esophagus bursting by varicosity [in Chinese]. *Jing Gang Shan Yi Yuan Xue Bao* 2001;8(3):44-5.

112. Zhu B, Zhang P, Qiao HC. Clinical observation on sandostatin and vasopessin in treatment of esophageal varices bleeding [in Chinese]. *Xin Xiang Yi Xue Yuan Xue Bao* 2002;19(5):401-2.

113. Ruszniewski P, Bommelaer G, Rougier P, Wemeau JL, Zeitoun P, Catus F, et al. Lanréotide (lan) versus octréotide (oct) dans le traitement du syndrome carcinoide (sc): étude prospective multicentrique chez 33 patients (pts). *Gastroenterol Clin Biol* 1997;21(2):A162.

114. Associations de recherche en chirurgie ARC, Fourtanier G. Intérèt de l'octréotide dans la prévention des complications chirurgicales post opératoires après pancréatectomie - étude prospective randomisée multiculturique. *Gastroenterol Clin Biol* 1997;21(2 bis):A64.

115. Habib E, Elhadad A, Fourtanier G, Chipponi J, Faniez PL, Hay JM, et al. Place de l'octréotide dans la prévention des complications chirurgicales après pancréatectomie. Étudie contrôlée multicentrique. *Ann Chir* 1998;52(7):671-2.

116. Pezzella G, Pisconti S. Octreotide verso loperamide nel controllo della diarrea indotta da chemioterapia [Octreotide versus loperamide in controlling chemotherapy-induced diarrhoea]. *G Ital Oncol* 1994;14(2):79-82.

117. Chevrel B. Carcinoides et vipomas. Étude Multicentrique Europe-États-Unis de la Sandostatine. *Med Chir Dig* 1989;18(8):489-92.

118. Ripamonti C, Mercadante S, Groff L, Zecca E, De Conno F, Casuccio A. Role of octreotide, scopolamine butylbromide, and hydration in symptom control of patients with inoperable bowel obstruction and nasogastric tubes: a prospective randomized trial. *J Pain Symptom Manage* 2000;19(1):23-34.

119. Beaugerie L, Baumer P, Chaussade S, Berard H, Rozenbaum W, Pialoux G, et al. Treatment of refractory diarrhoea in AIDS with acetorphan and octreotide: a randomized crossover study. *Eur J Gastroenterol Hepatol* 1996;8(5):485-9.

120. Lémann M, de Montigny S, Mahé S, Thuillier F, Huneau JF, Tomé D, et al. Effect of octreotide on fluid and electrolyte losses, nutrient absorption and transit in short bowel syndrome. *Eur J Gastroenterol Hepatol* 1993;5(10):817-22.

121. Shaffer JI, Hanrahan T, Rowntree S, Shipley K, Irving MH. Does somatostatin analogue (SMS 201-995) reduce high output stoma effluent? A controlled trial [abstract]. *Gut* 1988;29 Suppl 10:A1432-A1433.

122. Rodrigues CA, Lennard-Jones JE, Thompson DG, Farthing MJ. The effects of octreotide, soy polysaccharide, codeine and loperamide on nutrient, fluid and electrolyte absorption in the short-bowel syndrome. *Aliment Pharmacol Ther* 1989;3(2):159-69.

123. Chiodini PG, Cozzi R, Dallabonzana D. Medical treatment of acromegely with SMS 201-995, a somatostatin analog: a comparison with bromocriptine. *J Clin Endocrinol Metab* 1987;64(3):447-53.

124. Xiao V, Pho M, Aggarwal A, Wedlund P, Chow W, Liu W, et al. A genotyping method for human cytochrome P450 genes CYP2D6 and CYP2C19 based on oligonucleotide hybridization. *Pharm Res* 1997;14(11 Suppl):S211.

125. van der Hoek J, van der Lelij AJ, Feelders RA, de Herder WW, Uitterlinden P, Poon KW, et al. The somatostatin analogue SOM230, compared with octreotide, induces differential effects in several metabolic pathways in acromegalic patients. *Clin Endocrinol (Oxf)* 2005;63(2):176-84.

126. Looij BJ, Roelfsema F, Frölich M. The effect of calcitonin on growth hormone secretion in acromegaly. *Clin Endocrinol (Oxf)* 1989;31(5):573-9.

127. Lombardi G, Colao A, Ferone D, Sarnacchiaro F, Marzullo P, Di SA, et al. CV 205-502 treatment in therapy-resistant acromegalic patients. *Eur J Endocrinol* 1995;132(5):559-64.

128. Wass JA, Lytras N, Besser GM. Somatostatin octapeptide (SMS 201-995) in the medical treatment of acromegaly. *Scand J Gastroenterol Suppl* 1986;119:136-40.

129. Lamberts SW, Zweens M, Verschoor L, del PE. A comparison among the growth hormone-lowering effects in acromegaly of the somatostatin analog SMS 201-995, bromocriptine, and the combination of both drugs. *J Clin Endocrinol Metab* 1986;63(1):16-9.

130. Treiber G, Röcken C, Wex T, Malfertheiner P. Octreotide alone or in combination with rofecoxib as palliative treatment for advanced hepatocellular cancer. *Z Gastroenterol* 2007;45(5):369-77.

131. Treiber G, Heinrich U, Fostitsch P, Roecken C, Malfertheiner P. Palliative treatment of hepatocellular carcinoma (HCC) using octreotide, rofecoxib, or both [abstract]. Proceedings of the American Society of Clinical Oncology. 39th Annual Meeting of the American Society of Clinical Oncology; 2003 May 31; Chicago (IL). Abstract No. 1281. Available: http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=23&abstractID=101467 (accessed 2008 Apr 29).

132. Alexopoulou O, Abrams P, Verhelst J, Poppe K, Velkeniers B, Abs R, et al. Efficacy and tolerability of lanreotide Autogel therapy in acromegalic patients previously treated with octreotide LAR. *Eur J Endocrinol* 2004;151(3):317-24. Available: http://www.eje-online.org/cgi/reprint/151/3/317 (accessed 2008 Jan 31).

133. Cozzi R, Dallabonzana D, Attanasio R, Barausse M, Oppizzi G. A comparison between octreotide-LAR and lanreotide-SR in the chronic treatment of acromegaly. *Eur J Endocrinol* 1999;141(3):267-71.

134. de Herder WW, Uitterlinden P, van der Lely AJ, Hofland LJ, Lamberts SW. Octreotide, but not bromocriptine, increases circulating insulin-like growth factor binding protein 1 levels in acromegaly. *Eur J Endocrinol* 1995;133(2):195-9.

135. Kaal A, Frystyk J, Skjaerbaek C, Nielsen S, Jørgensen JOL, Bruns C, et al. Effects of intramuscular microsphere-encapsulated octreotide on serum growth hormone, insulin-like growth factors (IGFs), free IGFs, and IGF- binding proteins in acromegalic patients. *Metab Clin Exper* 1995;44(1 Suppl 1):6-14.

136. Kendall-Taylor P, Miller M, Gebbie J, Turner S, Al-Maskari M. Long-acting octreotide LAR compared with lanreotide SR in the treatment of acromegaly. *Pituitary* 2000;3(2):61-5.

137. Moon HJ, Heo JS, Choi SH, Joh JW, Choi DW, Kim YI. The efficacy of the prophylactic use of octreotide after a pancreaticoduodenectomy. *Yonsei Med J* 2005;46(6):788-93. Available: http://www.eymj.org/2005/pdf/12788.PDF (accessed 2008 Jan 31).

138. Morange I, De Boisvilliers F, Chanson P, Lucas B, Dewailly D, Catus F, et al. Slow release lanreotide treatment in acromegalic patients previously normalized by octreotide. *J Clin Endocrinol Metab* 1994;79(1):145-51.

139. Nakatsuka A, Yamaguchi K, Chijiiwa K, Tanaka M. Octreotide inhibits pancreatic exocrine secretion and prevents pancreatoenterostomy leakage. *Int Surg* 2000;85(2):124-9.

140. Popiela T, Kedra B, Sierzega M, Gurda A. Risk factors of pancreatic fistula following pancreaticoduodenectomy for periampullary cancer. *Hepatogastroenterology* 2004;51(59):1484-8.

141. Razzore P, Colao A, Baldelli R, Gaia D, Marzullo P, Ferretti E, et al. Comparison of six months therapy with octreotide versus lanreotide in acromegalic patients: a retrospective study. *Clin Endocrinol (Oxf)* 1999;51(2):159-64.

142. Ronchi C, Epaminonda P, Cappiello V, Beck-Peccoz P, Arosio M. Effects of two different somatostatin analogs on glucose tolerance in acromegaly. *J Endocrinol Invest* 2002;25(6):502-7.

143. Turner HE, Vadivale A, Keenan J, Wass JA. A comparison of lanreotide and octreotide LAR for treatment of acromegaly. *Clin Endocrinol (Oxf)* 1999;51(3):275-80.

144. Van Liessum PA, Pieters GF, Smals AG, Hermus AR, Benraad TJ, Kloppenborg PW. Single-dose response study of the somatostatin analogue octreotide in acromegaly. *Acta Endocrinol (Copenh)* 1989;121(5):714-20.

145. van Thiel SW, Romijn JA, Biermasz NR, Ballieux BEPM, Frolich M, Smit JWA, et al. Octreotide long-acting repeatable and lanreotide Autogel are equally effective in controlling growth hormone secretion in acromegalic patients. *Eur J Endocrinol* 2004;150(4):489-95.

146. Wagenaar AH, Harris AG, van der Lely AJ, Lamberts SW. Dynamics of the acute effects of octreotide, bromocriptine and both drugs in combination on growth hormone secretion in acromegaly. *Acta Endocrinol (Copenh)* 1991;125(6):637-42.

147. Amato G, Mazziotti G, Rotondi M, Iorio S, Doga M, Sorvillo F, et al. Long-term effects of lanreotide SR and octreotide LAR® on tumour shrinkage and GH hypersecretion in patients with previously untreated acromegaly. *Clin Endocrinol (Oxf)* 2002;56(1):65-71.

148. Jenkins PJ, Akker S, Chew SL, Besser GM, Monson JP, Grossman AB. Optimal dosage interval for depot somatostatin analogue therapy in acromegaly requires individual titration. *Clin Endocrinol (Oxf)* 2000;53(6):719-24.

149. Chanson P, Boerlin V, Ajzenberg C, Bachelot Y, Benito P, Bringer J, et al. Comparison of octreotide acetate LAR and lanreotide SR in patients with acromegaly. *Clin Endocrinol (Oxf)* 2000;53(5):577-86 (accessed 2005 Jun 30).

150. Colao A, Ferone D, Cappabianca P, Del Basso De Caro M, Marzullo P, Monticelli A, et al. Effect of octreotide pretreatment on surgical outcome in acromegaly. *J Clin Endocrinol Metab* 1997;82(10):3308-14.

151. Hansen TB, Gram J, Bjerre P, Hagen C, Bollerslev J. Body composition in active acromegaly during treatment with octreotide: a double-blind, placebo-controlled cross-over study. *Clin Endocrinol (Oxf)* 1994;41(3):323-9.

152. Andersen M, Hansen TB, Bollerslev J, Bjerre P, Schrøder HD, Hagen C. Effect of 4 weeks of octreotide treatment on prolactin, thyroid stimulating hormone and thyroid hormones in acromegalic patients. A double blind placebo-controlled cross-over study. *J Endocrinol Invest* 1995;18(11):840-6.

153. Ezzat S, Kontogeorgos G, Redelmeier DA, Horvath E, Harris AG, Kovacs K. In vivo responsiveness of morphological variants of growth hormone-producing pituitary adenomas to octreotide. *Eur J Endocrinol* 1995;133(6):686-90.

154. Ezzat S, Snyder PJ, Young WF, Boyajy LD, Newman C, Klibanski A, et al. Octreotide treatment of acromegaly. A randomized, multicenter study. *Ann Intern Med* 1992;117(9):711-8.

155. Fredstorp L, Harris A, Haas G, Werner S. Short term treatment of acromegaly with the somatostatin analog octreotide: the first double-blind randomized placebo-controlled study on its effects. *J Clin Endocrinol Metab* 1990;71(5):1189-94.

156. Fredstorp L, Werner S. Growth hormone and insulin-like growth factor-1 in blood and urine as response markers during treatment of acromegaly with octreotide: a double-blind placebo-controlled study. *J Endocrinol Invest* 1993;16(4):253-8.

157. Fredstorp L, Werner S, Bang P, Hall K. Inverse correlation between insulin-like growth factor binding protein-1 and insulin in patients with acromegaly during treatment with the somatostatin analogue octreotide. *Clin Endocrinol (Oxf)* 1994;41(4):495-501.

158. Halse J, Harris AG, Kvistborg A, Kjartansson O, Hanssen E, Smiseth O, et al. A randomized study of SMS 201-995 versus bromocriptine treatment in acromegaly: clinical and biochemical effects. *J Clin Endocrinol Metab* 1990;70(5):1254-61.

159. Colao A, Bouterfa H, Cappabianca P, Caron P, De Menis E, Farrall A, et al. A prospective, randomized study comparing octreotide LAR with surgical therapy in previously untreated acromegalic patients [abstract]. ENDO 2006, Endocrine Society 88th Annual Meeting; 2004 Jun 24; Boston (accessed 2006 Sep 12).

160. van der Hoek J, de Herder WW, Feelders RA, van der Lely AJ, Uitterlinden P, Boerlin V, et al. A single-dose comparison of the acute effects between the new somatostatin analog SOM230 and octreotide in acromegalic patients. *J Clin Endocrinol Metab* 2004;89(2):638-45.

161. Catnach SM, Anderson JV, Fairclough PD, Trembath RC, Wilson PAJ, Parker E, et al. Effect of octreotide on gall stone prevalence and gall bladder motility in acromegaly. *Gut* 1993;34(2):270-3.

162. Schmidt K, Leuschner M, Harris AG, Althoff PH, Jacobi V, Jungmann E, et al. Gallstones in acromegalic patients undergoing different treatment regimens. *Clin Investig* 1992;70(7):556-9.

163. Zhu XF, Harris AG, Yang MF, Shi YF, Zhou Q, Xu JY, et al. Effect of octreotide on dynamic excretion of bile in Chinese acromegalic patients assessed by [^{99m}Tc]EHIDA hepatobiliary scan. *Dig Dis Sci* 1994;39(2):284-8.

164. Kristof RA, Stoffel-Wagner B, Klingmüller D, Schramm J. Does octreotide treatment improve the surgical results of macro-adenomas in acromegaly? A randomized study. *Acta Neurochir (Wien)* 1999;141(4):399-405.

165. International Octreotide Varices Study Group. Double blind RCT of 5 day octreotide versus placebo, associated with sclerotherapy for trial/failures [abstract]. *Hepatology* 1996;24(4 Part 2):352A.

166. El Sayed SS, Farag FM, Abo Elmagd M, Wali H, Shiha G. Sandostatin in the control of bleeding oesophageal varices: a randomized controlled clinical trial [abstract]. *Endoscopy* 1995;27(7):S41.

167. Besson I, Ingrand P, Person B, Boutroux D, Heresbach D, Bernard P, et al. Sclerotherapy with or without octreotide for acute variceal bleeding. *N Engl J Med* 1995;333(9):555-60.

168. Morales GF, Pereira Lima JC, Hornos AP, Marques DL, Costa CS, Lima PL, et al. Octreotide for esophageal variceal bleeding treated with endoscopic sclerotherapy: a randomized, placebo-controlled trial. *Hepatogastroenterology* 2007;54(73):195-200.

169. Farooqi JI, Farooqi RJ, Haq N, Siddiq UR, Mahmood S. Treatment and outcome of variceal bleeding - a comparison of two methods. *J Coll Physicians Surg Pak* 2000;10(4):131-3.

170. Primignani M, Andreoni B, Carpinelli L, Capria A, Rocchi G, Lorenzini I, et al. Sclerotherapy plus octreotide versus sclerotherapy alone in the prevention of early rebleeding from esophageal varices: a randomized, double-blind, placebo-controlled, multicenter trial. *Hepatology* 1995;21(5):1322-7.

171. Shah HA, Mumtaz K, Jafri W, Abid S, Hamid S, Ahmad A, et al. Sclerotherapy plus octreotide versus sclerotherapy alone in the management of gastro-oesophageal variceal hemorrhage. *J Ayub Med Coll Abbottabad* 2005;17(1):10-4.

172. Shiha G, Hamid M, El-Said SS, Farag FM, Azzam F, Askalany H. Octreotide infusion plus emergency sclerotherapy versus sclerotherapy alone for the control of bleeding esophageal varices: a prospective randomized clinical trial. *Mansoura Medical Journal* 1996;26(1-2):109-21.

173. Signorelli S, Negrini F, Paris B, Bonelli M, Girola M. Sclerotherapy with or without somatostatin or octreotide in the treatment of acute variceal haemorrhage: our experience [abstract]. *Gastroenterology* 1996;110(4):A1326.

174. Signorelli S, Paris B, Negrini F, Bonelli M, Auriemma L. Esophageal varices bleeding: comparison between treatment with sclerotherapy alone vs sclerotherapy plus octreotide [abstract]. *Hepatology* 1997;26(4 Pt 2):137A.

175. Souza FC, Arantes V, Cambraia RD, Cangussu LOF, Couto OFM, Teixeira R. Randomized, double blind, trial of octreotide plus endoscopic treatment in controlling gastroesophageal variceal bleeding. *J Hepatol* 2003;38 Suppl 2:70-1.

176. Zuberi BF, Baloch Q. Comparison of endoscopic variceal sclerotherapy alone and in combination with octreotide in controlling acute variceal hemorrhage and early rebleeding in patients with low-risk cirrhosis. *Am J Gastroenterol* 2000;95(3):768-71.

177. Abd-Elrazek W, Omar N, Khalil M, Waked I, Saleh SM. Urgent endoscopy vs. octreotide in the management of acute variceal bleeding in patients with advanced encephalopathy [abstract]. 40th Annual Meeting of the European Association for the Study of the Liver; 2005 Apr 13; Paris. Available: http://www.kenes.com/easl2005sci/program/abstracts/226.doc (accessed 2008 Jan 31).

178. Freitas DS, Sofia C, Pontes JM, Gregório C, Cabral JP, Andrade P, et al. Octreotide in acute bleeding esophageal varices: a prospective randomized study. *Hepatogastroenterology* 2000;47(35):1310-4.

179. Jenkins SA, Shields R, Davies M, Elias E, Turnbull AJ, Bassendine MF, et al. A multicentre randomised trial comparing octreotide and injection sclerotherapy in the management and outcome of acute variceal haemorrhage. *Gut* 1997;41(4):526-33. Available: http://gut.bmjjournals.com/cgi/reprint/41/4/526 (accessed 2008 Jan 31).

180. Sivri B, Oksuzoglu G, Bayraktar Y, Kayhan B. A prospective randomized trial from Turkey comparing octreotide versus injection sclerotherapy in acute variceal bleeding. *Hepatogastroenterology* 2000;47(31):168-73.

181. Sung JJ, Chung SC, Lai CW, Chan FK, Leung JW, Yung MY, et al. Octreotide infusion or emergency sclerotherapy for variceal haemorrhage. *Lancet* 1993;342(8872):637-41.

182. Sung JJ, Chung SC, Yung MY, Lai CW, Lau JY, Lee YT, et al. Prospective randomised study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. *Lancet* 1995;346(8991-8992):1666-9.

183. Bildozola M, Kravetz D, Argonz J, Romero G, Suarez A, Jmelnitzky A, et al. Efficacy of octreotide and sclerotherapy in the treatment of acute variceal bleeding in cirrhotic patients. A prospective, multicentric, and randomized clinical trial. *Scand J Gastroenterol* 2000;35(4):419-25.

184. El-Jackie A, Rowaisha I, Waked I, Saleh S, Ghaffar YA. Octreotide vs. sclerotherapy in the control of acute variceal bleeding in schistosomal portal hypertension: a randomized trial [abstract]. *Hepatology* 1998;28(4 Pt 2):553A.

185. Lopez F, Vargas R, Guerrero M, Rizo T, Arguelles D. Octreotide vs sclerotherapy in the treatment of acute variceal bleeding. Final report of a prospective study. [abstract]. *Hepatology* 1999;30:574A.

186. Poo JL, Bosques F, Garduño R, Marin E, Morán MA, Bobadilla J, et al. Octreotide versus emergency sclerotherapy in acute variceal hemorrhage in liver cirrhosis. A randomized, multicenter study [abstract]. *Gastroenterology* 1996;110(4 Suppl):A1297.

187. Shaikh WM, Shaikh SM, Saikh MA, Solangi GA, Zuberi BF. A comparative study of efficacy of octreotide and sclerotherapy in variceal bleeding. *J Coll Physicians Surg Pak* 2002;12(11):677-81.

188. Yousuf MH, Rauf HA, Baig MI, Akram M, Rizwan Z. Initial management of acute variceal haemorrhage - comparison of octreotide and sclerotherapy. *J Coll Physicians Surg Pak* 2000;10(3):95-7.

189. McKee RF, Garden OJ, Anderson JR, Carter DC. A comparison of SMS 201-995 and oesophageal tamponade in the control of acute variceal haemorrhage. *HPB Surg* 1992;6(1):7-17.

190. Pedretti G, Elia G, Calzetti C, Magnani G, Fiaccadori F. Octreotide versus terlypressin in acute variceal hemorrhage in liver cirrhosis. Emergency control and prevention of early rebleeding. *Clin Investig* 1994;72(9):653-9.

191. Salih M, Hamid SS, Abid S, Mumtaz K, Shah HA, Abbas Z, et al. Efficacy and cost-effectiveness of terlipressin versus octreotide in bleeding esophageal varices in combination with endoscopic band ligation. *Hepatology* 2005;42(4 Suppl 1):211A.

192. Silvain C, Carpentier S, Sautereau D, Czernichow B, Métreau JM, Fort E, et al. Terlipressin plus transdermal nitroglycerin vs. octreotide in the control of acute bleeding from esophageal varices: a multicenter randomized trial. *Hepatology* 1993;18(1):61-5.

193. Huang CC, Sheen IS, Chu CM, Chuah SK, Chien RN, Peng SM, et al. A prospective randomized controlled trial of sandostatin and vasopressin in the management of acute bleeding esophageal varices. *Changgeng Yi Xue Za Zhi* 1992;15(2):78-83.

194. Hwang SJ, Lin HC, Chang CF, Lee FY, Lu CW, Hsia HC, et al. A randomized controlled trial comparing octreotide and vasopressin in the control of acute esophageal variceal bleeding. *J Hepatol* 1992;16(3):320-5.

195. Kusumobroto H, Djajapranata LI, Oesman N, Adi P, Nusi IA. Comparison of octreotide, vasopressin and SB tube for acute bleeding of esophageal varices. A prospective randomized trial [abstract]. *J Gastroenterol Hepatol* 1994;9(3):A34.

196. Zhang HB, Wong BC, Zhou XM, Guo XG, Zhao SJ, Wang JH, et al. Effects of somatostatin, octreotide and pitressin plus nitroglycerine on systemic and portal haemodynamics in the control of acute variceal bleeding. *Int J Clin Pract* 2002;56(6):447-51.

197. Vlachogiannakos J, Kougioumtzian A, Triantos C, Viazis N, Sgouros S, Manolakopoulos S, et al. Clinical trial: The effect of somatostatin vs. octreotide in preventing post-endoscopic increase in hepatic venous pressure gradient in cirrhotics with bleeding varices. *Aliment Pharmacol Ther* 2007;26(11-12):1479-87.

198. Kravetz D, Udaondo B, Posadas A. Octreotide vs sclerotherapy in the treatment of acute variceal bleeding. Prospective clinical controlled trial. Preliminary results. *Hepatology* 1996;24(4 Part 2):206A.

199. Cho SB, Lee WS, Park CH, Joo YE, Kim HS, Choi SK, et al. Comparison of terlipressin and octreotide as a combination therapy with endoscopic variceal ligitation in the control of acute esophageal variceal bleeding: a randomized, controlled study [abstract]. 41st Annual Meeting of the European Association for the Study of the Liver; 2006 Apr 26; Vienna.

200. Silvain C, Carpentier D, Metreau JM, Besson I, Ingrand P, Boyer J, et al. A randomized trial of glypressin plus transdermal nitroglycerin versus octreotide in the control of acute variceal hemorrhage a final report. *Gastroenterology* 1992;102(4 Pt 2):A889.

201. Fort E, Carpentier S, Sautereau D, Fratté S, Metreau JM, Ingrand P, et al. A randomized trial Of glypressin plus transdermal introglycerin versus octreotide in the control of acute variceal hemorrhage. *Eur J Gastroenterol Hepatol* 1991;3(Suppl):S99.

202. Silvain C, Carpentier S, Sautereau D, Fratté S, Metreau JM, Ingrand P, et al. A randomized trial of glypressin plus transdermal nitroglycerin versus octreotide in the control of acute variceal hemorrhage [abstract]. *Hepatology* 1991;14(4 Pt 2):133A.

203. McKee R. A study of octreotide in oesophageal varices. *Digestion* 1990;45 Suppl 1:60-5.

204. O'Toole D, Ducreux M, Bommelaer G, Wemeau JL, Bouche O, Catus F, et al. Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. *Cancer* 2000;88(4):770-6.

205. Ruszniewski P, Bommelaer G, Bouche O, Rougier P, Wemeau JL, Catus F, et al. Lanreotide (Lan) vs octreotide (Oct) in the treatment of the carcinoid syndrome (CS): a prospective multicentre crossover study [abstract]. *Gastroenterology* 1997;112(4 Suppl):A1183.

206. Rubin J, Ajani J, Schirmer W, Venook AP, Bukowski R, Pommier R, et al. Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. *J Clin Oncol* 1999;17(2):600-6.

207. Anthony LB. Long-acting formulations of somatostatin analogues. *Ital J Gastroenterol Hepatol* 1999;31 Suppl 2:S216-S218.

208. Saslow SB, O'Brien MD, Camilleri M, von der OM, Homburger HA, Klee GG, et al. Octreotide inhibition of flushing and colonic motor dysfunction in carcinoid syndrome. *Am J Gastroenterol* 1997;92(12):2250-6.

209. Jacobsen MB, Hanssen LE. Clinical effects of octreotide compared to placebo in patients with gastrointestinal neuroendocrine tumours. Report on a double-blind, randomized trial. *J Intern Med* 1995;237(3):269-75.

210. Öberg K, Norheim I, Theodorsson E, Ahlman H, Lundqvist G, Wide L. The effects of octreotide on basal and stimulated hormone levels in patients with carcinoid syndrome. *J Clin Endocrinol Metab* 1989;68(4):796-800.

211. Nikou GC, Dossios T, Samolada O, Bourlakis M, Kitsou E, Kiriaki D, et al. Treatment of metastatic carcinoids. Ten-year experience with octreotide. *Hellenic J Gastroenterol* 1996;9(4):317-21.

212. Hesse UJ, De DC, Houtmeyers P, Demetter P, Ceelen W, Pattyn P, et al. Prospectively randomized trial using perioperative low dose octreotide to prevent organ related and general complications following pancreatic surgery and pancreatico-jejunostomy. *Acta Chir Belg* 2005;105(4):383-7.

213. Hesse UJ, Meester D, Troisi R, Cathenis K, Lameire N, de Hemptinne B. The use of low dose octreotide prophylaxis in pancreatic transplants with enteric drainage. Results of a prospective randomized single center trial. *Clin Transplant* 2005;19(3):299-303.

214. Suc B, Msika S, Piccinini M, Fourtanier G, Hay JM, Flamant Y, et al. Octreotide in the prevention of intra-abdominal complications following elective pancreatic resection: a prospective, multicenter randomized controlled trial. *Arch Surg* 2004;139(3):288-94.

215. Yeo CJ, Cameron JL, Lillemoe KD, Sauter PK, Coleman J, Sohn TA, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. *Ann Surg* 2000;232(3):419-29.

216. Briceño Delgado FJ, López CP, Rufián PS, Solórzano PG, Miño FG, Pera MC. A prospective-randomized trial using Octreotide for prevention of complications following pancreaticoduodenectomy. *Rev Esp Enferm Dig* 1998;90(10):691-4.

217. Benedetti E, Coady NT, Asolati M, Dunn T, Stormoen BM, Bartholomew AM, et al. A prospective randomized clinical trial of perioperative treatment with octreotide in pancreas transplantation. *Am J Surg* 1998;175(1):14-7.

218. Montorsi M, Zago M, Mosca F, Capussotti L, Zotti E, Ribotta G, et al. Efficacy of octreotide in the prevention of pancreatic fistula after elective pancreatic resections: a prospective, controlled, randomized clinical trial. *Surgery* 1995;117(1):26-31.

219. Pederzoli P, Bassi C, Falconi M, Camboni MG, The Italian Study Group. Efficacy of octreotide in the prevention of complications of elective pancreatic surgery. *Br J Surg* 1994;81(2):265-9.

220. Stratta RJ, Taylor RJ, Lowell JA, Bynon JS, Cattral MS, Frisbie K, et al. Randomized trial of sandostatin prophylaxis for preservation injury after pancreas transplantation. *Transplant Proc* 1993;25(6):3190-2.

221. Lange JR, Steinberg SM, Doherty GM, Langstein HN, White DE, Shawker TH, et al. A randomized, prospective trial of postoperative somatostatin analogue in patients with neuroendocrine tumors of the pancreas. *Surgery* 1992;112(6):1033-7.

222. Büchler M, Friess H, Klempa I, Hermanek P, Sulkowski U, Becker H, et al. Role of octreotide in the prevention of postoperative complications following pancreatic resection. *Am J Surg* 1992;163(1):125-30.

223. Benedetti E, Coady NT, Asolati M, Dunn T, Stormoen BM, Raofi V, et al. Value of perioperative treatment with sandostatin after pancreas transplantation: a prospective randomized trial. *Transplant Proc* 1998;30(2):432-3.

224. Büchler M, Friess H. Inhibition of pancreatic secretion to prevent postoperative complications following pancreatic resection. *Acta Gastroenterol Belg* 1993;56(3-4):271-8.

225. Friess H, Klempa I, Hermanek P, Sulkowski U, Uhl W, Beger HG, et al. Prophylaxis of complications after pancreatic surgery: results of a multicenter trial in Germany. *Digestion* 1994;55 Suppl 1:35-40.

226. Büchler M, Friess H. Prevention of postoperative complications following pancreatic surgery. *Digestion* 1993;54 Suppl 1:41-6.

227. Büchler M, Friess H, Hermanek P, Sulkowsky U, Becker H, Klempa I, et al. The role of the somatostatin analogue octreotide in the prevention of postoperative complications following pancreatic resection results of a multicenter controlled trial [abstract]. *Digestion* 1991;49(1):11.

228. Oberlin P, Suc B, Pezet D, Fagniez P-L, Hay J-M. Prevention of intra-abdominal complications after pancreatic resection by octreotide. A prospective, multicenter, randomized trial [abstract]. *Gastroenterology* 2000;118(4 Suppl 2 Part 1):A463.

229. Lowy AM, Lee JE, Davidson BS, Pisters PWT, Evans DB. The role of octreotide in the prevention of pancreatic fistula after pancreaticoduodenectomy for periampullary malignancy: A prospective randomized trial. *Gastroenterology* 1996;110(4 Suppl):A1401.

230. Bassi C, Falconi M, Lombardi D, Briani G, Vesentini S, Camboni MG, et al. Prophylaxis of complications after pancreatic surgery: results of a multicenter trial in Italy. *Digestion* 1994;55 Suppl 1:41-7.

231. Lowy AM, Lee JE, Pisters PW, Davidson BS, Fenoglio CJ, Stanford P, et al. Prospective, randomized trial of octreotide to prevent pancreatic fistula after pancreaticoduodenectomy for malignant disease. *Ann Surg* 1997;226(5):632-41.

232. Mercadante S, Ripamonti C, Casuccio A, Zecca E, Groff L. Comparison of octreotide and hyoscine butylbromide in controlling gastrointestinal symptoms due to malignant inoperable bowel obstruction. *Support Care Cancer* 2000;8(3):188-91.

233. Mystakidou K, Tsilika E, Kalaidopoulou O, Chondros K, Georgaki S, Papadimitriou L. Comparison of octreotide administration vs conservative treatment in the management of inoperable bowel obstruction in patients with far advanced cancer: a randomized, double- blind, controlled clinical trial. *Anticancer Res* 2002;22(2B):1187-92.

234. Garcia Compean D, Ramos Jimenez J, Guzman De La Garza F, Saenz C, Maldonado H, Barragan RF, et al. Octreotide therapy of large-volume refractory AIDS-associated diarrhea: a randomized controlled trial. *AIDS* 1994;8(11):1563-7.

235. Garcia Compean D, Ramos Jimenez J, Guzman De La Garza F, Gonzalez F, Barragan RF. Effect of octreotide acetate (OA) on refractory diarrhea of patients with AIDS: randomized controlled trial [abstract]. *Gastroenterology* 1994;106 Suppl 4:A684.

236. Simon DM, Cello JP, Valenzuela J, Levy R, Dickerson G, Goodgame R, et al. Multicenter trial of octreotide in patients with refractory acquired immunodeficiency syndrome-associated diarrhea. *Gastroenterology* 1995;108(6):1753-60.

237. Simon D, Cello J, Valenzuela J, The Aids-Diarrhea Study Group. Multicenter placebo (PL)-controlled trial of octreotide (OCT) in patients with refractory AIDS-associated diarrhea [abstract]. *Gastroenterology* 1994;106(4 Suppl):A773.

238. Gebbia V, Carreca I, Testa A, Valenza R, Curto G, Cannata G, et al. Subcutaneous octreotide versus oral loperamide in the treatment of diarrhea following chemotherapy. *Anticancer Drugs* 1993;4(4):443-5.

239. Geller RB, Gilmore CE, Dix SP, Lin LS, Topping DL, Davidson TG, et al. Randomized trial of loperamide versus dose escalation of octreotide acetate for chemotherapy-induced diarrhea in bone marrow transplant and leukemia patients. *Am J Hematol* 1995;50(3):167-72.

240. Nikou GC, Polyzos A, Kostalas G, Avramopoulos H, Nikolopoulos A, Kitsou E, et al. Octreotide administration and gut hormone levels in patients with chemotherapy-induced diarrhea. *Hellenic J Gastroenterol* 1994;7(2):111-4.

241. Cascinu S, Fedeli A, Luzi Fl, Catalano. A randomized trial comparing octreotide (OC) and loperamide (LO) in the treatment of 5-fluorouracil (5FU) induced diarrhea [abstract]. *Ann Oncol* 1992;3(Suppl 5):179.

242. Geller RB, Topping DL, Gilmore CE, Dix SP, Davidson TG, Lin LS, et al. A randomized, dose escalation trial of octreotide versus loperamide for chemotherapy induced diarrhea in bone marrow transplant and leukemia [abstract]. *Blood* 1993;82(10 Suppl 1):419A.

243. Becker G, Allgaier HP, Olschewski M, Zähringer A, Blum HE, the HECTOR Study Group. Long-acting octreotide versus placebo for treatment of advanced HCC: a randomized controlled double-blind study. *Hepatology* 2007;45(1):9-15 (accessed 2007 Jan 5).

244. Barbare JC, Bouché O, Bonnetian F, Lombard-Rohas C, Faroux R, Dahan L, et al. Treatment of advanced hepatocellular carcinoma with long-acting octreotide: preliminary results of a randomized placebo-controlled trial (FFCD-ANGH 2001-01 CHOC) [abstract]. American Society of Clinical Oncology (ASCO) 2005 Annual Meeting; 2005 May 13; Orlando (FL). Abstract no 4036.

245. Yuen MF, Poon T-PR, Lai CL, Fan ST, Lo CM, Wong KW, et al. A randomized controlled study of long-acting octreotide for the treatment of advanced hepatocellular carcinoma. *Hepatology* 2002;36(3):687-91.

246. Kouroumalis EA, Skordilis P, Thermos K, Vasilaki A, Moschandrea J, Manousos O. Treatment of hepatocellular carcinoma with octreotide: a randomised controlled study. *Gut* 1998;42(3):442-7. Available: http://gut.bmjjournals.com/cgi/reprint/42/3/442 (accessed 2008 Jan 31).

247. Farooqi JI, Farooqi RJ. Efficacy of octreotide in cases of inoperable hepatocellular carcinoma: a clinical trial. *J Coll Physicians Surg Pak* 2000;10(7):258-60.

248. Verset G, Verslype C, Reynaert H, Borbath I, Langlet P, Vandebroek A, et al. Efficacy of the combination of long-acting release octreotide and tamoxifen in patients with advanced hepatocellular carcinoma: a randomised multicentre phase III study. *Br J Cancer* 2007;97(5):582-8. Available: http://www.nature.com/bjc/journal/v97/n5/pdf/6603901a.pdf (accessed 2008 Jan 31).

249. Dimitroulopoulos D, Xinopoulos D, Tsamakidis K, Zisimopoulos A, Andriotis E, Panagiotakos D, et al. Long acting octreotide in the treatment of advanced hepatocellular cancer and overexpression of somatostatin receptors: Randomized placebo-controlled trial. *World J Gastroenterol* 2007;13(23):3164-70.

250. Lersch C, Schmelz R, Erdmann J, Hollweck R, Schulte-Frohlinde E, Eckel F, et al. Treatment of HCC with pravastatin, octreotide, or gemcitabine--a critical evaluation. *Hepatogastroenterology* 2004;51(58):1099-103.

251. Gill ML, Atiq M, Sattar S, Khokhar N. Treatment outcomes with long acting octreotide in inoperable hepatocellular carcinoma: a local experience and review of literature. *J Pak Med Assoc* 2005;55(4):135-8.

252. Maurer U, Pederzoli P, Vollmer K, Büchler M, Kjaeve J, Van CE, et al. Treatment of unresectable stage 2, 3, 4, pancreatic cancer with SMS 201-995 pa LAR: Results of a placebo-controlled study with 185 patients [abstract]. *J Cancer Res Clin Oncol* 1998;124(Suppl 1):R58.

253. Salvia R, Caldiron E, Cavallini G, Maurer U, Vollmer K, BUECHLER M, et al. Phase 3 trial of SMS 201-995 pa LAR (SMS pa LAR) vs placebo in unresectable stage II, III and and IV pancreatic cancer [abstract]. *Ital J Gastroenterol Hepatol* 1998;30 Suppl 1:A16.

254. Schlag P, Roy A, Jacobs A, Bukowski R, Cunningham D, Hamm J, et al. Placebo-controlled study on the combination of continuous infusion (CI) of 5-FU with SMS 201-995 pa LAR in 281 Patients with unresectable stage 3 and 4 pancreatic cancer [abstract]. *Journal of Cancer Research & Clinical Oncology* 1998;124(Suppl 1):R58.

255. Pederzoli P, Maurer U, Vollmer K, BUECHLER M, Kjaeve J, Van Cutsem E, et al. Phase 3 trial of SMS 201-995 pa LAR (SMS pa LAR) vs. placebo in unresectable stage II, III and IV pancreatic cancer [abstract]. American Society of Clinical Oncology, 1998 Annual Meeting; 1998; (accessed 2006 Sep 29).

256. Roy A, Jacobs A, Bukowski R. Phase 3 trial of SMS 201-995 pa LAR (SMS pa LAR) and continuous infusion (CI) 5-FU in unresectable stage II,III and IV pancreatic cancer [abstract]. *Proc Am Soc Clin Oncol* 1998;17:257.

257. Drummond MF, Jefferson TO, BMJ Economic Evaluation Working Party. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996;313(7052):275-83. Available: http://www.bmj.com/cgi/content/full/313/7052/275 (accessed 2007 Feb 19).

258. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes* [Oxford medical publications]. 3rd ed. Oxford (UK): Oxford University Press; 2005.

259. Vanounou T, Pratt WB, Callery MP, Vollmer CM, Jr. Selective administration of prophylactic octreotide during pancreaticoduodenectomy: a clinical and cost-benefit analysis in low- and high-risk glands 31365. *J Am Coll Surg* 2007;205(4):546-57.

260. Schonfeld WH, Eikin EP, Woltering EA, Modlin IM, Anthony L, Villa KF, et al. The cost-effectiveness of octreotide acetate in the treatment of carcinoid syndrome and vipoma. *Int J Technol Assess Health Care* 1998;14(3):514-25.

261. Arcona S, Zacker C. An ex-ante cost-effectiveness analysis of octreotide for the primary and secondary prevention of variceal hemorrhage. *Gastroenterology* 1999;116(4 PART 2):A45.

262. Table 8 population by age group and sex (2006 to 2031) scenario 1 [tables]. In: *Population projections for canada, provinces and territories 2005-2032*. Ottawa: Statistics Canada; 2007. Available: http://www.statcan.ca/english/freepub/91-520-XIE/00105/tablesectionlist.htm (accessed 2008 Jan 31).

263. *Vanguard Studio* [computer program]. Cary (NC): Vanguard Software; 2007.

264. BC Palliative Care Benefits Program. *Physician Guide*. Victoria: British Columbia Ministry of Health. PharmaCare; 2005 Apr 1. Available: http://www.health.gov.bc.ca/pharme/outgoing/palliative_physguide.pdf (accessed 2008 Jan 31).

265. Saskatchewan Health. *Online Formulary Database* [database online]. Regina: Government of Saskatchewan; 2007. Available: http://formulary.drugplan.health.gov.sk.ca/ (accessed 2008 Jan 31).

266. Saskatchewan Health. *Appendix A: Exception Drug Status Program*. Regina: Government of Saskatchewan; 2007 Oct 1. Available: http://formulary.drugplan.health.gov.sk.ca/publications/APPENDIX%20A.pdf (accessed 2008 Jan 31).

267. Manitoba Health. *Manitoba Drug Interchangeability Formulary*. 22nd ed. Winnipeg: Manitoba Health; 2000 Mar 1. P60 - M.R. 13/2000. Available: http://web2.gov.mb.ca/laws/regs/2000/013.pdf (accessed 2008 Jan 31).

268. Manitoba Health. *Manitoba Drug Interchangeability Formulary*. 55th ed. Winnipeg: Manitoba Health; 2007 Mar 15. P60 - M.R. 20/2007. Available: http://www.gov.mb.ca/health/mdbif/mdif54.pdf (accessed 2008 Jan 31).

269. Nova Scotia Department of Health. *Nova Scotia pharmacare: formulary search* [database online]. Halifax: Nova Scotia Department of Health; 2007. Available: http://www.gov.ns.ca/health/pharmacare/formulary.asp (accessed 2008 Jan 31).

270. Government of New Brunswick. *New Brunswick prescription drug program formulary*. Fredericton: Government of New Brunswick; 2007 Sep. Available: http://www.gnb.ca/0212/pdf/NBPDP_Formulary/NBPDPFormularySept2007english.pdf (accessed 2008 Jan 31).

271. Alberta Health and Wellness. *Alberta Health and Wellness drug benefit list: revised October 1, 2007*. Rev. Edmonton: Ministry of Health and Wellness; 2007 Oct 1. Available: http://www.ab.bluecross.ca/dbl/pdfs/ahwdbl_full_list.pdf (accessed 2008 Jan 31).

272. Ontario Ministry of Health and Long-Term Care. *Ontario drug benefit formulary/comparative drug index* [database online]. Toronto: The Ministry; 2007. Available: http://www.health.gov.on.ca/english/providers/program/drugs/odbf_eformulary.html (accessed 2008 Jan 31).

273. Régie de l'assurance maladie du Québec. *List of medications*. Montreal: Régie de l'assurance maladie du Québec; 2007 Apr. Available: https://www.prod.ramq.gouv.qc.ca/DPI/PO/Commun/PDF/Liste_Med/Liste_Med/liste_med_2007_04_18_en.pdf (accessed 2008 Jan 31).

274. Government of Newfoundland & Labrador. *Newfoundland and Labrador Interchangeable Drug Products Formulary* [database online]. St. John's: Government of Newfoundland & Labrador. Department of Health and Community Services; 2007. Available: http://www.health.gov.nl.ca/health/nlpdp/fmlsearch.asp (accessed 2008 Jan 31).

275. Government of Prince Edward Island. *Drug Programs Formulary*. 2nd ed. Charlottetown: Government of Prince Edward Island. Department of Health and Social Services; 2003 Apr. Available: http://www.gov.pe.ca/photos/original/hss_dr_formu_2.pdf (accessed 2008 Jan 31).

276. Health Canada. *Drug benefit list*. July 2007. Ottawa: Health Canada. First Nations and Inuit Health. Non-Insured Health Benefits (NIHB) Program; 2007. Available: http://www.hc-sc.gc.ca/fniah-spnia/alt_formats/fnihb-dgspni/pdf/nihb-ssna/list_drug_med-eng.pdf (accessed 2008 Jul 15).

277. Yukon Health and Social Services. *Yukon drug programs formulary*. Whitehorse: Yukon Health and Social Services; 2005 Nov. Available: http://www.hss.gov.yk.ca/downloads/drug_formulary_05.pdf (accessed 2008 Jan 31).

278. Veterans Affairs Canada. *VAC drug formulary* [database online]. Ottawa: Veterans Affairs Canada; 2007. Available: http://www.vac-acc.gc.ca/clients/sub.cfm?source=services/poc/poc10/search (accessed 2008 Jan 31).

279. Silvain C, and a Multicentric Group. A comparison of octreotide combined with endoscopic sclerosis to endoscopic sclerosis alone in the treatment of acute variceal bleeding: a randomized double-blind placebo-controlled trial. *J Hepatol* 1995;23 Suppl 1:70.

280. Besson I, Ingrand P, Person B, Boutroux D, Heresbach D, Bernard P, et al. A comparison of octreotide combined with emergency sclerotherapy to sclerotherapy alone in the treatment of acute variceal bleeding: a randomized double-blind placebo-controlled trial [abstract]. *Gastroenterology* 1995;108(4 Suppl):A1034.

281. De Franchis R, Andreoni B, Primignani M, Nolte A, Carpinelli L, Marini A, et al. Octreotide does not reduce the incidence of early rebleeding in cirrhotics submitted endoscopic variceal sclerotherapy (EVS): interim analysis of a randomized, double-blind, placebo controlled, multicenter trial [abstract]. *Hepatology* 1992;16(4 Pt 2):82A.

282. Shah SHA, Jafri SMW, Ahmed A, Hamid SS, Khan AH. Octreotide use in acute variceal haemorrage: a prospective randomized study [abstract]. *Endoscopy* 1996;28:S51.

283. Zuberi BF, Shaikh WM, Balouch O. Endoscopic variceal, sclerotherapy and octreotide in management of acute variceal, haemorrhage and early re-bleeding [abstract]. *J Hepatol* 1999;30(Suppl 1):82.

284. Zuberi BF, Balouch Q. Endoscopic variceal sclerotherapy and octreotide in management of variceal haemorrhage and early early re-bleeding [abstract]. *J Gastroenterol Hepatol* 1999;14(3):A15.

285. Jenkins SA, Shields R, Sutton R, Kingsnorth AN, Davies M, Elias E, et al. Multicentre trial of octreotide versus injection sclerotherapy (IS) for acute variceal haemorrhage. *Gastroenterology* 1995;108(4 Suppl):A1091.

286. Jenkins SA, Copeland G, Kingsnorth A, Shields R. A prospective randomised controlled clinical trial comparing sandostatin (SMS) and injeection sclerotherapy in the control of acute variceal haemorrhage: an interim report [abstract]. *Gut* 1992;33(1):S56.

287. Shields R, Jenkins SA, Kingsnorth AN, Sutton R, Copeland G, Gilmore IT, et al. A prospective randomised controlled clinical trial comparing octreotide and endoscopic sclerotherapy (ES) in the control of acute variceal hemorrhage: An interim report. *Gastroenterology* 1993;104(4 Suppl):A991.

288. Sung JY, Chung SCS, Lai CW, Chan KL, Leung JWC, Kassianides C, et al. Octreotide versus emergency sclerotherapy in the treatment of acute variceal haemorrhage: a prospective randomized study [abstract]. *Gastroenterology* 1993;104(Suppl 4):A201.

289. Sung JY, Chung SCS, Leung VKS, Yung MY, Li AKC. Octreotide reduces early rebleeding from varices after endoscopic variceal ligation [abstract]. *Endoscopy* 1995;27(7):S92.

290. Allgaier H, Becker G, Olschewski M, Zaehringer A, Blum HE. Octreotide treatment in patients with advanced hepatocellular carcinoma: first results of the randomized placebo-controlled double-blind hector trial [abstract]. *Hepatology* 2003;38(4 Suppl 1):760A.

291. Verslype C, Verset G, Reyneart H, Borbath I, Langlet P, Vandebroek A, et al. Efficacy of long acting release octreotide in patients with advanced hepatocellular carcinoma: a randomized multicenter phase III study [abstract]. 41st Annual Meeting of the European Association for the Study of the Liver; 2006 Apr 26; Vienna (accessed 2008 Jan 31).

292. Dimitroulopoulos D, Xinopoulos D, Tsamakidis K, Zisimopoulos A, Andriotis E, Panagiotakos D, et al. The role of long acting octreotide in treating patients with advanced hepatocellular cancer (HCC). A randomized placebo-controlled trial [abstract]. *Gastroenterology* 2004;126(4 Suppl 2):A597.

293. Dimitroulopoulos D, Zisimopoulos A, Andriotis E, Xinopoulos D, Tsamakidis K, Fotopoulu A, et al. Benefit of a long acting Octreotide treatment in advanced hepatocellular cancer. A randomized placebo-controlled trial [abstract]. World Congress Gastroenterology 2005; 2005 Sep 12; Montreal. Abstract no R.0928. Available: http://www.pulsus.com/WCOG/abs/R.0928.htm (accessed 2008 Jan 31).

294. Lancranjan I, Bruns C, Grass P, Jaquet P, Jervell J, Kendall-Taylor P, et al. Sandostatin® LAR®: a promising therapeutic tool in the management of acromegalic patients. *Metabolism* 1996;45(8 Suppl 1):67-71.

295. Vinik A, Moattari AR. Use of somatostatin analog in management of carcinoid syndrome. *Dig Dis Sci* 1989;34(3 Suppl):14S-27S.

296. Patel YC, Ezzat S, Chik CL, Rorstad OP, Serri O, Ur E, et al. Guidelines for the diagnosis and treatment of acromegaly: a Canadian perspective. *Clin Invest Med* 2000;23(3):172-87.

297. Gemcitabine Plus Standard Chemoradiation Improves Survival in Patients with Pancreatic Head Tumors. In: *Clinical Trial Results*. Bethesda (MD): National Cancer Institute; 2007 (accessed 2007 Oct 5).

298. Surveillance, Epidemiology, and End Results (SEER) Program. *US Estimated Complete Prevalence Counts on 1/1/2004: All Ages, First Malignant Cancer Only By Cancer Site, Sex, and Race* [Prevalence Database].

Bethesda (MD): National Cancer Institute, DCCPS, Surveillance Research Program, Statistical Research and Applications Branch.; 2007 Apr. Available: http://canques.seer.cancer.gov/cgi-bin/cq_submit?dir=prev2004&db=9&rpt=TAB&sel=1%5e%5e%5e1%5e%5e%5e0&x=Site%5e0,72,51,53,16,54,13,79,68,42,86,88,31,43,49,85,82,1,57,36,62,14,63,76,67%5eSex%5e1,2,3&y=Years%20since%20Diagnosis%5e8,10,7&z=Race%5e11,1,2&dec=0&title=US+Estimated+Complete+Prevalence+Counts+on+1/1/2004~All+Ages,+First+Malignant+Cancer+Only~By+Cancer+Site,+Sex,+and+Race&template=faststats (accessed 2008 Jan 31).

299. U.S. Census Bureau. *Census Bureau Projects Nation's Population to Total: 295 Million on New Year's Day [press release]*. Washington: U.S. Census Bureau; 2004 Dec 28. Available: http://www.census.gov/Press-Release/www/releases/archives/population/003161.html (accessed 2008 Jan 31).

300. Mosdell KW, Visconti JA. Emerging indications for octreotide therapy, Part 2. *Am J Hosp Pharm* 1994;51(10):1317-30.

301. Buchler MW, Friess H, Wagner M, Kulli C, Wagener V, Z'Graggen K. Pancreatic fistula after pancreatic head resection. *Br J Surg* 2000;87(7):883-9.

302. *Pancreatitis*. Bethesda (MD): National Digestive Diseases Information Clearinghouse; 2004. Available: http://digestive.niddk.nih.gov/ddiseases/pubs/pancreatitis/index.htm (accessed 2008 Jan 31).

303. Pham J. *GI Bleeding: Surgery Half Day [presentation slides]*. Hamilton (ON): McMaster University, Faculty of Health Sciences, Department of Surgery; 2005 Sep 7. Available: http://fhs.mcmaster.ca/surgery/rescentre/documents/gi_bleeding.pdf (accessed 2008 Apr 29).

304. Surveillance, Epidemiology, and End Results (SEER) Program. US Estimated Complete Prevalence (Including Counts) on 1/1/2004. In: *Prevalence database*. Bethesda (MD): National Cancer Institute, DCCPS, Surveillance Research Program, Statistical Research and Applications Branch; 2007. Available: http://canques.seer.cancer.gov/cgi-bin/cq_submit?dir=prev2004&db=9&rpt=TAB&sel=1^^^1^^^0&x=Site^0,72,51,53,16,54,13,79,68,42,86,88,31,43,49,85,82,1,57,36,62,14,63,76,67^Sex^1,2,3&y=Years%20since%20Diagnosis^8,10,7&z=Race^11,1,2&dec=0 (accessed 2008 Jan 31).

305. Hepatocellular carcinoma. In: *A.D.A.M. Medical Encyclopedia [online]*. Atlanta (GA): A.D.A.M., Inc.; 2006. Available: http://www.nlm.nih.gov/medlineplus/ency/article/000280.htm (accessed 2008 Jan 31).

306. *Provincial and national trends in Canadian Cancer Statistics 2003 [media release]*. Vancouver: Canadian Cancer Society; 2003 Apr 16. Available: http://www.cancer.ca/ccs/internet/mediareleaselist/0,,3278_437890_40037705_langId-en.html (accessed 2008 Jan 31).

307. Macdonald D. Active Pass Pharmaceuticals Inc. [presentation notes]. BioFinance 2006; 2006 May 2; Toronto. Available: http://www.biofinance.ca/ActivePassPharmaceuticals (accessed 2008 Jan 31).

308. Estimates of HIV prevalence and incidence in Canada, 2002. *Can Commun Dis Rep* 2003;29(23). Available: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/03vol29/dr2923ea.html (accessed 2008 Jan 31).

309. *Population by year, by province and territory (number) [table]*. Ottawa: Statistics Canada; 2006. Available: http://www40.statcan.ca/l01/cst01/demo02.htm?sdi=population%20year%20province (accessed 2007 Aug 10).

310. Loftus EV, Bernstein CN, Blanchard JF, Sonnenberg A. *Epidemiology*. New York: Crohn's & Colitis Foundation of America; 2007 (accessed 2007 Sep 7).

311. Malekzadeh R, Varshosaz J, Merat,S et al. Crohn's disease: a review of 140 cases from Iran. *Irn J Med Sci* 2000;25:138-43.

312. Byrne TA, Persinger RL, Young LS, Ziegler TR, Wilmore DW. A new treatment for patients with short-bowel syndrome. Growth hormone, glutamine, and a modified diet. *Ann Surg* 1995;222(3):243-54.

313. Lennard-Jones JE. Indications and need for long-term parenteral nutrition: implications for intestinal transplantation. *Transplant Proc* 1990;22(6):2427-9.

314. Moreno JM, Planas M, Lecha M, Virgili N, Gomez-Enterria P, Ordonez J, et al. The year 2002 national register on home-based parenteral nutrition [in Spanish]. *Nutr Hosp* 2005;20(4):249-53.

315. *Incidence Statistics for Types of Bowel Obstruction*. Edge Hill (Australia): WrongDiagnosis.com, Adviware Pty Ltd.; 2007. Available: http://www.wrongdiagnosis.com/b/bowel_obstruction/incidence-types.htm (accessed 2008 Jan 31).

316. Krouse RS. Palliative Care for Oncologic Patients [presentation slides]. American College of Surgeons 31st Annual Spring Meeting; 2003; New York. Available: http://www.facs.org/spring_meeting/2003/gs14krouse.pdf (accessed 2008 Jan 31).

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