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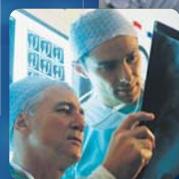
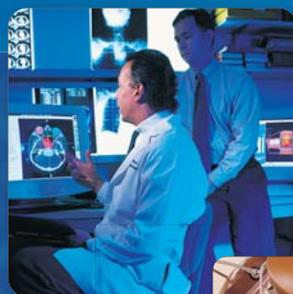
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Octreotide for Endocrine, Oncologic,
and Gastrointestinal Disorders:
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Supporting Informed Decisions

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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

July 2008

We thank Suzanne Morphet for her assistance in creating this overview from a longer report authored by Murphy et al.

This overview is based on the Technology Report commissioned by CADTH: Murphy G, Perras C, Desjardins B, Chen S, Moulton K, Jonker D, Perlman K, Pasiaka J, Ezzat S, Cripps C, Mensinkai M, Skidmore B. *Octreotide for endocrine, oncologic, and gastrointestinal disorders: systematic review and budget impact analysis* [Technology report number 111]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2008.

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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. Eighty-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, Pasiaka J, Ezzat S, Cripps C, Mensinkai M, Skidmore B. *Octreotide for Endocrine, Oncologic, and Gastrointestinal Disorders: Systematic Review and Budget Impact Analysis*.

1 Introduction

Octreotide is a synthetic analogue of somatostatin. It is useful in different conditions because it inhibits the endocrine and exocrine secretions associated with many diseases.¹ Health Canada has approved the drug for four indications: acromegaly, gastroenteropancreatic neuroendocrine tumours (GEPNETs), preventing complications after pancreatic surgery, and managing the emergency bleeding of gastro-esophageal varices in patients with underlying cirrhosis. Octreotide is also being used for other conditions, without Health Canada's approval.

Among the publicly funded drug plans in British Columbia, Manitoba, Saskatchewan, New Brunswick, and Nova Scotia, expenditures for octreotide grew from C\$510,000 in 1999-2000, when it was first reimbursed, to C\$2.3 million in 2005-2006. In this period, the cost per claimant doubled to approximately \$8,670, and the number of claimants increased from 142 to 267. (Data were provided by the publicly funded drug plans of British Columbia, Manitoba, Saskatchewan, New Brunswick, and Nova Scotia.)

In Canada, the drug is available as a short-acting injection formula that is delivered subcutaneously or intravenously (OCT-SA) and a long-acting depot formula that is delivered by intramuscular injection (OCT-LA) (Table 1). Four weeks of therapy costs between C\$112 and C\$2,975 for OCT-SA and between C\$1,272 and C\$2,124 for OCT-LA, depending on the dosage.²

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

ATC code=anatomic therapeutic chemical code; DDD=defined daily doses; DIN=drug identification number; mg=milligram; mL=millilitre; µg=microgram

*Unit cost data for octreotide products from Alberta Drug Benefit List;² Lanreotide price from Canadian Expert Drug Advisory Committee recommendation on lanreotide;³ Other sources: Product descriptions and DINs⁴⁻⁷, World Health Organization ATC index 2007⁸

2 Objectives

The purpose of this review was to assess the clinical and cost-effectiveness of octreotide for the four indications approved by Health Canada and for six 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.

The objectives were met by addressing five research questions:

1. What is the evidence regarding the clinical effectiveness of octreotide therapy for the four approved and six unapproved indications?
2. What is the evidence regarding the clinical effectiveness of the long-acting intramuscular depot (OCT-LA) formulation compared with the subcutaneous or intravenous (OCT-SA) formulation for the selected indications?
3. What is the optimal length of octreotide therapy for the selected indications?
4. What is the evidence regarding the cost-effectiveness of octreotide therapy for the selected indications, and for OCT-LA versus OCT-SA?
5. What is the budget impact on publicly funded drug programs in Canada of funding octreotide for the approved and unapproved indications?

3 Methods

Using a literature search strategy designed by our information specialists, we conducted staged electronic searches using the OVID interface on MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, BIOSIS Previews, and The Cochrane Library 2006 (Issues 2 and 3). Updates were done biweekly until the first week of February 2008, with no language or publication date restrictions, and all searches, except the economic search, were limited to human studies. We first sought systematic reviews and meta-analyses. When these did not meet our inclusion criteria, we searched for randomized and non-randomized clinical trials so that we could conduct a new systematic review. We also searched the Health Economic Evaluations Database (HEED) for economic evaluations.

We identified grey literature by searching the Internet, hand searching bibliographies and abstracts of select literature, and by contacting experts and agencies.

Two reviewers independently screened studies, first by titles and abstracts, then by full text if they were deemed to be relevant. Clinical studies were included if they were randomized clinical trials (RCTs) with parallel or crossover design, or controlled clinical trials (CCTs), either cohort or case control studies. Patients had one of the indications of interest. The studies compared OCT-SA with OCT-LA, or either formulation with placebo, no treatment, or active controls (specific to each indication). The outcomes, which varied with each indication, included health-related quality of life, adverse events, and serious adverse events.

Economic studies were included if they met the same criteria as those set for clinical studies in terms of population, interventions, and comparators. The primary outcomes of interest were

related to health (for example, life-years), costs, and incremental cost-effectiveness ratios. The study designs included cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, and cost comparison analysis.

At least two reviewers worked independently to extract or verify relevant data from the selected studies. Disagreements were resolved by consensus or with the help of a neutral third person. We assessed the quality of systematic reviews and meta-analyses using the Oxman and Guyatt Scale,⁹ and that of RCTs using the Jadad scale.¹⁰ We also assessed whether the studies took steps to prevent foreknowledge of the treatment allocation during patient enrolment.¹¹ Economic studies were evaluated using the BMJ 35-question checklist¹² or section 3 of Drummond *et al.*'s checklist for assessing economic evaluations.¹³

For the clinical studies, we did a meta-analysis, where appropriate. We used data from RCTs to assess efficacy. Data from RCTs and CCTs were used to analyze safety. For the economic review, we were limited to a narrative synthesis, because of the low number of studies.

Results – Clinical

We included 82 parallel or crossover RCTs in our systematic review and data on harms from nine CCTs. Seven (9%) RCTs had adequate allocation concealment, and 31 (38%) were of higher methodological quality according to their Jadad scores. Many RCTs had a small sample size, and most did not report health-related quality of life. Few studies reported harm, or they had limited data and their methods were poorly described. Furthermore, the populations that were studied were not always comparable. Consequently, we could not quantify harms systematically for any indication. Neither could we assess the optimal length of therapy for any indication.

Acromegaly

Ten RCTs that compared OCT-SA and OCT-LA with each other or to a control (placebo, no treatment, lanreotide, bromocriptine, or surgery) provided limited data. Treatment duration ranged from 14 days to 24 months. The study size varied from 12 to 125 patients, with half of the trials enrolling fewer than 30 patients. Allocation concealment could not be determined for all ten studies, and half of the studies scored two or less on the Jadad scale, indicating poorer quality. Most of the studies did not report the outcomes of interest, or the results could not be easily interpreted. Of the five studies comparing OCT-SA with placebo or no treatment, a meta-analysis of three of them showed that OCT-SA significantly decreased growth hormone and insulin-like growth factor levels.¹⁴⁻¹⁶ One study showed that more patients receiving OCT-SA obtained normal growth hormone levels compared with those receiving no treatment.¹⁴ If there were differences between OCT-LA and lanreotide, it was not possible to detect them, given the study limitations. Likewise, no conclusions could be reached about OCT-LA versus surgery or OCT-SA versus bromocriptine.

Emergency Management of Acute Variceal Bleeding

Twenty one RCTs compared OCT-SA with placebo or no treatment. The other trials compared OCT-SA with sclerotherapy (7), balloon tamponade (2), somatostatin (3), terlipressin (4), or vasopressin (4). Most often, the treatment duration was two days or five days, and ranged from 24 hours to 29 days (two RCTs did not report duration). The number of patients who were enrolled

varied from 31 to 564. Eight trials (22%) were of higher quality (a Jadad score of three or higher), and three (8%) had adequate allocation concealment.

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

OCT-SA reduced the risk of patients failing initial hemostasis compared with placebo, no treatment, terlipressin, or vasopressin. It also lowered the risk of rebleeding compared with placebo or no treatment. Of 27 RCTs reporting on blood transfusions, seven found that OCT-SA patients needed significantly fewer units of blood,¹⁷⁻²³ while three found that they needed significantly more.²⁴⁻²⁶ The absolute difference between groups in most trials was less than one unit of blood. The results were mixed for the length of hospitalization. Two RCTs reported that OCT-SA patients had a significantly shorter stay compared with those receiving placebo or no treatment,^{17,20} while three reported that OCT-SA patients needed significantly longer hospitalization than those on placebo, sclerotherapy, or terlipressin.^{24,27,28} Four other RCTs found no difference.

Gastroenteropancreatic Neuroendocrine Tumours

Four RCTs with a total of 149 patients compared OCT-SA with OCT-LA, lanreotide, or placebo. The treatment duration spanned 24 hours to 24 weeks. Two trials were of higher quality, and one had adequate allocation concealment. Because of differences in groups and duration of treatment, it was not possible to do a meta-analysis. Furthermore, studies did not report on several outcomes of interest, so few conclusions could be reached.

One study with 33 patients reported that the severity of flushing and diarrhea was similar among patients who were treated with OCT-SA compared with those who were treated with lanreotide.²⁹ In another study with 12 patients, those on OCT-SA had significantly less flushing, but a similar intensity of abdominal pain than those on placebo.³⁰ A study that measured treatment success by symptom control found no difference between OCT-SA and OCT-LA.³¹

Prevention of Complications after Pancreatic Surgery

Of 12 RCTs comparing OCT-SA with placebo or no treatment, seven were of higher methodological quality, and two had adequate allocation concealment. In 11 of the 12 trials, the treatment duration ranged from five to 10 days. In one trial, patients were treated for a mean of 20 to 25 days. The number of patients ranged from 17 to 383. The patients underwent surgery because of pancreatitis, a malignant or benign tumour, transplantation, or a combination of these conditions.

Data were pooled when heterogeneity permitted this. For three outcomes – fluid collection, number of pancreatic fistulas, and overall complication rate – patients on OCT-SA had significantly better results than those on placebo or no treatment. When data analysis was limited to the two trials with adequate allocation, however, the difference for these outcomes was not statistically significant.^{32,33} For the outcomes of death, infection, pancreatitis, abscess, bleeding, or length of hospital stay, no significant difference was observed between OCT-SA and placebo.

Bowel Obstruction

The two RCTs that were included, both of lower quality, compared OCT-SA with hyoscine butylbromide in a total of 86 patients with cancer and inoperable bowel obstruction. In one trial, patients were treated for three days. In the other trial, they were treated until death. Allocation concealment was unclear in both trials.

Both studies found that patients who were treated with OCT-SA for three days vomited less than those on hyoscine butylbromide and experienced significantly less severe nausea.^{34,35} For other outcomes such as pain, drowsiness, or dry mouth, there were no significant differences between treatments. Neither study reported data on the quality of life, hospital length of stay, or need for nasogastric tube insertion.

Diarrhea Related to Chemotherapy, HIV-AIDS, Crohn's Disease, or Ileostomy

No trials met the inclusion criteria for Crohn's disease or ileostomy. Of seven RCTs, five evaluated OCT-SA in patients with diarrhea related to chemotherapy, and two assessed the drug's efficacy in patients whose diarrhea was related to HIV-AIDS. Comparators were placebo, loperamide, or placebo plus loperamide and diphenoxylate. Four studies were of higher methodological quality. Allocation concealment was unclear in all studies.

The trials that involved between 16 and 43 chemotherapy patients lasted between one and four days. In the trial comparing OCT-SA with placebo, OCT-SA patients were significantly more likely to have a complete or major resolution of diarrhea.³⁶ The four studies comparing OCT-SA with loperamide could not be pooled because of heterogeneity (for example, different types of cancers, different chemotherapy medications, and different doses of OCT-SA). Two trials found that OCT-SA patients had a greater chance of responding to treatment,^{37,38} one trial found that loperamide patients were more likely to respond,³⁹ and one trial found no difference between treatments.⁴⁰

In the HIV-AIDS population, no significant difference was detected between OCT-SA and placebo or antidiarrheal agents.^{41,42} In these trials, a total of 149 patients were enrolled, and the treatment duration ranged from 10 to 21 days.

Hepatocellular Carcinoma

Of seven RCTs that compared OCT-SA or OCT-LA with a control (placebo, no treatment, or tamoxifen), five were of higher quality, with a Jadad score of three or higher. One had adequate allocation concealment. The duration of treatment ranged from six weeks to three years, with one study not reporting duration. The size of the groups ranged from 13 to 266 patients. Because of heterogeneity in treatment duration and length of follow-up, the results could not be pooled.

One study with 58 patients reported that significantly fewer patients died at six and 12 months in the OCT-SA group than in the group not receiving treatment, and that statistically fewer patients had their tumours progress.⁴³ Two studies found that OCT-SA and OCT-LA increased survival time compared with placebo or no treatment.^{43,44} Patients who were treated with octreotide did not show a survival benefit in four other studies.

Pancreatic Cancer

Four RCTs evaluated OCT-SA and OCT-LA in a total of 602 patients with advanced pancreatic cancer and inoperable tumours. Comparators were no treatment, chemotherapy, or placebo. Patients were treated for an average of eight to 12 weeks in two studies. The duration of treatment was not reported in the other two trials. Three trials were of lower quality with a Jadad score of two, and the allocation concealment in all four trials was inadequate or unclear.

One RCT reported that OCT-SA patients lived significantly longer than those who received no treatment, with an increase in median survival time of eight weeks.⁴⁵ None of the other RCTs found a significant difference in survival time. No effect on the pancreatic tumour was detected with octreotide compared with placebo, no treatment, or chemotherapy.

Pediatric Idiopathic or Persistent Hyperinsulinism

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

Short Bowel Syndrome

Five crossover RCTs met the inclusion criteria but could not be analyzed because they did not report data before the crossover. We tried to contact the authors for missing data but were unsuccessful.

Results – Economic

We included eight economic evaluations: three on acromegaly, one on esophageal variceal bleeding, two on GEPNET, and two on the prevention of complications after pancreatic surgery. No economic studies could be found regarding indications for which octreotide has not been approved by Health Canada.

Four studies came from Canada, including three unpublished reports (Novartis Pharmaceuticals Canada Inc., Dorval: unpublished data, January 1999 and May 1999; L. Wilson, University of California, San Francisco: unpublished data, 1999).⁴⁶ Three studies came from the US,⁴⁷⁻⁴⁹ and one originated in the UK.⁵⁰ Six of the eight evaluations included a cost-effectiveness or cost-efficacy study that showed the cost of treatment for a particular health effect, such as the cost of a patient reaching a certain growth hormone level or the cost of preventing one bleeding episode (Novartis Pharmaceuticals Canada Inc., Dorval: unpublished data, January 1999; L. Wilson, University of California, San Francisco: unpublished data, 1999).^{46,48-50} This type of analysis made it difficult to compare results. Also included were one cost-minimization analysis (Novartis Pharmaceuticals Canada Inc., Dorval: unpublished data, May 1999), one cost-benefit analysis,⁴⁷ and one cost-utility analysis.⁵⁰

While a societal perspective would have been useful for capturing a range of costs, most of the studies took the perspective of the health care system or drug plan payer and used a short-term time horizon of between one to 19 months. One study used a lifetime perspective.⁴⁸

Six studies, including the three unpublished reports,^{46,48,49} received all or part of their funding from the pharmaceutical industry. One study did not report funding sources.⁴⁷

Except for the Canadian study on patients who were undergoing pancreatic surgery,⁴⁶ the studies were not of high quality. Because of the lack of studies or limited methods, we could not reach any conclusions about the cost-effectiveness of octreotide for acromegaly, GEPNET, or emergency variceal bleeding.

For the prevention of complications after pancreatic surgery, the 1999 Canadian cost-effectiveness study showed that OCT-SA was cost-saving compared with placebo.⁴⁶ The authors created two models that used the complication rates from a meta-analysis of RCTs and the cost of hospitalization for patients who were undergoing pancreatic surgery. Model one predicted that OCT-SA saved C\$853 per patient, and model two showed a saving of C\$1,642 per patient. Furthermore, 16 additional patients in a theoretical cohort of 100 avoided complications when they were treated with OCT-SA. The analysis was high quality with robust one-way and two-way sensitivity analyses.

An American study that purported to be a cost-benefit analysis comparing OCT-SA to usual care for preventing fistulas after pancreatic duodenectomy did not put a monetary value on clinical outcomes, as a cost-benefit analysis should.⁴⁷ The authors reported that OCT-SA resulted in cost-savings of US\$4,249 per patient. The clinical value and cost savings were greatest in patients who were at high risk of fistulas. Caution must be used in interpreting these results because of the small number of patients who developed fistulas.

4 Limitations

The clinical review was limited to English and French papers. Of 17 relevant papers in neither of these languages, three with English abstracts could be included. A limited number of RCTs with small numbers of patients was available for many of the indications. Adverse events were poorly reported, and harms could not be quantified systematically. Almost two-thirds of reports (61%) were of lower methodological quality, with data often sparse or missing. Dissimilarities in treatment duration and comparators meant that data could not be pooled. The economic review was limited by the small number of acceptable studies, their dissimilarities, possible bias, and sometimes contradictory findings.

Health System Implications

The prevalence rate of each condition in Canada was estimated for 2006 to 2010. There are fewer than 8,500 potential beneficiaries for the approved indications in any of those years. For unapproved indications, the estimated number exceeds 180,000 in each year.

We determined the budget impact for the publicly funded drug plans in British Columbia, Saskatchewan, Manitoba, Nova Scotia, and New Brunswick, based on historical drug use. Using three scenarios, we determined that the drug budgets are sensitive to any expansion of the coverage for OCT-SA or OCT-LA. The reimbursement for the unapproved indications would lead to an estimated 76% to 137% increase in octreotide expenditures in 2009-2010. Reimbursement of all indications for palliative care beneficiaries resulted in a smaller budget increase.

5 Conclusion

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 about the impact of octreotide on health-related quality of life, the relative efficacy of OCT-SA compared with OCT-LA, or the optimal duration of octreotide therapy. A descriptive review of adverse events suggested that octreotide was not associated with substantial harms 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 about 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 who were 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 expenditures on octreotide.

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