

Reimbursement Recommendation

Pasireotide (Signifor LAR)

Indication: For the treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue

Sponsor: Recordati Rare Diseases Canada Inc.

Final Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Signifor LAR?

Canada's Drug Agency (CDA-AMC) recommends that Signifor LAR be reimbursed by public drug plans for the treatment of acromegaly if certain conditions are met.

Which Patients Are Eligible for Coverage?

Signifor LAR should only be covered to treat patients who have a confirmed diagnosis of acromegaly and are ineligible for, have contraindications to, or have demonstrated a lack of response to surgery, and who have shown inadequate disease control with a first-generation somatostatin analogue (SSA) for a 6-month trial.

What Are the Conditions for Reimbursement?

Signifor LAR should only be reimbursed if prescribed by specialists who have expertise in the diagnosis and management of acromegaly and if the cost of Signifor LAR does not exceed the drug program cost of treatment with a first-generation SSA for the treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that Signifor LAR likely improves the proportion of patients who achieve normalization of IGF-1, when compared to first-generation SSAs.
- With respect to whether Signifor LAR is able to meet patients' unmet needs, although there were signs of improvement on the Acromegaly Quality of Life Questionnaire, the clinical significance of these improvements is unclear, and it is uncertain whether it improves symptoms.
- Based on the CDA-AMC assessment of the health economic evidence, Signifor LAR does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Signifor LAR compared with first-generation SSAs.
- Based on public list prices, Signifor LAR is estimated to cost the public drug plans approximately \$9 million over the next 3 years. The budget impact is highly sensitive to the magnitude to which Signifor LAR is expected to displace Somavert.

Summary

Additional Information

What Is Acromegaly?

Acromegaly is a potentially lifelong disease that tends to get progressively worse over time and is characterized by excess secretion of growth hormone, resulting in changes to body structure and function as well as other illnesses such as diabetes and high blood pressure. Acromegaly is a rare disorder; out of every 1 million people in Canada, only 60 people have this disease.

Unmet Needs in Acromegaly

The major unmet need is that only half of patients experience a response to first-generation SSAs and must then resort to combination therapy, which causes more side effects.

How Much Does Signifor LAR Cost?

Treatment with Signifor LAR is expected to cost approximately \$65,859 per patient per year.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that pasireotide for injectable suspension be reimbursed for the treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with a first-generation somatostatin analogue, only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

Acromegaly is a rare, chronic, and progressive endocrine disorder characterized by excess growth hormone (GH) secretion, leading to structural and functional tissue changes as well as the development of secondary systemic illnesses and burdensome comorbidities. Only about half of patients experience a response to treatment with first-generation SSAs, and those who do not experience a treatment response then must typically resort to combination therapy, which carries an increased risk of side effects and is only modestly effective. The clinical experts consulted noted that pasireotide could be a treatment option after failure of first-line treatment with SSAs.

Two phase III randomized controlled trials (RCTs) (Study C2305 and Study C2402) suggested that treatment with pasireotide likely results in an improvement in the number of patients who achieve IGF-1 normalization, when compared to first-generation SSAs, in patients with and without a history of prior medical therapy with first-generation SSAs. The results also suggested that pasireotide may increase the number of patients who achieve GH and IGF-1 normalization compared to other SSAs. In Study C2305, the proportion of patients with normalized IGF-1 was 38.6% (95% confidence interval [CI], 31.4% to 46.3%) in the pasireotide arm and 23.6% (95% CI, 17.7% to 30.5%) in the octreotide arm, with an odds ratio (OR) of 2.087 (95% CI, 1.316 to 3.308; $P = 0.002$) in favour of pasireotide. The proportion of those who experienced a response to treatment (i.e., patients with GH < 2.5 mcg/L and normalized IGF-1) at month 12 was 31.3% (95% CI, 24.5% to 38.7%) in the pasireotide arm, and 19.2% (95% CI, 13.8% to 25.7%) in the octreotide arm, with an OR of 1.942 (95% CI, 1.190 to 3.168; $P = 0.007$) in favour of pasireotide. In Study C2402, the proportion of patients who achieved normalization of IGF-1 at week 24 (key secondary efficacy variable) was higher in those who received pasireotide 40 mg (24.6%; 95% CI, 14.77% to 36.87%) and pasireotide 60 mg (26.2%; 95% CI, 16.03% to 38.54%) compared to the active control arm (zero responders), for an OR of 30.12 (95% CI, 6.28 to infinity; $P < 0.0001$) in the pasireotide 40 mg group and 32.66 (95% CI, 6.84 to infinity; $P < 0.0001$) in the pasireotide 60 mg group. In the pasireotide 40 mg group, 10 patients (15.4%) achieved biochemical control at 24 weeks, compared with no patients in the active control arm (OR = 16.63; 95% CI, 3.32 to infinity; $P = 0.0006$). In the pasireotide 60 mg arm, 13 patients (20.0%) achieved biochemical control at 24 weeks (OR = 23.03; 95% CI, 4.72 to infinity; $P < 0.0001$). However, according to the clinical experts consulted, the clinical relevance of improving GH in acromegaly is less clear than IGF-1. In addition, the clinical experts noted that biochemical control of acromegaly is not a direct predictor of symptom control, and the effect of IGF-1 on patient-important outcomes and comorbidities is very uncertain. The patient groups reported that important outcomes from their point of view include shrinkage of the tumour, as well as lessening of acromegaly symptoms (such as limb growth and joint pain) and anxiety. With respect to the Acromegaly

Quality of Life Questionnaire (AcroQoL) score, pasireotide may improve this outcome compared to SSAs; however, the evidence is uncertain regarding whether pasireotide improves symptoms, and the clinical significance of any improvement in quality of life (QoL) is unclear.

In both trials, a higher proportion of patients treated with pasireotide reported adverse events (AEs) related to glucose metabolism compared to first-generation SSAs. In Study C2305, 57.3% of patients in the pasireotide arm, versus 21.7% of patients in the octreotide arm, had hyperglycemia-related AEs of any grade. In Study C2402, 33.3% of patients in the pasireotide 40 mg arm and 30.6% of patients in the pasireotide 60 mg arm reported hyperglycemia, versus 13.6% of patients in the active control arm (octreotide or lanreotide). In the same study, 20.6% of patients in the pasireotide 40 mg arm and 25.8% of patients in the pasireotide 60 mg arm reported diabetes mellitus, versus 7.6% of patients in the active control arm.

There was no direct evidence comparing pasireotide and pegvisomant, which was identified as the comparator of interest in the treatment of patients with acromegaly for whom surgery is not an option or has not been curative, and whose disease is inadequately controlled on treatment with a first-generation SSA. One indirect treatment comparison (ITC) using the Bucher method was submitted by the sponsor. However, due to important methodological limitations — including inappropriate choice of ITC method and intransitivity — no conclusions can be drawn from the ITC results.

The committee considered an analysis conducted by Canada's Drug Agency (CDA-AMC), using the sponsor's economic model in the reimbursement-requested population, which considered the cost-effectiveness of pasireotide relative to octreotide, lanreotide, and pegvisomant, based on IGF-1 normalization. The effects of IGF-1 on clinical end points and acromegaly comorbidities are uncertain. The committee discussed the lack of evidence for IGF-1 as a valid surrogate for clinical end points. Due to the uncertainty associated with the comparative clinical effectiveness and cost-effectiveness of pasireotide, and a higher risk of glucose-metabolism–related AEs compared to first-generation SSAs, the total drug cost of pasireotide should not exceed the total drug cost of first-generation SSAs.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients with a confirmed diagnosis of acromegaly and all of the following: 1.1. Patients must be ineligible for, have contraindications to, or demonstrated lack of response to surgery. 1.2. Patients must have shown inadequate control of disease with a first-generation SSA, octreotide, or lanreotide for a 6-month trial.	Evidence from 2 phase III RCTs (Study C2305 and Study C2402) suggests that treatment with pasireotide likely results in an improvement in the number of patients who achieve IGF-1 normalization, when compared to other SSAs. About 50% of patients do not respond to SSAs. In addition, the reimbursement request is for the treatment of patients whose disease is inadequately controlled on treatment with first-generation SSAs. The majority of patients enrolled in	Based on clinical expert opinion, a 6-month trial of a first-generation SSA would be reasonable for assessing eligibility for pasireotide. In Study C2305 and Study C2402, the diagnosis of acromegaly was confirmed according to the following criteria: • a lack of suppression of GH nadir to 5 mcg/L • elevated circulating IGF-1. Lack of response to surgery is demonstrated within 3 to 6 months

Reimbursement condition	Reason	Implementation guidance
	the trials received treatment at least 3 months after the previous surgery.	following surgery. Therefore, pasireotide treatment should not be initiated until at least 3 months have passed since surgery, to allow adequate time for assessing surgical outcomes. CDEC noted that patients with hemoglobin A1C > 8% were excluded from Study C2305 and Study C2402.
2. The maximum duration of initial authorization is 6 months.	In Study C2402, the primary end point was the proportion of patients achieving biochemical control (GH < 2.5 mcg/L and normalization of sex-adjusted and age-adjusted IGF-1) at week 24.	—
Renewal		
3. For renewal after the initial 6-month authorization, the physician must provide proof of either of the following: 3.1. age-normalized IGF-1 < ULN 3.2. a reduction of at least 50% in age-normalized IGF-1 levels from baseline, accompanied by improved symptom control. Additionally, at least 3 months must have passed since surgery.	The renewal criteria were informed by input from clinical experts, who advised CDEC that the criteria should be based on age-normalized IGF-1 levels. They further recommended that if there is evidence of a meaningful reduction in IGF-1 — defined as at least a 50% decrease — within 6 months of initiating treatment, accompanied by symptom improvement, the trial period can be extended beyond 6 months. Frequent assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.	Symptom control should be based on the clinician assessment. Based on clinical expert opinion, assessment of treatment effectiveness may include tumour growth control, reduction in tumour size, and the prevention and management of symptoms and comorbidities associated with acromegaly, in addition to biochemical control. The clinical experts noted that, although there is no consensus on the threshold for a clinically meaningful change in tumour volume, clinical studies typically define significant tumour shrinkage as a reduction of 10% to 25% in tumour volume or diameter. The clinical experts noted to CDEC that more than 90% of patients with acromegaly undergo surgery as first-line treatment. Repeat surgery is less common. If a patient is already receiving pasireotide after their first surgery and needs a second surgery, they should discontinue treatment with pasireotide for 3 to 6 months to assess the outcome of surgery and if acromegaly symptoms are not under control, treatment with pasireotide can be restarted. Pasireotide could be renewed similarly to pegvisomant as per the reimbursement criteria for each public drug plan.
4. For subsequent renewals following the initial renewal—beginning 12 months after treatment initiation and annually thereafter— the physician		

Reimbursement condition	Reason	Implementation guidance
must provide proof of age-normalized IGF-1 < ULN and improved symptom control		
Discontinuation		
5. If patients undergo radiotherapy while on treatment, they should remain on medical treatment until biological remission is achieved. If IGF-1 and GH are normalized, then drug therapy should be withheld.	The clinical experts noted that coverage should continue at least until patients achieve biochemical remission without the need for medical therapy; periodic assessment must be done, and once IGF-1 levels drop to low or below-normal levels, drug therapy should be withheld and biochemical assessment should be done.	—
Prescribing		
6. Pasireotide should be prescribed by specialists who have expertise in the diagnosis and management of acromegaly.	This is meant to ensure that pasireotide is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
Pricing		
7. Pasireotide should be negotiated so that it does not exceed the drug program cost of treatment with a first-generation SSA for the treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative.	The clinical trials for pasireotide consider IGF-1 normalization, which does not provide information on patient-important outcomes or comorbidities associated with acromegaly. As such, there is insufficient evidence to justify a cost premium for pasireotide over a first-generation SSA reimbursed for the treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative.	—

CDEC = Canadian Drug Expert Committee; GH = growth hormone; SSA = somatostatin analogue; ULN = upper limit of normal.

Discussion Points

Reconsideration request: The sponsor requested a minor reconsideration of the initial draft recommendation to reimburse with conditions pasireotide for the treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative and whose disease is inadequately controlled on treatment with a first-generation SSA. During the minor reconsideration discussion, a subpanel of the committee discussed the issue raised by the sponsor in their request for reconsideration, which involved a proposed change to the renewal criteria. CDEC also discussed feedback from the drug plans and the clinical experts on the initial draft recommendation.

Criteria for significant unmet need are met: CDEC deliberated on pasireotide considering the criteria for significant unmet need that are described in section 9.3.1 of the Procedures for Reimbursement Reviews.

Acromegaly is a rare and chronic disease with significant morbidity that affects patients' QoL. Treatment options for people with an inadequate response to first-generation SSAs are limited.

Efficacy: Results from the 2 included randomized trials suggest that pasireotide likely elicits a clinically significant improvement in the number of patients who achieve IGF-1 normalization. Whether this improvement in IGF-1 results in clinically significant improvements in health-related quality of life (HRQoL) or symptoms is unclear due to the lack of established minimally important clinical differences for the instruments used and the relatively modest changes observed for these outcomes with pasireotide compared to other SSAs. Symptoms and HRQoL are clearly important outcomes for patients. There were no trials that directly compared pasireotide to pegvisomant (the only GH receptor antagonist approved for treatment of acromegaly), and there were no trials that assessed the combination of these 2 drugs. No definitive conclusions could be drawn from the available ITC; therefore, there is no clear direct or indirect comparative evidence of the relative efficacy and harms of pasireotide compared to pegvisomant. A single-arm trial (Study C2413) was reviewed as supportive evidence on the use of pasireotide in patients with acromegaly whose disease was uncontrolled on maximal approved doses of SSAs, based on the current definitions of biochemical control, which have been updated since Study C2305 and Study C2402 were conducted. However, the exploratory nature of the trial and the absence of a comparator group limit the conclusions that can be drawn from this supportive evidence.

IGF-1 as a potential surrogate end point for clinical outcomes: CDEC noted that although biochemical outcomes were considered to be established key biomarkers in clinical practice, the clinical control of acromegaly symptoms may not correspond to biomarkers (e.g., due to long-term tissue changes, joint and soft tissue damage, comorbid conditions, and so on). CDEC noted that no evidence was provided to support a relationship between IGF-1 levels and clinical outcomes. There was no indication from either of the included studies that HRQoL was improved to a clinically significant extent with pasireotide, and the impact on symptoms is unknown. The clinical experts noted that biochemical control of acromegaly is not a direct predictor of symptom or comorbidity control and does not result in an immediate improvement in HRQoL, adding that the follow-up period of the trials may not have been sufficiently long to assess changes in symptoms and HRQoL.

Continuation of treatment: During the reconsideration meeting, the CDEC subpanel reviewed the sponsor's proposed changes to the renewal criteria, along with feedback from clinician groups and clinical experts consulted by CDA-AMC for this review. No feedback was received from patient groups on the draft recommendation. The clinical experts advised CDEC that a GH level less than 1 should not be used as a renewal criterion; instead, they suggested basing renewal decisions on age-adjusted serum IGF-1 levels. The CDEC subpanel also deliberated on whether patients demonstrating a partial response to treatment should continue therapy. The outcomes of these discussions are reflected in the renewal conditions outlined in [Table 1](#).

Harms: CDEC discussed the higher incidence of grade 3 or 4 AEs, serious adverse events (SAEs), and withdrawals due to AEs compared to first-generation SSAs in Study C2305 and Study C2402. Given that diabetes and hyperglycemia were noted to be comorbidities of acromegaly by the clinical experts and in

patient input, CDEC noted that evidence from these 2 randomized trials demonstrated that pasireotide increases the risk of hyperglycemia compared to other SSAs. Furthermore, pasireotide is contraindicated in patients who have uncontrolled diabetes mellitus.

Uncertain economic evidence: CDEC discussed the uncertainty regarding the use of IGF-1 normalization to predict QoL and comorbidities, which is the driver of the sponsor's economic model, as well as the limitations of the indirect evidence comparing pasireotide with pegvisomant, assumptions regarding subsequent treatment, and assumption of sustained IGF-1 normalization over the patient's lifetime. In addition, CDEC noted that evidence of the higher rates of hyperglycemia from the clinical trials (Study C2402 and Study C2305) and the subsequent risk of diabetes were not fully captured in the sponsor's economic model (e.g., increased monitoring costs, treatment of diabetes), which could increase the total cost associated with treatment with pasireotide.

Background

Acromegaly is a rare, chronic endocrine disorder caused by excessive GH secretion, often due to a benign pituitary adenoma, resulting in elevated IGF-1 levels that stimulate cell proliferation and inhibit cell death. This hormonal imbalance leads to structural tissue changes and various comorbidities. Although rare, acromegaly has a prevalence of 60 cases per 1 million people in Canada, affecting women slightly more than men. In 2024, the Acromegaly Consensus Group introduced guidelines for diagnosis, highlighting that IGF-1 levels more than 1.3 times higher than the age-adjusted upper limit confirm the condition in symptomatic patients, with additional tests like oral glucose tolerance tests recommended for ambiguous cases, also considering factors such as body mass index, diet, and genetic background.

Acromegaly is typically managed through multimodal treatment including surgery (first line), pharmacotherapy (second line), and adjunctive radiation therapy. The clinical experts noted that small and noninvasive tumours tend to have a high initial remission of more than 80%, albeit with a significant risk of recurrence. There are 2 categories of medical therapy: drugs that reduce GH secretion (dopamine agonists [which are rarely effective] and SSA, both first- and second-generation), and GH receptor antagonists like pegvisomant. The clinical experts added that radiation therapy is used if there is an inoperable tumour, and that repeat surgery is an option but is seldom effective. The clinical experts noted that a major unmet need is that half of patients do not experience a response to SSAs, which leads to combination therapy, which can be expensive depending on the patients' access to public and/or private reimbursement and increases the risk of side effects.

The recommended initial dose of pasireotide for the treatment of acromegaly is 40 mg administered by deep intramuscular injection every 4 weeks. The dose may be increased to a maximum of 60 mg for patients whose GH and/or IGF-1 levels are not controlled after 3 months of treatment with pasireotide at 40 mg. Pasireotide is a second-generation cyclohexapeptide injectable SSA. Pasireotide exerts its pharmacological activity via binding to multiple somatostatin receptors (SSTRs). Pasireotide binds with high affinity to 4 of the 5 SSTRs: SSTR5, SSTR2, SSTR3, and SSTR1.

Pasireotide underwent the standard review process at Health Canada and received an Notice of Compliance (NOC) on May 21, 2020. Pasireotide is indicated for the treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative. The sponsor's reimbursement request is for the treatment of acromegaly in adult patients for whom surgery is not an option or has not been curative and whose disease is inadequately controlled on treatment with a first-generation somatostatin analogue.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 2 phase III RCTs in patients with active acromegaly, and 1 ITC
- patients' perspectives gathered by 2 patient groups, Acromegaly Canada and the Canadian Association for Rare Disorders
- input from public drug plans that participate in the Reimbursement Review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with acromegaly
- input from 1 clinician group, the Canadian Society of Endocrinology and Metabolism (CSEM)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the sponsor's request for minor reconsideration (described subsequently)
- feedback on the draft recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to the review team's call for input and from clinical experts consulted for the purpose of this review.

Patient Input

Two patient groups, Acromegaly Canada and the Canadian Association for Rare Disorders, provided input on pasireotide for patients with acromegaly for whom surgery is ineffective or unavailable. Another group, Acromegaly Community (a US-based support network that has members who live in Canada), also helped to collect data from patients with acromegaly. Feedback was gathered via interviews with 6 patients and a survey of 26 participants (64% in Canada and 36% in the US), revealing that most patients face severe symptoms like hand and foot enlargement, facial feature changes, joint pain, and various comorbidities (diabetes, sleep apnea, hypertension). Although SSAs were seen as generally effective, side effects such as injection site pain and gastrointestinal discomfort were common. Among 6 users of pasireotide (5 patients in US and 1 in Canada), satisfaction was high, with reports of mild to moderate side effects, contrasting with other treatments that were rated as less effective or only moderately effective. Patient group input

reported that important outcomes from their point of view included shrinkage of the tumour and lessening of acromegaly symptoms (such as limb growth and joint pain) and anxiety.

Clinician Input

Input From Clinical Expert Consulted for This Review

The clinical experts noted a major unmet need is that 50% of patients do not experience a response to first-generation SSAs, which leads to combination therapy, which has an increased risk of side effects and modest efficacy. The clinical experts noted that they see pasireotide being used in patients who do not experience a response to SSA therapy and who do not have dysglycemia, and that it may also be used in combination with pegvisomant in patients whose disease remains unresponsive. The clinical experts also noted that pasireotide could be used first-line in centres where SSTR staining is available, to identify patients who express the target SSTRs for pasireotide and not for first-generation SSA therapy. The clinical experts believed that the patients most likely to benefit from pasireotide are those who have adequate SSTR staining, those who have not experienced a response to first-generation SSAs, and those whose tumours are densely granulated on pathology and have a normal glucose profile. The clinical experts believed that those least suitable are those who have uncontrolled hyperglycemia. The clinical experts noted that biochemical response (serum GH and IGF-1) is a key method for assessing response, as are radiological response (tumour stability or shrinkage), symptoms, and QoL.

Clinician Group Input

CSEM, comprising 15 physicians, highlighted that the primary goals in acromegaly treatment are normalizing GH and IGF-1 levels, reducing tumour size, and managing symptoms and comorbidities. Treatments include surgery, medical therapies, and radiotherapy, with first-generation SSAs like octreotide and lanreotide as initial pharmacotherapy. They noted that more than 40% of patients do not achieve full biochemical control with SSAs, and that access to pegvisomant, a second-line GH receptor antagonist, is limited. CSEM noted that pegvisomant, while controlling IGF-1, does not affect GH, and its daily injections pose adherence challenges. They emphasized that achieving control of both GH and IGF-1 is crucial for reducing acromegaly's overall burden. Their experience in using pasireotide is proposed as a promising alternative for patients whose disease is uncontrolled by SSAs or pegvisomant, with the potential to lessen treatment burden and improve QoL.

Drug Program Input

Input was obtained from the drug programs that participate in the Reimbursement Review process. The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Which specialists primarily diagnose and treat patients with acromegaly?	The clinical experts noted to CDEC that patients with acromegaly present to, and may be initially diagnosed by, several specialties — including rheumatology (for joint disease), dental surgery (for jaw and teeth issues), cardiology (for cardiac issues), and family medicine — and the diagnosis is confirmed by a specialist endocrinologist. According to the clinical experts, the primary treatment is the removal of adenoma, performed by neurosurgery, and then medical treatment and lifelong follow-up are done by endocrinologists. In patients whose disease is not responding to medical therapy, radiation therapy may be administered by radiation oncologists.
Considerations for initiation of therapy	
In Study C2402, 60% to 77% of patients had previous surgery and few patients had previous radiation therapy. Questions: • Is it reasonable for patients to have surgery, radiation therapy, and failure of an SSA before initiating pasireotide? • What is a reasonable duration of trial (e.g., 6 months) with a first-generation SSA before transitioning to pasireotide? • What level of GH and/or IGF-1 or severity of symptoms is considered treatment failure? • What are common contraindications to surgery? • In your experience, what percentage of patients have subsequent surgery for pituitary adenomas?	Radiotherapy is reserved for patients who have declined, experienced treatment failure with, or are deemed unfit for surgical and/or medical treatments, due to its potential complications, such as pituitary dysfunction, according to the clinical experts. As pasireotide is expected to be used when surgery and medical management with a first-generation SSA fail to provide biochemical control, it is reasonable for patients to have surgery and experience treatment failure with a first-generation SSA before initiating pasireotide. The clinical experts added that radiation therapy may take several years to reach full effect and medical therapy may be required during that time. The clinical experts indicated that a 6-month trial of a first-generation SSA would be reasonable. According to the clinical experts, failure of normalization of GH and IGF-1 (random GH < 1 mcg/L and age-normalized IGF-1 < ULN) has since been recommended by the Pituitary Society, the Acromegaly Consensus Group, and the Endocrine Society. The clinical experts added that symptoms may improve only partially (due to long-term tissue changes, joint and soft tissue damage, comorbid conditions, and so on after chronic exposure to excess GH and IGF-1). Common contraindications to pituitary surgery for acromegaly, according to the clinical experts, are as follows: • Patient refusal: Surgery cannot proceed without the patient's consent. • Severe cardiomyopathy: Significant heart disease can increase the risks associated with anesthesia and surgical complications. • Respiratory disease: Severe respiratory conditions can complicate both anesthesia and postoperative recovery. • Advanced age or debility: Older patients or those with significant frailty may not tolerate the stress of surgery well. • Lack of an available skilled surgeon: The absence of a surgeon experienced in pituitary surgery can be a contraindication due to the complexity of the procedure. • Location and size of pituitary tumour: Medical therapy would be preferred for a GH-secreting microadenoma with cavernous sinus invasion.

Implementation issues	Response
	In the experience of the clinical experts, about 90% of patients have subsequent surgery for pituitary adenomas.
Considerations for continuation or renewal of therapy	
In the PAOLA trial (Study C2402), the primary end point was the proportion of patients with GH < 2.5 mcg/L and normalized IGF-1 at week 24. • Pasireotide 40 mg every 28 days: 15% of patients reached the primary end point. • Pasireotide 60 mg every 28 days: 20% of patients reached the primary end point. Questions: • Should normalization of GH and IGF-1 be used as parameters for renewal of coverage? If not, what assessment tools should be implemented for renewal of coverage? • Is 24 weeks a reasonable time frame to assess efficacy of pasireotide, or should a longer time frame for initial coverage be considered? • Is there an MCID for AcroQoL score? Should this be considered as a measure to assess renewal of coverage? • To assess suitability for renewal of coverage, how often should the following markers be monitored? ◦ IGF-1 ◦ GH ◦ AcroQoL score	The clinical experts indicated that biochemical parameters are the key outcome they use to monitor patient progress in clinical practice; this view is supported by consensus guidelines, and IGF-1 has emerged as the most important biochemical parameter (ahead of GH). Based on this input, and the primary outcomes of the clinical trials reviewed, biomarker normalization appears to be the most relevant and objective parameter to determine effect of treatment with pasireotide. The clinical experts further noted that the assessment of treatment effect may include tumour growth control, reduction in tumour size, and the prevention and management of symptoms and comorbidities associated with acromegaly, in addition to biochemical control. Although there is no consensus on the threshold for a clinically meaningful change in tumour volume, the clinical experts noted that clinical studies typically define significant tumour shrinkage as a reduction of 10% to 25% in tumour volume or diameter. The clinical experts added that if pasireotide monotherapy proves to be ineffective, a combination therapy involving cabergoline and pasireotide may be considered. The clinical experts noted that 24 weeks is a reasonable time frame to assess the efficacy of pasireotide — adding, however, that if pasireotide monotherapy proves to be ineffective, a combination therapy involving cabergoline and pasireotide may be considered. Currently, there is no established MCID for AcroQoL score. One clinical expert explained that considering the AcroQoL as a measure for assessing the renewal of coverage for drugs for acromegaly could be beneficial, as it provides valuable insights into the patient's quality of life, which is an important aspect of treatment effectiveness beyond biochemical control and tumour size reduction, adding that including such patient-reported outcomes in coverage decisions could ensure a more holistic approach to patient care. The other clinical expert believed that requiring the AcroQoL for renewal is not ideal, as this is somewhat subjective, and suggested using biochemical markers like IGF-1, also adding that an OGTT is not ideal in patients taking SSA therapy. According to 1 clinical expert, to assess suitability for renewal of coverage, these biomarkers (IGF-1 and GH) and AcroQoL score should be monitored every 6 to 12 months. CDEC recommended that, for renewal after initial authorization and each subsequent annual renewal, the physician must provide proof of normalization of GH and IGF-1 as follows: random GH < 1 mcg/L and age-normalized IGF-1 < ULN. Additionally, the patient should not have undergone surgery within the past 3 to 6 months. CDEC also recommended that pasireotide not be reimbursed when used in combination with cabergoline or pegvisomant.

Implementation issues	Response
Considerations for discontinuation of therapy	
If a patient receives subsequent radiation therapy or surgery while on pasireotide, should coverage be discontinued? If normalization of GH and IGF-1 are used as parameters for renewal, what levels of GH and/or IGF-1 would be considered a failure of treatment, and at which point should pasireotide be discontinued?	According to the clinical experts, surgical or radiation treatment outcomes may be successful, partially successful, or unsuccessful. Therefore, coverage should continue at least until the patients achieve biochemical remission without the need for medical therapy; periodic assessment must be done, and once IGF-1 levels drop to low or below-normal levels, drug therapy should be withheld and biochemical assessment should be done. The clinical experts noted that normalization of GH and IGF-1 is as follows: random GH < 1 mcg/L and age-normalized IGF-1 < ULN. However, the clinical experts added that assessment of treatment effectiveness may include tumour growth control, reduction in tumour size, and the prevention and management of symptoms and comorbidities associated with acromegaly, in addition to biochemical control. The clinical experts noted that although there is no consensus on the threshold for a clinically meaningful change in tumour volume, clinical studies typically define significant tumour shrinkage as a reduction of 10% to 25% in tumour volume or diameter. The clinical experts added that if pasireotide monotherapy proves to be ineffective, a combination therapy involving cabergoline and pasireotide may be considered. The clinical experts also noted that patients should continue to receive pasireotide until they either do not achieve a clinical benefit from therapy or are unable to tolerate the treatment. CDEC recommended that if patients undergo radiotherapy while on treatment, they should remain on medical treatment until biological remission is achieved. If IGF-1 and GH are normalized, then drug therapy should be withheld.
Considerations for prescribing of therapy	
In the pivotal study, only 15% to 20% of patients had normalized IGF-1 and GH values at week 24. Would the next step in therapy be to add on another agent to pasireotide, such as cabergoline or pegvisomant?	The clinical experts responded that yes, a combination therapy may be considered. CDEC noted that, due to a lack of evidence to support the use of pasireotide in combination with pegvisomant or cabergoline, pasireotide should not be reimbursed when used in combination with cabergoline or pegvisomant.
Generalizability	
Health Canada indication for pasireotide is for adult patients. Would off-label pediatric use be anticipated for this product?	The clinical experts noted that off-label use in pediatric patients could be considered in certain circumstances, however, this would depend on the clinical judgment of health care providers, who would weigh the potential benefits against the risks due to the lack of extensive data on its safety and efficacy in children. The clinical experts added that due to the rarity of acromegaly in pediatrics, the chance of off-label pediatric use would be very low. CDEC noted that there is no evidence provided on the efficacy and safety of pasireotide in pediatric patients, and hence recommended to restrict reimbursement to adult patients.

AcroQoL = Acromegaly Quality of Life Questionnaire; GH = growth hormone; MCID = minimally clinically important difference; OGTT = oral glucose tolerance test; SSA = somatostatin analogue; ULN = upper limit of normal.

Clinical Evidence

Systematic Review

Description of Studies

Two multicentre, sponsor-funded, phase III RCTs (Study C2305 and Study C2402), were included in this review. Study C2305 was a blinded study of pasireotide versus octreotide in patients with active acromegaly who had not received previous medical treatment, over a 12-month treatment period. In Study C2402, patients were randomly allocated to receive either pasireotide 40 mg or pasireotide 60 mg (in double-blind fashion), or to continue on the maximum indicated dose of octreotide 30 mg or lanreotide autogel (ATG) 120 mg as before randomization (in an open-label, active control arm). The treatment course was 24 weeks. The primary outcome of each study was the proportion of patients with a reduction of GH level to less than 2.5 mcg/L and normalization of IGF-1 to within normal limits (age-related and sex-related). Secondary outcomes assessed normalization of IGF-1, change from baseline in AcroQoL score, and symptoms.

Across both studies, the average patient age was 45 years, and there were slightly more females than males (52% of patients were female in Study C2305, and 55% were female in Study C2402). The majority of patients were white in both studies (60% in Study C2305 and 81% in Study C2402). Patients had been diagnosed with acromegaly for approximately 20 months in Study C2305, and for approximately 72 weeks in Study C2402.

Efficacy Results

Proportion of Patients With a Reduction of GH Level to Less Than 2.5 mcg/L and Normalization of IGF-1

Study C2305

The proportion of patients with a treatment response (i.e., patients with GH < 2.5 mcg/L and normalized IGF-1) at month 12 was 31.3% (95% CI, 24.5 to 38.7) in the pasireotide arm and 19.2% (95% CI, 13.8 to 25.7) in the octreotide arm, with an OR of 1.942 (95% CI, 1.190 to 3.168) in favour of pasireotide.

When analyzed by stratum, the response rates were slightly higher for patients who had undergone surgery, relative to de novo patients for both pasireotide and for octreotide. The OR indicated a treatment effect in favour of pasireotide for patients who had undergone surgery (OR = 2.337; 95% CI, 1.140 to 4.790), while the difference between the treatments was less marked for de novo patients (OR = 1.654; 95% CI, 0.846 to 3.234).

The results of the analysis of the primary efficacy end point for the per-protocol set, and where patients with missing values were considered as not having a response to treatment, were consistent with the primary efficacy analysis.

Study C2402

In the pasireotide 40 mg arm, 10 patients (15.4%) achieved biochemical control at 24 weeks compared with none in the active control arm (OR = 16.63; 95% CI, 3.32 to infinity). In the pasireotide 60 mg arm, 13 patients (20.0%) achieved biochemical control at 24 weeks (OR = 23.03; 95% CI, 4.72 to infinity).

Patients With Normalization of IGF-1

Study C2305

The proportion of patients with normalized IGF-1 was 38.6% (95% CI, 31.4% to 46.3%) in the pasireotide arm, and 23.6% (95% CI, 17.7% to 30.5%) in the octreotide arm, with an OR of 2.087 (95% CI, 1.316 to 3.308) in favour of pasireotide. By strata, the response rates for patients who had undergone surgery were 50.7% for pasireotide and 26.9% for octreotide; for de novo patients, the response rates were 30.5% for pasireotide and 21.2% for octreotide.

Study C2402

The proportion of patients who achieved normalization of IGF-1 at week 24 (key secondary efficacy end point) was higher for both pasireotide 40 mg (24.6%; 95% CI, 14.77% to 36.87%) and pasireotide 60 mg (26.2%; 95% CI, 16.03% to 38.54%) in those with a treatment response compared to the active control arm (no patients with a response), for an OR of 30.12 (95% CI, 6.28 to infinity; $P < 0.0001$) in the pasireotide 40 mg group and 32.66 (95% CI, 6.84 to infinity; $P < 0.0001$) in the pasireotide 60 mg group.

Acromegaly Quality of Life Questionnaire

Study C2305

The AcroQoL scale ranges from 22 (worst QoL) to 110 (best QoL). From a baseline mean of 58.4 (standard deviation [SD] = 19.97) in the pasireotide group (N = 173) and 55.6 (SD = 19.79) in the octreotide group (N = 178), the AcroQoL total score mean change from baseline to 12 months was 7.0 (SD = 14.54) in the pasireotide group (N = 133) and 4.9 (SD = 15.50) in the octreotide group (N = 146).

Study C2402

At baseline, mean AcroQoL scores were [REDACTED] in the pasireotide 40 mg group (N = 62), [REDACTED] in the pasireotide 60 mg group (N = 60), and [REDACTED] in the active control group. At week 24, the mean change from baseline in AcroQoL total score was 2.6 [REDACTED] in the pasireotide 40 mg group (N = 57), [REDACTED] in the pasireotide 60 mg group (N = 55) and [REDACTED] in the active control group (N = 62).

Symptoms of Acromegaly

Study C2305

The symptoms scale used by the sponsor ranged from 0 (absent) to 4 (severe). From a mean baseline of 0.9 (SD = 1.05) in the pasireotide group (N = 175) and 1.0 (SD = 1.14) in the octreotide group (N = 181), after 12 months, the mean change from baseline in headache scores was -0.3 (SD = 1.17) in the pasireotide group (N = 138) and -0.4 (SD = 0.94) in the octreotide group (N = 149). From a mean baseline of 1.0 (SD = 1.05) in the pasireotide group (N = 174) and 1.3 (SD = 1.26) in the octreotide group (N = 178), after 12 months,

the mean change from baseline in osteoarthralgia scores was -0.4 (SD = 1.07) in the pasireotide group (N = 137) and -0.6 (SD = 1.20) in the octreotide group (N = 146).

Study C2402

From a mean baseline of 1.3 (SD = [REDACTED]) in the pasireotide 40 mg group (N = 65), 1.2 (SD = [REDACTED]) in the pasireotide 60 mg group (N = 64), and 1.1 (SD = [REDACTED]) in the active control group (N = 67), after 24 weeks, the mean change from baseline in headache scores was [REDACTED] (SD = [REDACTED]) in the pasireotide 40 mg group (N = 59), [REDACTED] in the pasireotide 60 mg group (N = 58), and [REDACTED] in the active control group (N = 65). From a mean baseline of [REDACTED] in the pasireotide 40 mg group (N = 63), [REDACTED] in the pasireotide 60 mg group (N = 64), and [REDACTED] in the active control group (N = 67), after 24 weeks, the mean change from baseline in osteoarthralgia scores was [REDACTED] in the pasireotide 40 mg group (N = 59), [REDACTED] in the pasireotide 60 mg group (N = 58), and $-$ [REDACTED] [REDACTED] in the active control group (N = 65).

Harms Results

Adverse Events

Study C2305

Most patients experienced at least 1 AE during the core phase of the study. The most frequent event in both treatment groups was diarrhea (39.3% versus 45.0% for pasireotide versus octreotide). By preferred term, AEs that were more frequent (at least 5% difference) in the pasireotide than the octreotide group were all related to glucose metabolism: hyperglycemia, diabetes mellitus, increased blood glucose, and type 2 diabetes mellitus. AEs that were more frequent (at least 5% difference) in the octreotide group were diarrhea, cholelithiasis, headache, and nausea.

The incidence of grade 3 or 4 AEs was slightly higher in the pasireotide group ([REDACTED]) than the octreotide group ([REDACTED]) this difference was mainly due to a higher proportion of grade 3 or 4 hyperglycemia-related AEs (e.g., hyperglycemia, diabetes mellitus) in the pasireotide group.

Study C2402

The most frequently reported AEs in all 3 treatment groups, with at least a 10% difference between pasireotide 40 mg and pasireotide 60 mg versus active control, respectively, were hyperglycemia (33.3% and 30.6% versus 13.6%), diabetes mellitus (20.6% and 25.8% versus 7.6%), and diarrhea (15.9% and 19.4% versus 4.5%). Overall, grade 3 or grade 4 AEs were reported more frequently in the pasireotide 40 mg and pasireotide 60 mg groups compared to the active control group. This difference was mainly due to grade 3 or 4 hyperglycemia-related AEs (e.g., hyperglycemia, diabetes mellitus) in both pasireotide groups. Four patients in the pasireotide 40 mg group had a first-degree atrioventricular block. In addition, 1 patient in the pasireotide 60 mg group had a similar event (atrioventricular block). These events were all grade 1. For 3 of the 5 patients, the atrioventricular block was present before the start of treatment.

Serious Adverse Events

Study C2305

Overall, there were 35 patients (19.7%) receiving pasireotide and 27 patients (15.0%) receiving octreotide who reported an SAE. The most frequent SAE was cholelithiasis (in 4 patients [2.2%] receiving pasireotide and 3 patients [1.7%] receiving octreotide).

Study C2402

Overall, few patients had SAEs: 6 patients (9.5%) in the pasireotide 40 mg group, 2 patients (3.2%) in the pasireotide 60 mg group, and 3 (4.5%) in the active control group. There was no specific SAE that occurred in more than 1 patient.

Withdrawals Due to Adverse Events

Study C2305

AEs leading to discontinuation were slightly more frequent in the pasireotide group (9.0%) than in the octreotide group (5.0%). Apart from diabetes mellitus and hyperglycemia, each preferred term was reported for no more than 1 patient in each group.

Study C2402

Seven patients (3 in the pasireotide 40 mg group and 4 in the pasireotide 60 mg group) had AEs that led to discontinuation. Six of the 7 patients discontinued treatment due to a hyperglycemia-related event.

Mortality

Study C2305

There was 1 death in the octreotide group, and there were no deaths in the pasireotide group. The death was due to a myocardial infarction.

Study C2402

There were no deaths in Study C2402.

Notable Harms

Study C2305

In the core phase, the only category of AEs of special interest that occurred with a higher frequency in the pasireotide group (at least a 5% difference) was hyperglycemia-related AEs (57.3% versus 21.7% for pasireotide versus octreotide).

In the octreotide group, the following categories of AEs of special interest occurred with a higher frequency (at least a 5% difference, for octreotide versus pasireotide, respectively): diarrhea-related AEs (45.0% versus 39.3%), gallbladder and biliary-related AEs [REDACTED] and nausea-related AEs [REDACTED]

Study C2402

The most frequent category in all treatment groups was hyperglycemia-related AEs: 66.7% and 61.3% in the pasireotide 40 mg and 60 mg groups, respectively, and 30.3% in the active control group. Hyperglycemia-related events that were severe (grade 3) were only reported for pasireotide (none were grade 4).

Gallbladder and biliary-related AEs were also common and equally frequent with all 3 treatments. [REDACTED] the most frequent preferred term was cholelithiasis. None of these events were SAEs. Apart from hyperglycemia-related AEs, the only other AE category with a higher incidence reported with pasireotide than in the active control group was diarrhea-related AEs (15.9% and 19.4% with pasireotide 40 mg and 60 mg, respectively, versus 4.5% in the active control group). In addition to the patient with an AE of liver injury, 4 patients had AEs related to the category of “liver safety”: 2 patients in the pasireotide 40 mg group (grade 1 alanine aminotransferase [ALT] increased, grade 2 “liver function test abnormal”), 1 patient in the pasireotide 60 mg group (ALT and gamma-glutamyl transferase [GGT] increased, both grade 1), and 1 patient in the active control group (aspartate transaminase [AST] and GGT increased, both grade 1). The event “liver function test abnormal” and the ALT elevations resolved without intervention.

Critical Appraisal

The open-label design of Study C2402 may bias assessment of outcomes, particularly patient-reported outcomes like AcroQoL and symptoms. Although the AcroQoL instrument is validated, the symptom scales used in both studies were not, and minimal important differences (MIDs) were not available for any of these outcomes, limiting the review team’s ability to assess the clinical relevance of the findings. There was a relatively large number of withdrawals in Study C2305, and there were more withdrawals in the pasireotide group than in the octreotide group (20% versus 14%). As a result, there was a large amount of data missing from patient-reported outcomes, limiting confidence in these analyses. With respect to external validity, Study C2402 was designed so that patients enrolled into the active control group were all patients who continued on therapies with which they were already experiencing treatment failure, which may have biased results when compared to the same patients who were randomized to pasireotide.

The clinical experts noted that the dose of octreotide used in the included trials was lower (20 mg or 30 mg) than the dose typically used in Canada (40 mg), which may bias efficacy results in favour of pasireotide and harms results against pasireotide. Although pasireotide is likely going to be used in the second line, there are no studies that directly compare the 2 drugs.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was based on the sponsor’s Summary of Clinical Evidence, consultation with the clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: proportion of patients with normalization of GH or IGF-1 (primary outcome of both included studies), proportion of patients with normalization of IGF-1, change from baseline in AcroQoL score, change from baseline in symptoms (headache, osteoarthralgia), and notable harms (hyperglycemia-related events).

Table 3: Summary of Findings for Pasireotide vs. Octreotide or Lanreotide for Patients With Acromegaly

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
GH or IGF-1 response				
Patients with a reduction of mean GH level to < 2.5 mcg/L and the normalization of IGF-1 to within normal limits (age-related and sex-related), n per N (%) Follow-up indicated in parentheses	Study C2305: N = 358 Study C2402: N = 133	Study C2305 (12 months) • Pasireotide: 313 per 1,000 • Octreotide: 192 per 1,000 • Risk difference (95% CI): 120 more per 1,000 (31 more to 210 more) Study C2402 (24 weeks) • Pasireotide: 154 per 1,000 • Active control: 0 per 1,000 • Risk difference (95% CI): 154 more per 1,000 (66 more to 242 more)	Low ^a	Pasireotide may result in an improvement in the number of patients achieving GH or IGF-1 normalization compared to other SSAs. The clinical significance of this improvement is unknown.
IGF-1 response				
Patients with normalization of IGF-1, n per N (%) Follow-up indicated in parentheses	Study C2305: N = 358 Study C2402: N = 133	Study C2305 (12 months) • Pasireotide: 386 per 1,000 • Octreotide: 236 per 1,000 • Risk difference (95% CI): 150 more per 1,000 (55 more to 245 more) Study C2402 (24 weeks) • Pasireotide: 246 per 1,000 • Active control: 0 per 1,000 • Risk difference (95% CI): 246 more per 1,000 (141 more to 351 more)	Moderate ^b	Pasireotide likely results in an improvement in the number of patients achieving IGF-1 normalization compared to other SSAs. The clinical significance of this improvement is unknown.
HRQoL: AcroQoL				
AcroQoL total scores, LS mean (SE) change from baseline (22-item, 5-point Likert scale, with total scores ranging from 22 [worst QoL] to 110 [best QoL]) Follow-up indicated in parentheses	Study C2305: Pasireotide N = 133 Octreotide N = 146 Study C2402: Pasireotide N = 57 Control N = 62	Study C2305 (12 months) • Pasireotide: 7.2 (1.27) • Octreotide: 4.8 (1.21) • LS mean difference between groups (95% CI): 2.5 (-1.0 to 5.9) Study C2402 (24 weeks) • Pasireotide: 3.67 (2.26) • Active control: 1.91 (2.16) • LS mean difference between groups (95% CI): 1.75 (-3.83 to 7.34)	Low ^c	Pasireotide may result in an improvement in AcroQoL compared to other SSAs. The clinical significance of this improvement is unknown.
Acromegaly symptoms				
Mean (SD) change from baseline in	Study C2305: Pasireotide N = 138	Osteoarthritis Study C2305 (12 months)	Very low ^d	The evidence is very uncertain about the effects of pasireotide

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
symptoms (5-point symptom scale ranging from 0 [absent] to 4 [very severe]). Follow-up indicated in parentheses	Octreotide N = 149 Study C2402: Pasireotide N = 57 Control N = 62 Study C2305: Pasireotide N = 138 Octreotide N = 149 Study C2402: Pasireotide N = 59 Control N = 65	• Pasireotide: -0.4 (1.07) • Octreotide: -0.6 (1.20) • Mean difference between groups (95% CI): NR Study C2402 (24 weeks) • Pasireotide: -0.3 (0.92) • Active control: -0.1 (1.03) Mean difference between groups (95% CI): NR Headache Study C2305 (12 months) • Pasireotide: -0.3 (1.17) • Octreotide: -0.4 (0.94) • Mean difference between groups (95% CI): NR Study C2402 (24 weeks) • Pasireotide: -0.7 (1.11) • Active control: -0.0 1.23 • Mean difference between groups (95% CI): NR		on headaches and on osteoarthritis compared to other SSAs.
Harms				
Hyperglycemia-related AEs Follow-up indicated in parentheses	Study C2305: N = 358 Study C2402: N = 129	Study C2305 (12 months) • Pasireotide: 64 per 100 • Octreotide: 25 per 100 • Risk difference (95% CI): 38 more per 100 (29 more to 48 more) Study C2402 (24 weeks) • Pasireotide: 67 per 100 • Active control: 30 per 100 • Risk difference (95% CI): 36 more per 100 (20 more to 52 more)	High	Pasireotide results in an increased risk of hyperglycemia compared to other SSAs.

AcroQoL = Acromegaly Quality of Life Questionnaire; AE = adverse event; CI = confidence interval; CSR = Clinical Study Report; GH = growth hormone; HRQoL = health-related quality of life; LS = least squares; MID = minimal important difference; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; SSA = somatostatin analogue; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

^aRated down 2 levels: 1 level due to indirectness (unclear how GH impacts clinical outcomes and the cut-off for GH has changed) and 1 level because the lower bound of the 95% CI did not exceed the MID identified by the clinical experts.

^bRated down 1 level because the lower bound of the 95% CI did not exceed the MID in Study C2305.

^cRated down 2 levels for crossing the null.

^dRated down 3 levels: 2 levels for lack of between-group point estimate with 95% CI and 1 level for lack of validity of the instrument.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence and from the CSRs for Studies C2305 and C2402.

Long-Term Extension Studies

No additional long-term extension studies were reported by the sponsor.

Indirect Comparisons

In the absence of direct evidence between pasireotide and pegvisomant, the sponsor performed an ITC using the Bucher ITC method. This ITC aimed to estimate the effectiveness of pasireotide LAR compared to pegvisomant monotherapy and pegvisomant in combination with SSAs. The only outcome assessed was IGF-1 normalization.

Efficacy Results

IGF-1 Normalization or Biochemical Response

There were no significant differences in IGF-1 normalization when comparing either dose of pasireotide (40 mg or 60 mg combined), pegvisomant monotherapy (10 mg, 15 mg, or 20 mg combined), or combination therapy with SSAs. In the sensitivity analysis, there were no differences in terms of IGF-1 normalization that were observed in the comparison of pasireotide (40 mg and 60 mg) and pegvisomant (20 mg/day in monotherapy or combination therapy with SSAs).

Harms Results

No harms were assessed in the ITC.

Critical Appraisal

In this ITC report, the authors did not describe their methods for data extraction or conduct a quality assessment of the 3 included studies. Details of a systematic literature search and strategy for this ITC were not reported separately. The absence of a clear study selection process, a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart, and a formal quality assessment introduces potential selection and reporting biases, which may affect the validity of the conclusions. Only 3 studies were included in this ITC report, with a small number of events. This limited sample size increased the imprecision of the estimates presented in the report.

There were several sources of heterogeneity across the studies, particularly in treatment doses and comparison types. Differences in baseline characteristics and clinical factors between studies were not addressed or adjusted for. For instance, in StudyC2402 and the 2009 study by Trainer et al., patients had inadequate disease control on SSAs, while the 2000 study by Trainer et al. included a broader patient population with a mix of patients with acromegaly, regardless of their prior treatment exposure or response. Moreover, in the 2000 study by Trainer et al., eligible patients at the second screening had serum IGF-1 concentrations at least 1.3 times greater than the upper limit of the age-adjusted normal range, whereas the other studies did not conduct a second screening. These imbalances in study populations could influence the treatment effect.

The authors used Bucher's method for ITC analysis, which may not be suitable for the included studies and network structure. Bucher's model is designed for 2-arm trials with independent pairwise comparisons. However, the included studies (Study C2402, Trainer et al. [2000], and Trainer et al. [2009]) had more than 2

arms, resulting in correlated estimates that Bucher's method cannot adequately address. Another limitation was the lack of adjustment for effect modifiers. Due to inconsistencies and imbalances in treatment effect modifiers — such as differences in study populations and drug dosages — the authors did not attempt to analytically address this potential bias. There was likely heterogeneity in IGF-1 normalization estimates across different dosages and treatment methods, particularly when comparing pasireotide with pegvisomant (15 mg/day) combined with an SSA (octreotide). Although the authors mentioned using Bucher's fixed-effect model, they did not justify this choice. Given the heterogeneity and imbalance in effect modifiers, a random-effects model would likely have been more appropriate for this ITC analysis.

A significant source of intransitivity in the report was the assumption that SSAs and placebo were equivalent, which impacted the comparability of outcomes. According to the clinical experts consulted by CDA-AMC, SSAs were superior to placebo in several trials; thus, the efficacy of SSAs cannot be considered equivalent to placebo. This assumption also prevented the authors from assessing several outcomes that are important to patients, including tumour volume reduction, acromegaly symptoms, patient QoL, and safety outcomes. Due to the uncertainty in the evidence presented in the ITC report, definitive conclusions cannot be drawn from the results.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

Study C2413 was a prospective, phase IIIb, multicentre, open-label, single-arm study designed to evaluate the biochemical control of acromegaly using the latest, stricter criteria recommended, which had changed since Study C2305 and Study C2402 were conducted. The primary aim of Study C2413 was to assess the efficacy and safety of pasireotide in patients with acromegaly whose disease remained uncontrolled despite treatment with maximal approved doses of octreotide or lanreotide. In this study, adults with uncontrolled acromegaly (defined as mean GH [mGH] ≥ 1 mcg/L and IGF-I $> 1.3 \times$ ULN) who had received at least 3 months of maximal doses of long-acting octreotide or lanreotide were administered open-label pasireotide LAR 40 mg every 28 days. If biochemical control was not achieved by week 12, the dose could be increased to a maximum of 60 mg every 28 days; doses could also be reduced to as low as 10 mg every 28 days if necessary for tolerability. Patients who completed the 36-week treatment phase were eligible to continue into an extension phase (weeks 36 to 72), where concomitant acromegaly medications were permitted. The primary end point was the proportion of patients with mGH levels less than 1 mcg/L and IGF-1 levels less than the ULN at week 36, with additional assessments of biochemical control during the extension phase. Other outcomes of interest to this review that were assessed in Study C2413 included AcroQoL score, self-reported signs and symptoms of acromegaly, and harms.

Efficacy Results

By week 36, 14.6% of patients (18 of 123; 95% CI, 8.9 to 22.1) had both mGH levels less than 1.0 mcg/L and IGF-1 levels below the ULN. Mean mGH and IGF-I levels showed a progressive reduction from baseline through week 36 across all groups previously treated with first-generation SSAs.

At baseline, during the core phase, the mean AcroQoL score was 58.6 (SD = 19.2; n = 123), which increased to 63.2 (SD = 4.6; n = 110) by week 36. Among patients who progressed to the extension phase, the mean AcroQoL score was 64.0 (SD = 19.3; n = 88) at the extension baseline, increasing to 65.1 (SD = 18.7; n = 74) by week 72.

No significant changes in acromegaly symptoms were observed during the study. In the core phase, the proportion of patients without specific symptoms at baseline compared to after baseline was as follows: headache (41.5% versus 36.6%), fatigue (36.6% versus 26.0%), excessive sweating (43.1% versus 37.4%), joint pain (osteoarthralgia) (33.3% versus 26.8%), and tingling (paresthesia) (54.5% versus 47.2%). Similar proportions were seen in the extension phase.

Harms Results

Most patients (93.5%) experienced at least 1 treatment-emergent AE during the study, regardless of the study drug relationship. The majority of these AEs were grade 1 to 2. Metabolism and nutrition disorders were the most frequently reported system organ class AEs (██████████). Other system organ class AEs of any grade reported in more than 20% of all patients were infections and infestations (██████████), gastrointestinal disorders (██████████), investigations (██████████), musculoskeletal and connective tissue disorders (██████████), general disorders and administrative site conditions (██████████), and nervous system disorders (██████████).

Critical Appraisal

The open-label, single-arm design of the trial was a key limitation to interpreting the results of the study. The absence of a comparator precludes conclusions as to whether any observed effect could be attributed to pasireotide. Further, the open-label study design could increase risk of bias in subjective outcomes (e.g., patient-reported outcomes such as HRQoL and symptoms), and some AEs may have been influenced by patients' expectations of treatment. However, the presence and extent of such bias could not be determined from the trial data alone. The study enrolled its target sample size based on the primary outcome. However, another key limitation of the study was that it was exploratory in nature, with no formal hypothesis-testing planned.

Based on the views of the clinicians consulted by the CDA-AMC review team, the population of patients enrolled in Study C2413 was representative of the patients they encounter in daily practice in Canada. Additionally, the included patients aligned with the approved indication specified in the Health Canada product monograph, although it more closely aligned with the sponsor's reimbursement request because it enrolled patients with acromegaly whose disease remained uncontrolled despite treatment with maximal approved doses of octreotide or lanreotide. Furthermore, from the clinical experts' point of view, pasireotide generally would be considered for second-line treatment, typically prescribed after SSAs are found to be ineffective, which also aligns with this study's patient population.

The dosage of pasireotide used in the trial also generally reflects the recommended dosage described in the product monograph. The primary end point was defined according to the latest definition of biochemical control from the Endocrine Society, reflecting the current standard for managing acromegaly. Other outcomes

important to patients and clinicians were also assessed, including QoL, signs and symptoms of acromegaly (e.g., osteoarthritis, headache), and safety. QoL was measured using AcroQoL score, which was validated in 2014. However, this measure does not have an established MID.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree followed by a Markov model
Target population	Adult patients with acromegaly for whom surgery is not an option or has not been curative and whose disease is inadequately controlled on treatment with a first-generation SSA
Treatment	Pasireotide
Dose regimen	Deep intramuscular injection, 40 mg every 4 weeks, dose may increase to 60 mg if inadequate control after 3 months of initial treatment
Submitted prices	• \$5,048.76 per 40 mg vial • \$5,048.76 per 60 mg vial
Submitted treatment cost	\$65,859 annually per patient
Comparators	• Lanreotide • Octreotide • Pegvisomant
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (100 years)
Key data sources	• Comparative clinical efficacy for SSAs (i.e., pasireotide, lanreotide and octreotide) was obtained from the PAOLA clinical trial (Study C2402) • Sponsor-submitted ITC informed pegvisomant
Key limitations	• The comparative efficacy of pasireotide vs. all comparators is uncertain. To be enrolled in the PAOLA trial (Study C2402), patients were not experiencing disease control on their current therapy, with patients in the active control group continuing on the failing treatment. In addition, the maximum dosage of octreotide studied is lower than the typical dose prescribed in Canada. Together, this could bias efficacy results in favour of pasireotide. Additionally, there is no direct evidence comparing pasireotide to pegvisomant. The sponsor-submitted ITC had several limitations including heterogeneity in the patient population and treatment doses, and imbalances in effect modifiers that were not addressed. This results in uncertainty of the comparative efficacy of pasireotide and pegvisomant in both magnitude and direction of effects. • Pegvisomant drug costs were misaligned with clinical disease management. The sponsor assumed that, among patients who achieve a partial response, the dose would escalate to 30 mg; however, lower strengths are available. Clinical expert feedback indicated that pegvisomant dosing would follow a stepwise titration, with escalation beginning with lower strengths available. • Administration costs for lanreotide and pegvisomant were overestimated, given that a

Component	Description
	proportion of patients treated with lanreotide and all patients on pegvisomant are expected to self-administer treatment. • The effect of IGF-1 normalization on comorbidities is uncertain. Sources provided by the sponsor did not reflect the reimbursement request population. Although clinical expert feedback obtained by CDA-AMC noted the biological plausibility in a relationship between IGF-1 and comorbidities, there are no published studies that report on how changes to IGF-1 will impact comorbidities. • The incidence rate of AEs and the discontinuation rate due to AEs were obtained from Study C2305 for pasireotide and octreotide and the LANTERN trial for lanreotide, which captures a drug-naïve population and does not reflect the reimbursement request population. • The sponsor assumed that all patients would receive radiotherapy and octreotide combination therapy as subsequent therapy, which is not reflective of clinical practice according to clinical expert feedback received.
CDA-AMC reanalysis results	• The CDA-AMC reanalyses included adjusting the pegvisomant dosage to reflect the weighted dose required to achieve IGF-1 normalization according to the sponsor-submitted ITC, revising administration costs for lanreotide and pegvisomant, capturing the AE incidence and discontinuation rates reported in the PAOLA trial (Study C2402), and changing the distribution for subsequent treatments. • In the CDA-AMC base-case reanalysis, the ICER for pasireotide compared to octreotide was \$215,757 per QALY gained (incremental costs: \$434,636; incremental QALYs: 2.01) in adult patients with acromegaly for whom surgery is not an option or has not been curative, and who have inadequate disease control on treatment with a first-generation SSA. A price reduction of 71% would be necessary for pasireotide (from \$5,049 to \$1,474 per vial) to be considered cost-effective at a willingness-to-pay threshold of \$50,000 per QALY gained. • To address uncertainties regarding the effect of IGF-1 normalization on comorbidities, and to account for jurisdictions that do not provide coverage for pegvisomant, CDA-AMC conducted scenario analyses. The ICERs for pasireotide in these scenario analyses were higher than estimated in the CDA-AMC base-case reanalysis.

AE = adverse event; CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life-year; QALY = quality-adjusted life-year; SSA = somatostatin analogue.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: there was an overestimation of pegvisomant dosing; the market uptake of pasireotide was uncertain; the availability of pegvisomant in Nova Scotia is limited; the market share for pegvisomant was overestimated; the costs of subsequent treatments were not considered; and the epidemiological approach to calculate the patient population did not consider patients who do not express SSTRs. Based on CDA-AMC reanalyses, the 3-year budget impact for funding pasireotide for the treatment of acromegaly in adult patients for whom surgery is not an option or has not been curative and who are experiencing inadequate disease control on treatment with a first-generation SSA is \$9,154,091 (year 1: \$2,780,068; year 2: \$3,048,402; year 3: \$3,325,621).

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for pasireotide for injectable suspension for the treatment of adult patients with acromegaly for whom surgery is not an option or has not

been curative and whose symptoms are inadequately controlled on treatment with a first-generation SSA. In their request, the sponsor identified the following issue:

- The sponsor indicated that the renewal criteria were not aligned with clinical practice, guidelines, or the trial definitions, and that the renewal criteria failed to acknowledge that partial responders may benefit from additional time on therapy.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- feedback from 2 clinical specialists with expertise in diagnosing and treating patients with acromegaly
- feedback on the draft recommendation from 1 clinician group, CSEM
- feedback on the draft recommendation from the public drug plans that participate in the Reimbursement Review process.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunskey, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: February 26, 2025

Regrets: One expert committee member did not attend.

Conflicts of interest: None

Minor reconsideration CDEC subpanel meeting date: June 26, 2025



Canada's Drug Agency
L'Agence des médicaments du Canada
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