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

Reimbursement Recommendation

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(Draft)

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.

Recommendation: Reimburse with Conditions

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Recommendation

The CDA-AMC 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 analogues 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 respond to treatment with first generation somatostatin analogues (SSAs), and non-responders then typically must 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 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 SSA 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 SSA. In Study C2305, the proportion of patients with normalized IGF-1 was 38.6% (95% CI: 31.4, 46.3) in the pasireotide arm, and 23.6% (95% CI: 17.7, 30.5) in the octreotide arm, with an odds ratio (OR) of 2.087 (95% CI: 1.316, 3.308; p=0.002) in favor of pasireotide. The proportion of responders (i.e. patients with GH <2.5 mcg/L and normalized IGF-1) at Month 12 was 31.3% (95% CI: 24.5, 38.7) in the pasireotide arm, and 19.2% (95% CI: 13.8, 25.7) in the octreotide arm, with an OR of 1.942 (95% CI: 1.190, 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 both pasireotide 40 mg, 24.6% (95% CI: 14.77, 36.87) and 60 mg, 26.2% (95% CI: 16.03, 38.54) responders compared to the active control arm (zero responders), for an OR of 30.12 (95% CI: 6.28, infinity; p<0.0001) in the pasireotide 40 mg goup and 32.66 (95% CI: 6.84, 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 none in the active control arm (OR=16.63; 95% CI: 3.32, infinity; p=0.0006). In the pasireotide 60 mg arm, 13 patients (20.0%) achieved biochemical control at 24 weeks (OR=23.03 with 95% CI: 4.72, 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 tumor, lessening of acromegaly symptoms (such as limb growth, joint pain), and anxiety. With respect to the Acromegaly Quality of Life Questionnaire score, pasireotide may improve this outcome compared to SSA, however the evidence is uncertain regarding whether pasireotide improves symptoms, and the clinical significance of any improvement in quality of life 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% vs 21.7% of patients in the pasireotide vs octreotide arm, had any grade hyperglycemia-related AEs. In Study C2402, in the pasireotide 40 mg and pasireotide 60 mg vs the active control arm (octreotide or lanreotide), 33.3% and 30.6% vs. 13.6% of patients reported hyperglycemia, and 20.6% and 25.8% vs 7.6% of patients reported diabetes mellitus.

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 who are inadequately controlled on treatment with a first-generation somatostatin analogue. 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 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 endpoints and acromegaly comorbidities is uncertain. The committee discussed the lack of evidence for IGF-1 as a valid surrogate for clinical endpoints. 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, have contraindications, 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 months 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 who are inadequately controlled on treatment with first-generation SSAs. The majority of patients enrolled in the trials received treatment at least 3 month from the previous surgery	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 µg/L • elevated circulating IGF-1 Lack of response to surgery is demonstrated within 3 to 6 months from surgery, and hence treatment with pasireotide should not be initiated if the patient has undergone surgery within the past 3 to 6 months
2. The maximum duration of initial authorization is 6 months.	In Study C2402 trial, the primary endpoint was the proportion of patients achieving biochemical control (GH < 2.5ug/L and normalization of sex-and age-adjusted IGF-1) at Week 24.	
Renewal		
3. 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 µg/L and age normalised IGF-1 <ULN. Additionally, the patient should not have undergone surgery within the past 3 to 6 months.	In Study C2402 trial, the primary endpoint was the proportion of patients with GH < 2.5ug/L and normalized IGF-1 at Week 24. Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.	Based on clinical expert opinion, assessment of treatment effectiveness may include tumor growth control, reduction in tumor 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 tumor volume, noted the clinical experts, clinical studies typically define significant tumor shrinkage as a reduction of 10% to 25% in tumor volume or diameter. The clinical experts noted to CDEC that over 90% of acromegaly patients

Reimbursement condition	Reason	Implementation guidance
		undergo surgery as first line treatment. Repeat surgery is less common. If a patient is already receiving pasireotide after first surgery and needs a second surgery, then, such patients should discontinue treatment with pasireotide for 3 to 6 months to assess the outcome of surgery and if disease comes under control, and if acromegaly is not under control restart treatment with pasireotide
Discontinuation		
4. 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 the patients achieve biochemical remission without the need for medical therapy, and 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		
5. 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	—
6. Pasireotide should not be reimbursed when used in combination with pegvisomant or cabergoline	There was no evidence submitted to CDEC to support the use of pasireotide in combination with pegvisomant or cabergoline	—
Pricing		
7. Pasireotide should be negotiated so that it does not exceed the drug program cost of treatment with 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 first generation SSA reimbursed for the treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative	—

GH = growth hormone; IGF-1 = insulin-like growth factor; SSA = somatosatin analogue; ULN = upper limit of normal; ULN = upper limit of normal.

Discussion Points

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 quality of life of patients. Treatment options for people with 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 normalization of their IGF-1. Whether this improvement in IGF-1 results in clinically significant improvements in health-related quality of life or symptoms is unclear due to the lack of established minimally important clinical differences for the instruments used and a relatively modest changes observed for these outcomes with pasireotide compared to other SSAs. Symptoms and health-related quality of life 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, nor were there any trials that assessed the combination of these two 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 who were uncontrolled on maximal approved doses of SSAs based on the current definitions of biochemical control, which were updated since study C2305 and study C2402 were conducted. However, the exploratory nature of the trial and the absence of a comparator group limits the conclusions that can be drawn from this supportive evidence.

IGF-1 as a potential surrogate endpoint for clinical outcomes: CDEC discussed 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, for example due to long-term tissue changes, joint and soft tissue damage, comorbid conditions etc. 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 health-related quality of life 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 cormorbidity control and does not result in an immediate improvement in health-related quality of life, adding that the follow-up period of the trials may not have been sufficiently long to assess changes in symptoms and health-related quality of life.

Harms: CDEC discussed the higher incidence of grade 3 or 4 AEs, serious AEs 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 quality of life and comorbidities which is the driver of the sponsor's economic model; 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 life time. In addition, CDEC noted that evidence of the higher rates of hyperglycemia from the clinical trials (C2402 and 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 million in Canada, affecting women slightly more than men. In 2024, the Acromegaly Consensus Group introduced guidelines for diagnosis, highlighting that IGF-I levels above 1.3 times the age-adjusted upper limit confirms the condition in symptomatic patients, with additional tests like oral glucose tolerance tests (OGTT) recommended for ambiguous cases, especially considering factors like body mass index, diet, and genetic background.

Acromegaly is typically managed through multi-modal treatment including surgery (first line), pharmacotherapy (second line) and adjunctive radiation therapy. The clinical experts noted that small and non-invasive tumours tend to have a high initial remission of over 80%, albeit with a significant risk of recurrence. There are 2 categories of medical therapy, drugs that reduce GH secretion (dopamine agonists [rarely effective], and SSA, both first and second generation) and then GH receptor antagonists like pegvisomant. The clinical experts added that radiation therapy is used if there is an inoperable tumor, 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 respond to SSAs, which leads to combination therapy, that 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 four of the five SSTRs: SSTR5, SSTR2, SSTR3, SSTR1.

Pasireotide underwent the standard review process at Health Canada and received an 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 who are 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 randomized controlled trials in patients with active acromegaly , and 1 indirect treatment comparison
- patients' perspectives gathered by 2 patient groups, Acromegaly Canada and Canadian Association for Rare Disorders
- input from public drug plans that participate in the reimbursement review process
- 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

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 expert consulted for the purpose of this review.

Patient Input

Two patient groups, Acromegaly Canada and 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 USA-based support

network and has members who live in Canada), also helped to collect the data from acromegaly patients. Feedback was gathered via interviews with six patients and a survey of 26 participants (64% were people in Canada and 36% identified as living in the USA), revealing that most patients face severe symptoms like hand and foot enlargement, facial feature changes, joint pain, and various comorbidities (diabetes, sleep apnea, hypertension). Though SSAs were seen as generally effective, side effects such as injection site pain and gastrointestinal discomfort were common. Among six users of pasireotide (5 patients in USA and 1 in Canada), satisfaction was high, with reports of mild to moderate side effects, contrasting with other treatments that were rated less effective or only moderately effective. Patient group input reported that important outcomes from their point of view include shrinkage of the tumor, acromegaly symptoms (such as limb growth, 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 respond to first generation SSAs, which leads to combination therapy, that has increased risk of side effects and modest efficacy. The clinical experts noted that they see pasireotide being used in patients who do not respond to SSA therapy, who do not have dysglycemia, and that it may also be used in combination with pegvisomant in patients who remain unresponsive. The clinical experts also noted that pasireotide could be used first line in centres where somatostatin receptor staining is available, in order to identify patients who express the target somatostatin receptors 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 somatostatin receptor staining, those who have not responded to first generation SSAs, 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 is radiological response tumour stability or shrinkage, as well as symptoms and quality of life.

Clinician Group Input

The Canadian Society of Endocrinology and Metabolism (CSEM), comprising 15 physicians, highlighted that the primary goals in acromegaly treatment are normalizing GH and IGF-1 levels, reducing tumor 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 over 40% of patients fail to achieve full biochemical control with SSAs, and access to pegvisomant, a second-line GH receptor antagonist, is limited. The CSEM group noted that pegvisomant, while controlling IGF-1, does not affect GH, and its daily injections pose adherence challenges. They emphasize 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 uncontrolled by SSAs or pegvisomant, with the potential to lessen treatment burden and improve quality of life.

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 surgeon (jaw and teeth issues), cardiology (cardiac issues) or family physician and the diagnosis is confirmed by a specialist endocrinologist. According to the clinical experts, the primary treatment is the removal of adenoma, done by neurosurgery, then medical treatment and lifelong follow up is done by endocrinologists. In

Implementation issues	Response
	patients not responding to medical therapy, radiation therapy may be administered by radiation oncologists.
Considerations for initiation of therapy	
In Study C2402, 60-77% 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 a somatostatin analogue before initiating pasireotide? • What is a reasonable duration of trial (i.e., 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, failed, 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 first generation SSA fails to provide biochemical control, it is reasonable for patients to have surgery and failure of 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 µg/L and age normalised IGF-1 <ULN) have since been recommended by the Pituitary Society, the Acromegaly Consensus Group and the Endocrine Society. The clinical experts added that symptoms may improve just partially due to long-term tissue changes, joint and soft tissue damage, comorbid conditions, etc after chronic exposure to excess of 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 tumor:** medical therapy would be preferred for GH-secreting microadenoma with cavernous sinus invasion. 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 endpoint was the proportion of patients with GH < 2.5ug/L and normalized IGF-1 at Week 24. - Pasireotide 40mg every 28 days – 15% of patients reached the primary endpoint	The clinical experts consulted indicated that biochemical parameters are the key outcome they use to monitor patient progress in clinical practice, and 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,

Implementation issues	Response
- Pasireotide 60mg every 28 days – 20% of patients reached the primary endpoint **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 a MCID for AcroQoL? 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	biomarker normalization appears to be the most relevant and objective parameter to assess to determine effect of treatment with pasireotide. The clinical experts further noted that the assessment of treatment effect may include tumor growth control, reduction in tumor 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 tumor volume, the clinical experts noted that clinical studies typically define significant tumor shrinkage as a reduction of 10% to 25% in tumor 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 the AcroQoL. 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 tumor size reduction addeding 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 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 somatostatin analogue therapy. According to one clinical expert, to assess suitability for renewal of coverage, these biomarkers (IGF-1 and GH) and AcroQoL should be monitored very 6-12 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 µg/L and age normalised IGF-1 <ULN. Additionally, the patient should not have undergone surgery within the past 3 to 6 months. CDEC also recommended that pasireotide should not be reimbursed when used in combination with cabergoline or pegvisomant.
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 level 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, and periodic assessment must be done and once IGF-1 levels drop to low or below normal levels, drug

Implementation issues	Response
	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 µg/L and age normalised IGF-1 <ULN. However, the clinical experts, added that assessment of treatment effectiveness may include tumor growth control, reduction in tumor 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 tumor volume, clinical studies typically define significant tumor shrinkage as a reduction of 10% to 25% in tumor 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 fail to 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 15-20% of patients had normalized IGF-1 and GH values at week 24. Would the next step in therapy 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 recommended that due to a lack of evidence, 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 healthcare 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 reimbursment to adult patients.

MCID = minimally clinically important difference; ULN = upper limit of normal.

Clinical Evidence

Systematic Review

Description of Studies

Two multicentre, sponsor-funded Phase 3 RCTs, studies C2305 and C2402, were included in this review. Study C2305 was a blinded study of pasireotide vs. 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 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 <2.5 mcg/L and normalization of IGF-1 to within normal limits (age and sex-related). Secondary outcomes assessed normalization of IGF-1, change from baseline in AcroQoL, and symptoms.

Across both studies, patients were approximately 45 years of age, and there were slightly more females than males (52% in study C2305, and 55% in study C2402). The majority of patients were Caucasian in each study (study C2305: 60%; study C2402: 81%). Patients in study C2305 had been diagnosed with acromegaly for approximately 20 months, and for approximately 72 weeks in study C2402.

Efficacy Results

Proportion of patients with a reduction of GH level to <2.5 mcg/L and normalization of IGF-1

Study C2305

The proportion of responders (i.e. patients with GH <2.5 mcg/L and normalized IGF-1) at Month 12 was 31.3% (95% CI: 24.5, 38.7) in the pasireotide arm, and 19.2% (95% CI 13.8, 25.7) in the octreotide arm, with an odds ratio of 1.942 (95% CI: 1.190, 3.168) in favor of pasireotide.

When analyzed by stratum, the response rates were slightly higher for patients who were post surgery relative to de novo patients for both pasireotide and for octreotide. Odds ratio indicated a treatment effect in favor for pasireotide for patients who were post surgery (2.337 [95% CI: 1.140, 4.790]), while the difference between the treatments was less marked for de novo patients (1.654 [95% CI: 0.846, 3.234]).

The results of the analysis of the primary efficacy endpoint for the per protocol set and where patients with missing values were considered as non-responders 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 with 95% CI: 3.32, infinity). In the pasireotide 60 mg arm, 13 patients (20.0%) achieved biochemical control at 24 weeks (OR=23.03 with 95% CI: 4.72, infinity)

Patients with normalization of IGF-1

Study C2305

The proportion of patients with normalized IGF-1 was 38.6% (95% CI 31.4, 46.3) in the pasireotide arm, and 23.6% (95% CI 17.7, 30.5) in the octreotide arm, with an odds ratio of 2.087 (95% CI 1.316, 3.308) in favor of pasireotide. By strata, the response rates for post surgery patients 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 endpoint) was higher in both pasireotide 40 mg: 24.6% (95% CI: 14.77, 36.87) and pasireotide 60mg: 26.2% (95% CI: 16.03, 38.54),responders compared to the active control arm (zero responders), for an OR of 30.12 (95% CI: 6.28, infinity), p<0.0001 in the pasireotide 40mg group and 32.66 (95% CI: 6.84, infinity), p<0.0001 in the pasireotide 60mg group.

Acromegaly quality of life

Study C2305

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

Study C2402

At baseline, mean (SD) 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 (SD) change from baseline in AcroQoL total score was 2.6 [redacted] in the pasireotide 40mg 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 (SD) baseline of 0.9 (1.05) in the pasireotide group (N=175) and 1.0 (1.14) in the octreotide group (N=181), after 12 months, the mean (SD) change from baseline in headache scores was -0.3 (1.17) in the pasireotide group (N=138) and -0.4 (0.94) in the octreotide group (N=149). From a mean (SD) baseline of 1.0 (1.05) in the pasireotide group (N=174) and 1.3 (1.26) in the octreotide group (N=178), after 12 months, the mean (SD) change from baseline in osteoarthralgia scores was -0.4 (1.07) in the pasireotide group (N=137) and -0.6 (1.20) in the octreotide group (N=146).

Study C2402

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

Harms Results

Adverse events

Study C2305

Most patients experienced at least one AE during the core phase of the study. The most frequent event in both treatment groups was diarrhea (39.3% vs. 45.0% for pasireotide vs. 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, blood glucose increased, 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 three treatment groups, and with at least a 10% difference between pasireotide 40 mg and pasireotide 60 mg vs. active control, were hyperglycaemia (33.3%, 30.6% vs. 13.6%), diabetes mellitus (20.6%, 25.8% vs. 7.6%), and diarrhoea (15.9%, 19.4% vs. 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 active control. 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 an atrioventricular block first degree. In addition, one patient in the pasireotide 60 mg group had a similar event (atrioventricular block). These events were all grade 1. For three of the five patients, atrioventricular block was present before start of treatment.

Serious Adverse Events

Study C2305

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

Study C2402

Few patients overall had SAEs: 6 patients (9.5%) in the pasireotide 40 mg group, 2 patients (3.2%) in the pasireotide LAR 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 one patient in each group.

Study C2402

Seven patients (three in the pasireotide 40 mg group and four in the pasireotide 60 mg group) had AEs that lead to discontinuation. Six of the seven patients discontinued due to a hyperglycemia-related event.

Mortality

Study C2305

There was one death, in the octreotide group, and 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 AE of special interest category that occurred with a higher frequency in the pasireotide group (at least 5% difference) was hyperglycemia-related AEs (57.3% vs. 21.7% for pasireotide vs. octreotide).

In the octreotide group, the following AE of special interest categories occurred with a higher frequency (at least 5% difference, octreotide vs. pasireotide): diarrhea-related AEs (45.0% vs. 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 and 30.3% in the active control group. Hyperglycemia-related events that were severe (grade 3) were only reported on pasireotide (none were grade 4). Gallbladder and biliary-related AEs were also common and equally frequent on all three 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 on pasireotide than active control was diarrhea-related events (15.9% and 19.4% on pasireotide 40 mg and 60 mg vs. 4.5% on active control). In addition to the patient with an AE of liver injury, four patients had AEs related to the category of “liver safety”: two patients in the pasireotide 40 mg group (grade 1 ALT increased, grade 2 “liver function test abnormal”), one patient in the pasireotide 60 mg group (ALT and GGT increased, both grade 1), and one patient in the active control (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 MIDs were not available for any of these outcomes, limiting the review team's ability to assess clinical relevance of the findings. There were a relatively large number of withdrawals in study C2305, and more withdrawals in the pasireotide group than in octreotide (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 that they were already failing on, 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 second-line, there are no studies that directly compare the two drugs.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with the clinical expert, 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/IGF-1 (primary outcome of both included studies), proportion of patients with normalization of IGF-1, change from baseline in AcroQoL, change from baseline in symptoms (headache, osteoarthralgia), notable harms (hyperglycemia-related events).

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

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
GH/IGF-1 response				
Patients with a reduction of mean GH level to <2.5 µg/L and the normalization of IGF-1 to within normal limits (age and sex related), n/N (%) Follow-up indicated in parentheses	Study C2305 : N=358 Study C2402: N=133	Study C2305 (12 months) • Pasireotide: 313 per 1000 • Octreotide: 192 per 1000 • RD (95% CI): 120 more per 1000 (31 more to 210 more) Study C2402 (24 weeks) • Pasireotide: 154 per 1000 • Active control:0 per 1000 • RD (95% CI): 154 more per 1000 (66 more to 242 more)	Low[a]	Pasireotide may result in an improvement in the number of patients achieving GH/IGF-1 normalization compared to other SSA. The clinical significance of this improvement is unknown.
IGF-1 response				
Patients with normalization of IGF-1, n/N (%) Follow-up indicated in parentheses	Study C2305 : N=358 Study C2402: N=133	Study C2305 (12 months) • Pasireotide: 386 per 1000 • Octreotide: 236 per 1000 • RD (95% CI): 150 more per 1000 (55 more to 245 more) Study C2402 (24 weeks) • Pasireotide: 246 per 1000 • Active control:0 per 1000 • RD (95% CI): 246 more per 1000 (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 SSA. The clinical significance of this improvement is unknown.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Health-related quality of life: 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 : PSR N=133 OCT N=146 Study C2402: PSR N=57 CON 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, 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, 7.34)	Low[c]	Pasireotide may result in an improvement in AcroQol compared to other SSA. The clinical significance of this improvement is unknown.
Acromegaly symptoms				
Mean (SD) change from baseline in symptoms (5 point symptom scale ranging from 0 [absent] to 4 [very severe]). Follow-up indicated in parentheses	Study C2305 : PSR N=138 OCT N=149 Study C2402: PSR N=57 CON N=62 Study C2305: PSR N=138 OCT N=149 Study C2402: PSR N=59 CON N=65	**Osteoarthralgia** Study CC (12 months) • 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	Very low[d]	The evidence is very uncertain about the effects of pasireotide on headaches and on osteoarthralgia compared to other SSA
Harms				
Hyperglycemia-related AE 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 SSA

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens

AE=adverse events; CI=confidence interval; CON=active control; GH=growth hormone; HRQoL = health-related quality of life; IGF-1=insulin-like growth factor-1; LS=least square; NR=not reported; OCT=octreotide; OR=odds ratio; PSR=pasireotide; RCT = randomized controlled trial; SD=standard deviation; SE=standard error; SSA=somatostatin analogues

Note: Study limitations (which refers 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.

[a]Rated down 2 levels: 1 level due to indirectness (unclear how GH impacts clinical outcomes and the cutoff 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

[b]Rated down 1 level because the lower bound of the 95% CI did not exceed the MID in study C2305

[c]Rated down 2 levels for crossing null

[d]Rated 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 extensions studies are reported by the sponsor.

Indirect Comparisons

In the absence of direct evidence between pasireotide LAR and pegvisomant, the sponsor performed an indirect treatment comparison (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/Biochemical response

There were no significant differences in IGF-1 normalization when comparing either dose of pasireotide LAR (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 pasirotide LAR (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 three 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 PRISMA flow chart, and a formal quality assessment introduces potential selection and reporting biases, which may affect the validity of the conclusions. Only three 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, patients in the C2402 and Trainer 2009 studies were inadequately controlled on SSAs, while the Trainer 2000 study included a broader patient population with a mix of acromegaly patients regardless of their prior treatment exposure or response. Moreover, in the Trainer 2000 trial, eligible patients at the second screening had serum IGF-1 concentrations at least 1.3 times 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 the Bucher's method for ITC analysis, which may not be suitable for the included studies and network structure. Bucher's model is designed for two-arm trials with independent pairwise comparisons. However, the included studies (Study C2402, Trainer 2000, Trainer 2009) had more than two 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 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 clinical experts consulted by the CDA-AMC, SSAs were superior to placebo in several trials, and thus, the efficacy of SSAs cannot be considered equivalent to placebo. This assumption also prevented the authors from assessing several outcomes important to patients, including tumor volume reduction, acromegaly symptoms, patient quality of life, 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, multicenter, 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 LAR in patients with acromegaly who remained uncontrolled despite treatment with maximal approved doses of octreotide or lanreotide. In this study, adults with uncontrolled acromegaly (defined as mean GH [mGH] more or equal to 1 µg/L and IGF-I more than 1.3× ULN) who had received at least 3 months of maximal doses of long-acting octreotide or lanreotide were administered open-label pasireotide LAR at 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 36–72), where concomitant acromegaly medications were permitted. The primary endpoint was the proportion of patients achieving mGH less than 1 µg/L and IGF-I less than 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 the AcroQoL, self-reported signs and symptoms of acromegaly, and harms.

Efficacy Results

By week 36, 14.6% of patients (18/123; 95% CI: 8.9–22.1) achieved both mGH less than 1.0 µg/L and IGF-I 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 somatostatin analogs.

At baseline during the core phase, the mean ± SD AcroQoL score was 58.6 ± 19.2 (n = 123), which increased to 63.2 ± 4.6 (n = 110) by week 36. Among patients who progressed to the extension phase, the mean ± SD AcroQoL score was 64.0 ± 19.3 (n = 88) at extension baseline, increasing to 65.1 ± 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% vs. 36.6%), fatigue (36.6% vs. 26.0%), excessive sweating (43.1% vs. 37.4%), joint pain (osteoarthralgia; 33.3% vs. 26.8%), and tingling (paresthesia; 54.5% vs. 47.2%). Similar proportions were seen in the extension phase.

Harms Results

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

Critical Appraisal

The open-label single-arm design of the trial is 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 be 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 clinicians consulted by the CDA-AMC review team, the population of patients enrolled in Study C2413 is representative of the patients they encounter in daily practice in Canada. Additionally, the included patients align with the approved indication specified in the Health Canada product monograph, although it more closely aligned with the sponsor's reimbursement request since it enrolled patients with acromegaly who 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 endpoint 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 quality of life, signs and symptoms of acromegaly (e.g., osteoarthralgia, headache), and safety. The primary endpoint 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 quality of life, signs and symptoms of acromegaly (e.g., osteoarthralgia, headache), and safety. Quality of life was measured using the AcroQoL score, which was validated in 2014. However, this measure does not have an established minimal important difference (MID).

Economic Evidence

Cost and Cost-Effectiveness

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 who are inadequately controlled on treatment with a first-generation somatostatin analogue
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 C2402 clinical trial • Sponsor-submitted indirect treatment comparison informed pegvisomant.
Key limitations	• Comparative efficacy of pasireotide versus all comparators is uncertain. Patients on PAOLA C2402 were inadequately controlled on their current therapy to be enrolled in the study with patients in the active control group continuing on treatment that they were failing. 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

Component	Description
	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, amongst patients who achieve partial response, 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 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 requested population. Although clinical expert feedback obtained by CADTH noted the biological plausibility in a relationship between IGF-1 and co-morbidities, 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 the C2305 trial for pasireotide and octreotide and LANTERN trial for lanreotide which captures a drug naïve population and does not reflect the reimbursement requested 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.
CADTH reanalysis results	• The CADTH 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 C2402 trial; and, changing the distribution for subsequent treatments. • In the CADTH 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 are inadequately controlled on treatment with a first-generation somatostatin analogue. 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, CADTH conducted scenario analyses. The ICERs for pasireotide in these scenario analyses were higher than estimated in the CADTH base-case reanalysis.

AE = adverse event; ICER = incremental cost-effectiveness ratio; IGF-1 = insulin-like growth factor 1; ITC = indirect treatment comparison; LY = life-year; QALY= quality-adjusted life-year; SSA = somatostatin analogue.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: overestimation of pegvisomant dosing; the market uptake of pasireotide was uncertain; availability of pegvisomant in Nova Scotia is limited; market shares for pegvisomant was overestimated; cost of subsequent treatments were not considered; and epidemiological approach to calculate the patient population did not consider patients who do not express somatostatin receptors. Based on CADTH 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 inadequately controlled on treatment with a first-generation somatostatin analogue is $9,154,091 (Year 1: $2,780,068; Year 2: $3,048,402; Year 3: $3,325,621).

CDEC Information

Members of the Committee:

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, 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 27, 2025

Regrets: One expert committee member did not attend.

Conflicts of interest: None