



CDEC FINAL RECOMMENDATION

PASIREOTIDE

(Signifor — Novartis Pharmaceuticals Canada)

Indication: Cushing Disease

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that pasireotide not be listed.

Reasons for the Recommendation:

CDEC considered the clinical benefit of pasireotide for the treatment of Cushing disease to be uncertain, due to limitations in the design of the single uncontrolled trial (B2305; N = 162), the absence of a clear rationale for the response rate threshold (i.e., 15% of patients), the failure to achieve the primary end point with the 0.6 mg twice daily recommended dose of pasireotide, and the high proportion of participants who discontinued treatment within 12 months (60%).

Background:

Pasireotide has a Health Canada indication for the treatment of adults with Cushing disease for whom surgery is not an option or for whom surgery has failed, as long as clinical benefit is derived. Clinical benefit (treatment response) is defined in the product monograph as a decrease of at least 50% in urinary free cortisol (UFC) levels and/or improvement in signs or symptoms of the disease. The recommended initial dose of pasireotide is 0.6 mg twice daily through subcutaneous (SC) injection, but it may be increased to 0.9 mg twice daily based on response and tolerance to the treatment.

Summary of CDEC Considerations:

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trial (RCTs) and pivotal studies of pasireotide, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to individuals living with Cushing disease.

Patient Input Information

The following is a summary of key information provided by one patient group, consisting of patients and caregivers, which responded to the CDR call for patient input:

- Patients reported that the effects of Cushing disease on their lives were “devastating,” with the disease having negative influences on their physical, psychological, social, and financial well-being.
- The condition has a significant impact on both caregivers and their families. Respondents indicated that families must cope with not having regular family or social lives as patients experience problems with their self-image and tend to self-isolate.
- Respondents stated that surgery is considered the most effective treatment for Cushing disease; however, it is important to have alternative treatment options available, as surgery fails to achieve durable results in a significant proportion of patients.
- Respondents noted that the adverse event profile of pasireotide is a deterrent to use.

Clinical Trials

The CDR systematic review included one partially blinded, uncontrolled randomized trial. B2305 (N = 162) evaluated the efficacy and safety of pasireotide 0.6 mg twice daily and 0.9 mg twice daily in adults (≥ 18 years of age) with a confirmed diagnosis of Cushing’s disease that is persistent or recurrent despite previous surgical treatment, or who were not candidates for surgery. The majority of patients (79%) had received previous surgical treatment for Cushing’s disease and nearly half (48%) had been previously treated with medications.

Pasireotide was administered on a double-blind basis for three months. Patients meeting the pre-specified criteria for improvement moved forward in the study with the same dosage for an additional three months (i.e., no dose adjustment); the remaining patients were unblinded at three months and were required to increase the dose of pasireotide by 0.3 mg twice daily. All doses were revealed at six months, at which time the primary outcome was assessed. After six months, a subsequent six-month open-label phase commenced. The dose of pasireotide could be increased by 0.3 mg twice daily (up to a maximum dose of 1.2 mg twice daily) during the open-label phase if the UFC level was above the normal range, or reduced in steps of 0.3 mg twice daily at any time throughout the trial in the event of unacceptable toxicity.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Proportion of UFC responders — a responder was defined as a patient in whom UFC levels returned to within the normal range and in whom the dose of pasireotide was not increased prior to month six.
- Partial UFC responders — defined as a patient with UFC levels above the normal range but decreased by at least 50% compared to baseline.
- Improvements in clinical signs and symptoms of hypercortisolism.
- Health-related quality of life — assessed using the self-administered Cushing Quality of Life (Cushing QoL) questionnaire, which addresses the following areas: sleep issues, wound healing, mood, self-confidence, physical appearance, ability to participate in daily activities, social concerns, memory issues, and future health concerns.
- Beck Depression Inventory score.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

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Efficacy

- Only the 0.9 mg twice daily group met the predefined effectiveness threshold of a 15% response rate. The response rates after six months were 14.6% (95% confidence interval [CI], 7.0 to 22.3) in the pasireotide 0.6 mg twice daily group and 26.3% (95% CI, 16.6 to 35.9) in the 0.9 mg twice daily group.
- The mean percentage changes from baseline in UFC levels were reported as follows:
 - 0.6 mg twice daily: –28% (95% CI, –56% to 1%) at six months and –41% (95% CI, –66% to –17%) at 12 months
 - 0.9 mg twice daily: –48% (95% CI, –57% to –40%) at six months and –55% (95% CI, –65% to –44%) at 12 months.
- Mean changes from baseline (standard deviation [SD]) on the Cushing syndrome health-related quality of life questionnaire were reported as follows:
 - 0.6 mg twice daily: 6.2 (16.0) at six months and 9.4 (17.4) at 12 months
 - 0.9 mg twice daily: 12.9 (14.8) at six months and 12.8 (20.4) at 12 months.
- There were small improvements in blood pressure at six months, with mean changes (SD) from baseline reported as follows:
 - Systolic blood pressure: –6.8 mm Hg (19.4) with 0.6 mg twice daily and –11.4 mm Hg (15.9) with 0.9 mg twice daily
 - Diastolic blood pressure: –4.2 mm Hg (13.5) with 0.6 mg twice daily and –5.0 mm Hg (11.6) with 0.9 mg twice daily.
- The proportion of patients who achieved a partially controlled response was 18.3% in the 0.6 mg BID treatment group and 12.5% in the 0.9 mg BID group.
- Beck Depression Inventory scores showed improvement from baseline at six months in both the 0.6 mg twice daily group (mean change –4.6; SD 9.5) and the 0.9 mg twice daily group (mean change –5.5; SD 8.8).

Harms (Safety and Tolerability)

- At least one serious adverse event was reported for 23% of patients in the 0.6 mg twice daily group and 26% of patients in the 0.9 mg twice daily group. The most commonly reported serious adverse events were pituitary-dependent Cushing syndrome, diabetes mellitus, hyperglycemia, cholelithiasis, and adrenal insufficiency.
- At least one adverse event was reported for 98% and 99% of patients in the 0.6 mg twice daily and 0.9 mg twice daily groups, respectively.
- Withdrawals due to adverse events were reported for 16% and 19% of patients in the 0.6 mg twice daily and 0.9 mg twice daily groups, respectively.
- Hyperglycemia-related adverse events were experienced by 74% and 71% of patients in the 0.6 mg twice daily and 0.9 mg twice daily treatment groups, respectively. A total of 40% of patients had a last available glycated hemoglobin (A1C) value of $\geq 7\%$, and mean A1C in both groups increased from 5.8% at baseline to more than 7% throughout the trial. The proportion of patients receiving concomitant antihyperglycemic medication also increased during the trial.
- Notable adverse events reported for patients treated with pasireotide (0.6 mg and 0.9 mg twice daily, respectively), included the following: gall bladder and biliary adverse events (33% and 36%), liver-related adverse events (21% and 11%), bradycardia-related adverse events (18% and 10%), and QT-prolongation adverse events (7% and 9%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost analysis for the use of pasireotide in adults with Cushing disease who do not require immediate surgery or for whom surgery has failed. The perspective is that of a Canadian public health payer with a time horizon of up to two years. No discounting was applied. The annual expected cost of pasireotide was estimated using the overall response rates achieved in study B2305, with patients who were non-responders discontinued after an initial three or six months of therapy. Total costs in the first and second years of treatment were estimated using the cost of pasireotide therapy, the cost of complications due to severe adverse events, an additional cost due to hyperglycemia, and the costs associated with monitoring. The manufacturer then estimated the costs, which might be offset by the use of pasireotide, such as radiotherapy or secondary transsphenoidal surgery (TSS) or bilateral adrenalectomy.

The manufacturer estimated that the total cost per patient associated with pasireotide therapy was \$65,497 in the first year and \$130,994 over two years. Lower costs were reported based on treatment discontinuation for non-responders and incremental costs or savings were estimated comparing pasireotide therapy with radiotherapy, bilateral adrenalectomy, and TSS.

A number of key limitations were identified in the submission:

- Clinical efficacy and safety were uncertain due to limitations in the clinical evidence.
- Offset costs of other therapies were uncertain and transient.
- Costs associated with some patients using above-recommended dosing in the trial were not considered.
- The submission included a number of transcription and computational errors.
- The stopping rule as described is not reflective of probable clinical practice.
- The existence of non-indicated therapies used in clinical practice was not considered.

There is a great deal of uncertainty regarding the clinical efficacy, safety, and cost-effectiveness associated with pasireotide therapy for Cushing disease. While the use of pasireotide may delay the need for radiotherapy, additional surgeries, or off-label medical therapy in a percentage of patients, the cost of treatment at \$62,426 annually (drug cost only) warrants an understanding of the clinical benefits that may be realized by patients receiving therapy. The lack of comparative clinical data and, as a result, the lack of comparative cost-effectiveness information, and the uncertainty as to the impact of UFC response on clinically important outcomes complicate the assessment of value of pasireotide.

Other Discussion Points:

CDEC noted the following:

- The absence of a control group in study B2305 makes it challenging to evaluate the magnitude of changes in the efficacy end points.
- The dosage of pasireotide recommended in the product monograph is 0.6 mg twice daily to 0.9 mg twice daily; however, patients in study B2305 received doses ranging from 0.3 mg twice daily up to 1.2 mg twice daily.
- The maintenance of the observed effect with pasireotide is difficult to evaluate from study B2305. The UFC levels of individual patients shifted in and out of control, and many of the patients whose UFC levels were controlled at 12 months were not the same as those who were controlled at six months.

- Despite the chronic nature of Cushing disease, whether the efficacy of pasireotide is maintained over the longer term is unclear, because neither treatment group met the effectiveness threshold after 24 months of follow-up, and few patients (< 10% after 36 months) continued pasireotide treatment during the long-term follow-up phase of Study B2305.
- CDEC expressed concern that the Health Canada–approved product monograph for pasireotide includes the following serious warnings and precautions: risk of hepatotoxicity, risk of cardiovascular adverse events, and risk of hyperglycemia.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- The efficacy and safety of pasireotide in the treatment of Cushing disease have not been evaluated in any active or placebo-controlled studies.
- Long-term efficacy and safety of treating Cushing disease with pasireotide are uncertain.
- Patients with uncontrolled diabetes or clinically significant impairment in cardiovascular or liver function were excluded from study B2305.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

January 21, 2015 Meeting

Regrets:

None

Conflicts of Interest:

None

About this Document:

CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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