# Common Drug Review
## *Pharmacoeconomic Review Report*

**August 2015**

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|---|---|
| **Drug** | pasireotide (Signifor) (0.3 mg/mL, 0.6 mg/mL and 0.9 mg/mL injection) |
| **Indication** | Treatment of adult patients with Cushing disease for whom surgery is not an option or for whom surgery has failed, as long as clinical benefit is derived. |
| **Listing request** | Treatment of patients with Cushing disease for whom medical therapy is appropriate. |
| **Manufacturer** | Novartis Pharmaceuticals Canada Inc. |

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in endocrinology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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# ABBREVIATIONS

| | |
|---|---|
| **CDR** | CADTH Common Drug Review |
| **mUFC** | mean urinary free cortisol |
| **TSS** | transsphenoidal surgery |
| **UFC** | urinary free cortisol |

# SUMMARY

# 1. BACKGROUND

Pasireotide (Signifor) is indicated for the treatment of adult patients with Cushing disease for whom surgery is not an option or for whom surgery has failed, as long as clinical benefit (normalization of urinary free cortisol [UFC] or greater than 50% decrease in UFC) are derived. Pasireotide is available in ampoules for subcutaneous injection in 300 mcg, 600 mcg, and 900 mcg doses. The 300 mcg dose is available at a cost of $76.68 per ampoule, while the 600 mcg and 900 mcg doses cost $85.52. At the recommended dose of 600 mcg to 900 mcg twice daily, the daily cost of pasireotide is $171 (or $62,427 annually).

# 2. SUMMARY OF THE ECONOMIC ANALYSIS SUBMITTED BY THE MANUFACTURER

The manufacturer submitted a cost analysis for the use of pasireotide in adult patients 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 the randomized, uncontrolled trial B2305,[1,2] with patients who were nonresponders discontinued after an initial three or six months of therapy. Total costs in years 1 and 2 of treatment were estimated using the cost of pasireotide therapy, the cost of complications due to severe adverse events,[1-3] an additional cost due to hyperglycemia,[4] and the costs associated with monitoring.[5,6] The manufacturer then estimated the costs that might be offset by the use of pasireotide, such as radiotherapy or secondary transsphenoidal surgery (TSS) or bilateral adrenalectomy.[7] All costs were reported in 2013 dollars.

The manufacturer estimated that the total per-patient cost associated with pasireotide therapy was $65,497 in year 1 and $130,994 over two years. Lower costs were reported based on treatment discontinuation for nonresponders. The manufacturer estimated an incremental cost of $23,336 per patient for pasireotide therapy when compared with radiotherapy, an incremental cost of $8,493 when compared with bilateral adrenalectomy, and an incremental savings of $903 when compared with TSS in the first year of treatment (Table 6).

## 2.1 Key Limitations

### 2.1.1 Uncertain Clinical Efficacy and Safety

The pasireotide pivotal trial was small and uncontrolled; response rates were relatively low and many patients discontinued. With no control group within the trial, or even a historical or similarly estimated control, it is not possible to ascertain the extent to which the observed results and adverse events were treatment-related. Forty-eight per cent of patients had previously taken medical therapies for Cushing disease,[2] and per protocol had washout periods of as little as one week before baseline assessment. As such, it is unclear whether this may have influenced baseline values and thus results. Additionally, response rate and discontinuation rules were based on mean urinary free cortisol (mUFC) levels, which may not always correlate well with clinical outcomes (see CDR Clinical Report, Validity of Outcome Measures). It is uncertain to what extent patients classified as “responders” using the controlled and

partially controlled criteria of the mUFC outcome in the trial are in fact deriving the clinical benefits implied, particularly patients who are partially controlled; thus, the value of being a responder at a given time point is uncertain.

### 2.1.2 Offset Costs are Uncertain and Transient

Given that the overall response rate (controlled and partially controlled patients) for patients receiving pasireotide at one year is 28.4% and at two years is 15.4%,[1,2] the majority of patients using pasireotide would be delaying the need for radiotherapy, surgery, or alternate medical therapy rather than precluding the need. As a result, for these patients, treatment with pasireotide increases the lifetime condition management costs without avoiding further, often invasive, treatment. Without a full assessment of the cost-effectiveness of pasireotide, the value of treatment is uncertain, as the cost and side effects of pasireotide cannot be evaluated in the context of potential health benefits.

### 2.1.3 Use of Increased Dosage of Pasireotide

The cost analyses presented do not consider the possibility of dose escalation of pasireotide to 1,200 mcg twice daily. While this dosage is not specifically recommended in the product monograph, 19 of 162 patients (11.7%) in study B2305, the source of the clinical data in this submission, received 1,200 mcg twice daily at 12 months. Reported response rates in study B2305 were based on higher doses of pasireotide for some patients.

### 2.1.4 Errors Throughout Submission

The manufacturer's submission included a number of transcription and computational errors, including assumed costs left out of totals, errors in the reporting of which dataset was used in calculations, two-year incremental costs that did not include the first-year cost of alternate therapies, and the use of first-line costs for offset therapies when the patient population is second line. While the direction of bias for these errors is not always in favour of pasireotide, it does raise some concerns about the validity of the manufacturer's results.

### 2.1.5 Pasireotide Stopping Rule

The manufacturer assumed that patients who become nonresponsive to pasireotide after the initial three or six months of therapy would discontinue treatment immediately; whereas, patients in clinical settings would likely be discontinued only when nonresponsive readings were reported over three or six months (or next scheduled visits). This led to an underestimation of the expected cost of pasireotide therapy.

### 2.1.6 Data Presentation

The manufacturer presented its findings as an average cost per patient treated with pasireotide. This estimate fails to make clear the extent to which the costs are lowered due to discontinuation. A more helpful metric may be the average cost per responder, assuming that response as defined by the manufacturer leads to clinical meaningful benefits to patients. At 12 months, and with a three-month stopping rule, the manufacturer's costs-per-patient estimate led to an average cost of approximately $113,500 per responder.

# 3. ISSUES FOR CONSIDERATION

## 3.1 Currently Used (But Not Indicated) Drug Therapies

While pasireotide is the only drug therapy indicated for Cushing disease, other less expensive drugs are frequently used off-label with some evidence of effectiveness but with associated side effects, including but not limited to gastrointestinal symptoms, neurological effects, dyslipidemia, increased risk of severe hepatotoxicity, increased risk of cardiovascular disease, and increased risk of hypogonadism in men.[8,9] Additionally, the clinical expert consulted by the CADTH Common Drug Review (CDR) suggested that in the case of partial response or a loss of previous response to pasireotide, it is likely that practitioners would prescribe other drug therapies concomitantly with pasireotide at least in the short term in order to achieve a full response.

# 4. RESULTS AND CONCLUSIONS

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 potentially 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 warrants an understanding of the clinical benefits that may be realized by patients receiving therapy. The lack of comparative clinical data, the resulting lack of comparative cost-effectiveness information, and the uncertainty about the impact of mUFC response on clinically important outcomes are challenges in attempting to assess the value of pasireotide.

# 5. COST COMPARISON TABLE

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices unless otherwise specified.

**TABLE 1: COST COMPARISON TABLE FOR PHARMACEUTICALS USED TO TREAT CUSHING DISEASE**

| Drug or Comparator | Strength | Dosage Form | Price ($) | Recommended Dose | Average Daily Drug Cost ($) | Average Annual Drug Cost ($) |
|---|---|---|---|---|---|---|
| **Pasireotide (Signifor)** | **300 mcg<br>600 mcg<br>900 mcg** | **1 mL ampoule** | **76.6790[a]<br>85.5160[a]<br>85.5160[a]** | **600 mcg to 900 mcg SC twice daily** | **171.03** | **62,427** |
| **Treatments used but not currently indicated for Cushing disease** | | | | | | |
| Cabergoline (generic) | 0.5 mg | Tab | 10.6188[b] | 0.5 to 7 mg per week[8] | 1.52 to 21.24 | 534 to 7,752 |
| Ketoconazole (generic) | 200 mg | Tab | 0.9393[c] | 200 to 1,200 mg daily in divided doses[8] | 0.94 to 5.64 | 343 to 2,057 |
| Mitotane (Lysodren) | 500 mg | Tab | 4.8831[b] | 2.5 to 12 g per day[8,9] | 2.44 to 117.19 | 891 to 42,778 |

SC = subcutaneous injection.
[a] Manufacturer's publicly available market price.
[b] McKesson Canada wholesale price (November 2014), includes markup.
[c] Ontario Drug Benefit Formulary (November 2014).

# APPENDIX 1: REVIEWER WORKSHEETS

## Summary of Manufacturer's Submission

**TABLE 2: SUMMARY OF MANUFACTURER'S SUBMISSION**

| | |
|---|---|
| **Drug Product** | Pasireotide (Signifor) |
| **Treatment** | 600 mcg or 900 mcg twice daily |
| **Comparator(s)** | None |
| **Study Question** | [None stated] |
| **Type of Economic Evaluation** | Cost analysis |
| **Target Population** | Patients with Cushing disease who do not require immediate surgery or for whom surgery has failed |
| **Perspective** | Canadian public health payer |
| **Outcome Considered** | Costs only |
| **Key Data Sources** | |
| **Cost** | Manufacturer-supplied cost for pasireotide, Ontario Case Costing Initiative for adverse events, Harris et al. 2007 for diabetes costs, Ontario physician schedule for monitoring, unpublished burden-of-illness study |
| **Clinical Efficacy** | Study B2305, a randomized uncontrolled trial |
| **Harms** | Study B2305 |
| **Time Horizon** | 12 and 24 months, discounting not applied |
| **Results for Base Case** | One-year cost per patient for one year treatment for responders and three months for nonresponders: $32,243 |

## Manufacturer's Results

In its base case, the manufacturer assumed that patients would be assessed at three months and nonresponders would be discontinued from treatment with pasireotide thereafter, with a sensitivity analysis including six months of drug costs for nonresponders under the assumption that they would receive a higher dose from months 3 to 6. Expected costs per patient were reported for one and two years (Table 3).

Note that although the manufacturer's pharmacoeconomic submission report[10] specifies that the base case costs are derived from the response rates of the 600 mcg arm of study B2305,[1,2] it in fact uses the overall response rates for both dose arms (600 mcg and 900 mcg).

**TABLE 3: MANUFACTURER'S EXPECTED COST PER PATIENT: OVERALL RESPONSE DATA**

| Scenario | Details | Average Total Cost Per Patient |
|---|---|---|
| **Base Case** | 12 months for responders, 3 months for nonresponders | $32,243 |
| **Sensitivity** | 12 months for responders, 6 months for nonresponders | $43,260 |
| | 24 months for responders, 3 months for nonresponders | $45,711 |
| | 24 months for responders, 6 months for nonresponders | $56,728 |

Source: Manufacturer's pharmacoeconomic submission, Table 6.

The manufacturer estimated the expected cost of adverse events associated with pasireotide use by averaging the in-patient and acute care costs available in the 2011 Ontario Case Costing Initiative data, inflating the costs to 2013 dollars, and multiplying them by the overall frequency of grade 3 and 4 events observed in Study B2305 (Table 4). The cost of diabetes was reportedly estimated using a 2007 cost-of-management study.[4] The manufacturer also considered an additional cost due to hyperglycemia and the cost of monitoring for adverse events. These costs were combined into an estimated total cost of pasireotide treatment (Table 5).

**TABLE 4: MANUFACTURER'S ESTIMATION OF THE COST OF ADVERSE EVENTS AT 12 MONTHS**

| Adverse Event | Unit Costs | Overall Frequency (Grade 3 or 4) | Expected Costs |
|---|---|---|---|
| Diarrhea | $296 | 3.1% | $9.19 |
| Nausea | $1,711 | 2.5% | $42.78 |
| Hyperglycemia | $2,622 | 13.0% | $340.92 |
| Cholelithiasis | $2,921 | 1.2% | $35.06 |
| Headache | $1,855 | 1.9% | $35.24 |
| Abdominal pain | $1,931 | 1.9% | $36.68 |
| Fatigue | $4,746 | 1.9% | $90.17 |
| Asthenia | $4,746 | 2.5% | $118.64 |
| Hypoglycemia | $2,466 | 1.9% | $0.00 |
| Myalgia | $1,532 | 0.6% | $0.00 |
| Diabetes mellitus | $3,806 | 11.7% | $445.25 |
| Fluid and electrolyte abnormalities | $3,503 | 6.8% | $238.18 |
| **Total** | | | **$1,153.93**[a] |

[a] The manufacturer's estimation includes errors: The expected costs of myalgia and hypoglycemia should not be $0, and the cost of fluid and electrolyte abnormalities was left out of the total. The manufacturer's total expected costs due to adverse events should have been reported as $1,448.16.

**TABLE 5: MANUFACTURER'S TOTAL COST OF PASIREOTIDE TREATMENT**

| Cost | Year 1 | Year 2 |
|---|---|---|
| Annual cost of pasireotide | $62,427 | $62,427 |
| Cost of complications | $1,154[a] | $1,154[a] |
| Additional cost due to hyperglycemia | $120 | $120 |
| Annual monitoring costs | $1,797 | $946[b] |
| Total annual costs | $65,497 | $64,646 |
| Total two-year costs | | $130,143 |

[a] The $1,154 cost should have been $1,448; this error was propagated throughout all subsequent calculations and is therefore left in error in this table.
[b] The manufacturer's pharmacoeconomic report stated a year 2 cost of $1,797 for monitoring; however, this error was not propagated through subsequent calculations and is therefore presented in its corrected form here.

The manufacturer then calculated the incremental cost of pasireotide over radiotherapy, TSS, and bilateral adrenalectomy in an effort to estimate possible cost offsets (Table 6).

**TABLE 6: MANUFACTURER'S ESTIMATE OF INCREMENTAL COST OF PASIREOTIDE OVER ALTERNATE THERAPIES OVER ONE YEAR, WITH THREE-MONTH STOPPING RULE**

| Therapy | Cost[a] | Incremental Cost of Pasireotide[b] |
|---|---|---|
| Radiotherapy (1st-line setting) | $8,907 | $23,336 |
| Transsphenoidal surgery (2nd-line setting) | $33,146 | –$903 |
| Bilateral adrenalectomy (2nd-line setting) | $23,750 | $8,493 |

[a] Cost estimates for radiotherapy and surgeries taken from unpublished burden-of-illness study.[7]
[b] Pasireotide cost is the expected cost over one year, assuming the three-month discontinuation rule.

**TABLE 7: MANUFACTURER'S ESTIMATE OF INCREMENTAL COST OF PASIREOTIDE OVER ALTERNATE THERAPIES OVER TWO YEARS, WITH THREE-MONTH STOPPING RULE**

| Therapy | Cost[a] | Incremental Cost of Pasireotide[b] |
|---|---|---|
| Radiotherapy (1st-line setting) | $2,227 | $43,484 |
| Transsphenoidal surgery (2nd-line setting) | $7,476 | $38,235 |
| Bilateral adrenalectomy (2nd-line setting) | $5,937 | $39,774 |

[a] Cost estimates for radiotherapy and surgeries taken from unpublished burden-of-illness study.[7] Although the manufacturer presents the costs of alternate therapies as the two-year costs, they are in fact the estimated costs in year 2 after therapy (i.e., they do not include the first year of costs), leading to a large underestimation of the two-year costs.
[b] Pasireotide cost is the expected cost over two years, assuming the three-month discontinuation rule.

Based on the cost approach, the manufacturer reported that the two-year incremental cost of pasireotide ranges from $38,000 to $43,000 per patient (Table 7). It is challenging to interpret the results as the clinical benefits associated with the interventions have not been included. The approach is more relevant where the benefits associated with the interventions are identical (e.g., cost minimization analysis). In the current assessment of pasireotide, there are numerous considerations with pasireotide (such as low response rates, need for retreatment, combination treatment with non-indicated drugs) and with surgical interventions (such as complications) that have not been included that render the analysis incomplete and, as a result, minimally informative.

### CADTH Common Drug Review Results

Given the available clinical data, the clinical efficacy of pasireotide relative to best supportive care is uncertain. The absence of a control group or even a historical control makes it difficult to determine the likely clinical benefits and the extent to which adverse events are treatment-related. In addition, the value of a response given the surrogate nature of the primary efficacy outcome complicates the assessment of the cost-effectiveness of pasireotide.

The manufacturer-submitted economic analysis is simplistic in nature, and as a result does not provide a platform in which any of these areas of uncertainty can be explored.

Based on Table A1 from the B2305 clinical study report,[2] partial to complete control of mUFC was reported to be 32.72% at 6 months and 28.40% at 12 months. Also, it was estimated that patients remained on treatment for a mean duration of 11 months. Assuming a stopping rule where patients cease pasireotide treatment after three months of nonresponse, then over a 12-month period the average cost of pasireotide per patient (drug cost only) would be $33,044 or an average cost per responder at 12 months of $116,372. When considering treatment without a stopping rule, over a 12-month period the cost of pasireotide treatment (drug cost only) would be $62,427 or an average cost per responder of $219,813. When considering potential dose escalation to 1,200 mcg twice daily by 11.7% of patients (assuming 11.7% of patients increase dose from month 6 onward), the annual cost would be $64,847 or an average cost per responder of $228,336.

When considering the implementation of a six-month stopping rule, based on data from Table 11-14 of the clinical study report of B2305[11] (the six-month results of which do not align with the six-month results reported in table A1[2]), 38% of patients achieved control or partial control of mUFC at month 6. Assuming these patients continue on treatment, based on clinical trial information, 59% of six-month responders will continue to respond at 12 months (22% of total patients). The average cost per responder in this case is $195,350.

Given the patient population, based on clinical expert feedback, failure to respond to pasireotide may result in concomitant treatment with other non-indicated drugs. As the response rate of this strategy is unknown, the strategy cannot be examined in reanalyses.

The interpretation of these results is limited as the results are not comparative in nature (i.e., do not account for medical management that might otherwise be received by patients). Also, interpretation is predicated on the assumption that the response is clinically meaningful to patients.

### Addressing Limitations and Errors in the Manufacturer's Analysis

While the approach taken by the manufacturer is subject to limitations in the interpretation of the results, as detailed earlier in the report, CDR identified a number of errors as detailed here.

Under the assumption that a response yields beneficial outcomes of clinical or patient-centric relevance, the manufacturer's method takes into account three or six months of nonresponder costs, but only for the initial three or six months of therapy. Patients who then fail to respond after the initial months (i.e., cease responding) are assumed to stop treatment immediately upon receiving an mUFC reading above the responder threshold using the manufacturer's calculation methods. This is unlikely to be consistent with clinical practice. A CDR reanalysis (Table 8) accounts for the cost of therapy for all patients for the initial three or six months and then removes the percentage of patients who were nonresponders during the previous two (three-month stopping rule) or three (six-month stopping rule)

three-month periods. This still overestimates the proportion of patients who would stop treatment; it assumes all patients responding at a time point were also responders at the previous time point, whereas a transition matrix provided by the manufacturer (Manufacturer-provided clinical study report, Table 11-14[11]) showed that 10 patients who were responders at month 12 were nonresponders at month 6. The stopping rule as applied in the analyses does not reflect the possibility that some patients gain response throughout the treatment, which is possible based on the results of the clinical trial. This raises the possibility that patients in practice may stop treatment only after a lengthy trial of pasireotide to confirm nonresponse.

**TABLE 8: CADTH COMMON DRUG REVIEW'S REANALYSIS OF AVERAGE COST PER PATIENT: OVERALL RESPONSE DATA**

| Scenario[a] | Average Total Cost Per Patient |
|---|---|
| 12 months for responders, 3 months for nonresponders | $34,830 |
| 12 months for responders, 6 months for nonresponders | $45,391 |
| 2 years for responders, 3 months for nonresponders | $50,527 |
| 2 years for responders, 6 months for nonresponders | $63,633 |

CDR = CADTH Common Drug Review.

[a] It is assumed that patients will be discontinued in clinical practice only if they were nonresponders at both (three-month stopping rule) or all three (six-month stopping rule) of the most recent time points, e.g., because there is a higher number of responders at month 9 than at month 6, it was assumed that 35.8% of patients continued on drug from month 9 to month 12 rather than 32.7%, as 3.1% of patients would have tested as nonresponders at month 6 but as responders at month 9 and would therefore not have stopped treatment.

Example calculation: Three-month discontinuation rule costs at month 21 = 22.2% (larger of the response numbers at months 18 and 21) × $64,951 (annual costs in year 2, Table 10) ÷ 4 (number of three-month periods in a year) = $3,591.

CDR recalculated the expected cost of severe adverse events. Slight differences in most event costs from the manufacturer's estimates result from using the Bank of Canada's inflation calculator[12] methodology to inflate costs from 2011 to 2013 dollars rather than the manufacturer's use of Bank of Canada historical numbers. The cost of diabetes mellitus was assumed to be similar to the manufacturer's estimate despite an unclear method of estimation from its cited source.[4]

**TABLE 9: CADTH COMMON DRUG REVIEW'S REANALYSIS OF COST OF ADVERSE EVENTS**

| Adverse Event | Unit Costs | Overall Frequency (Grade 3 or 4) | Expected Costs |
|---|---|---|---|
| Diarrhea | $299 | 3.1% | $9.29 |
| Nausea | $1,729 | 2.5% | $43.22 |
| Hyperglycemia | $2,649 | 13.0% | $344.44 |
| Cholelithiasis | $2,951 | 1.2% | $35.41 |
| Headache | $1,880 | 1.9% | $35.72 |
| Abdominal pain | $1,950 | 1.9% | $37.05 |
| Fatigue | $4,794 | 1.9% | $91.10 |
| Asthenia | $4,794 | 2.5% | $119.86 |
| Hypoglycemia | $2,491 | 1.9% | $47.33 |
| Myalgia | $1,548 | 0.6% | $9.29 |
| Diabetes mellitus | $3,806 | 11.7% | $445.25 |
| Fluid and electrolyte abnormalities | $3,538 | 6.8% | $240.62 |
| **Total** | | | **$1,458.57** |

**TABLE 10: CADTH COMMON DRUG REVIEW TOTAL COST OF PASIREOTIDE TREATMENT**

| Cost | Year 1 | Year 2 |
|---|---|---|
| Annual cost of pasireotide | $62,427 | $62,427 |
| Cost of complications | $1,459 | $1,459 |
| Additional cost due to hyperglycemia[a] | $120 | $120 |
| Annual monitoring costs[a] | $1,797 | $946 |
| Total annual costs | $65,802 | $64,951 |
| Total two-year costs | | $130,752 |

[a] Annual monitoring costs and the additional cost due to hyperglycemia were assumed to be similar enough to the manufacturer's estimates to not yield a significant difference.

CDR also recalculated the incremental cost of pasireotide therapy over radiotherapy, TSS, and bilateral adrenalectomy. Changes from the manufacturer's calculation include the following:

- All therapies (radiotherapy, TSS, bilateral adrenalectomy) were assumed to use second-line costs from the burden-of-illness study,[7] as most patients (71 of 86) in that study received TSS therapy as first line; this is consistent with the pasireotide indication "in those in whom surgery has failed."
- The annual cost of a full year of pasireotide therapy was used rather than the expected cost in all patients as only patients who were continuing to receive pasireotide would in fact be delaying the need for other therapies.
- The cost for the first and second year of the alternate therapies was included in the two-year incremental calculations.
- Costs from the 2011 burden-of-illness study were inflated to 2013 dollars using the Bank of Canada's inflation calculator rather than historical data.

### TABLE 11: CADTH COMMON DRUG REVIEW'S ESTIMATE OF INCREMENTAL COST OF PASIREOTIDE OVER ALTERNATE THERAPIES OVER ONE YEAR

| Therapy | Cost[a] | Incremental Cost of Pasireotide[b] |
|---|---|---|
| Radiotherapy (2nd-line setting) | $15,079 | $50,722 |
| Transsphenoidal surgery (2nd-line setting) | $33,057 | $32,745 |
| Bilateral adrenalectomy (2nd-line setting) | $23,686 | $42,116 |

[a] Cost estimates for radiotherapy and surgeries taken from unpublished burden–of-illness study.[7]
[b] Pasireotide cost is the full cost over one year ($65,802), as alternate therapies are offset only as long as the patient is responding.

### TABLE 12: CADTH COMMON DRUG REVIEW'S ESTIMATE OF INCREMENTAL COST OF PASIREOTIDE OVER ALTERNATE THERAPIES OVER TWO YEARS

| Therapy | Cost[a] | Incremental Cost of Pasireotide[b] |
|---|---|---|
| Radiotherapy (2nd-line setting) | $17,300 | $113,452 |
| Transsphenoidal surgery (2nd-line setting) | $40,513 | $90,239 |
| Bilateral adrenalectomy (2nd-line setting) | $29,607 | $101,145 |

[a] Cost estimates for radiotherapy and surgeries taken from unpublished burden–of-illness study.[7]
[b] Pasireotide cost is the full cost of two years of therapy ($130,752), as the alternate therapies are offset only as long as the patient is responding.

Due to the uncertainty in the extent to which pasireotide caused the adverse events and other costs reported in the clinical trial and assumed by the manufacturer, CDR ran a sensitivity analysis removing all costs except the cost of pasireotide (Table 13).

### TABLE 13: CADTH COMMON DRUG REVIEW ESTIMATE OF EXPECTED COST PER PATIENT INCLUDING DRUG COSTS ONLY

| Scenario | Expected Cost Per Patient |
|---|---|
| 12 months for responders + 3 months for nonresponders | $33,044 |
| 12 months for responders + 6 months for nonresponders | $43,063 |
| 24 months for responders + 3 months for nonresponders | $48,072 |
| 24 months for responders + 6 months for nonresponders | $60,596 |

**TABLE 14: KEY LIMITATIONS**

| Identified Limitation | Description | Implication |
|---|---|---|
| Clinical efficacy uncertain | The available randomized trial for pasireotide[1] was uncontrolled; as such it is not possible to determine how pasireotide directly compares with either placebo or an active comparator (i.e., off-label ketoconazole). | Uncertainty in the clinical efficacy and safety of pasireotide compared with best supportive care or medical management. |
| Clinical and resource-use impact of lowering mUFC uncertain | While studies have associated higher UFC levels with more severe cognitive impairment, major depression, and risk of serious infection, a recent study failed to find a correlation between UFC levels and clinical features of Cushing related to A1C, BMI, beta-cell function, or blood pressure.[13] The exclusion of patients with baseline readings between ULN and 1.5 times ULN does limit the applicability of this study for assessing the appropriateness of judging efficacy by normalized UFC level, but it does lead to increased uncertainty in the assumption that lowering UFC equates to reducing Cushing symptoms and subsequent health care use.<br><br>While Figure 3 of the pasireotide trial[1] shows changes in clinical and quality-of-life parameters that appear to be strongly correlated to mUFC levels, the large withdrawal rate, presumably mostly of nonresponders (those with still-high UFC levels) and patients with serious adverse events (those more likely to have poor clinical readings), lessens certainty in the observed correlations. | The mUFC may be less predictive of clinical or quality-of-life improvement than assumed. It is uncertain whether patients judged to be responders or partial responders for the cost analysis are achieving the full clinical benefits implied and reducing the expected downstream health care resource use. |
| Off-label comparators omitted | No drugs other than pasireotide have a Health Canada indication for the treatment of Cushing disease; however, some are used in clinical practice, such as ketoconazole, cabergoline, and mitotane. Of these, the clinical expert consulted by CDR believed ketoconazole to be the most commonly used in Cushing disease.<br><br>Additionally, the expert believed it likely that in the event of partial response or loss of response to pasireotide in clinical practice, ketoconazole would be added to pasireotide therapy before choosing to discontinue. | With only weak evidence[8] exploring the efficacy of these off-label comparators, and no direct or indirect comparison of them to pasireotide, the relative effectiveness and cost-effectiveness is unknown.<br><br>Concurrent use of pasireotide and ketoconazole or other off-label medications would increase costs with an unknown effect on efficacy and safety. |

| Identified Limitation | Description | Implication |
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| Dataset errors | Although the manufacturer stated that the base case costs were derived from the response rates of the 600 mcg arm of trial B2305[1] (manufacturer's PE submission, section 3.1.1.4 and Table 5), the base case costs were in fact derived from the overall response rate of the trial.<br><br>The costs reported as being based on the 900 mcg response rates (manufacturer's PE submission, Table 10) and the overall response rates (manufacturer's PE submission, Table 11) were in fact both derived from the 600 mcg response rates of study B2305. | The manufacturer-calculated costs for one year of treatment for responders and three months for nonresponders should have been reported as:<br>600 mcg: $32,149<br>900 mcg: $32,339<br>Overall: $32,243 |
| Uncertainty in costs associated with harms | The manufacturer used an unweighted average of the in-patient and ambulatory care mean costs from the 2011 Ontario Case Costing Initiative data to estimate the costs of grade 3 or 4 adverse events at the frequencies reported in Study B2305. The costs were then inflated to 2013 dollars. These costs would likely vary substantially depending on circumstance and jurisdiction.<br><br>There is considerable variation in the likelihood of a grade 3 or 4 adverse event resulting in hospitalization between event types (e.g., significantly lower rates for severe hyperglycemia versus severe abdominal pain); however a 50% approximation does not seem unreasonable given the severity of higher grade events. CDR reviewers were unable to exactly match the manufacturer's inflation calculations using the Bank of Canada's inflation calculator methodology, though these differences were trivial. The manufacturer's results should have included a $47 cost for hypoglycemia and a $9 cost for myalgia (Excel errors). Additionally, the manufacturer neglected to include the $238 expected cost of fluid and electrolyte abnormalities in the total costs (Excel error). Without these errors, the manufacturer would have reported expected costs of adverse events to be $1,448.16.<br><br>The error in Table 4 of manufacturer's PE submission for year 2 monitoring costs (should be $946 not $1,797) is a typo and did not affect the subsequent calculations. | The expected costs of adverse events associated with pasireotide are uncertain, but are likely underestimated in the manufacturer's report. CDR calculations using similar methodology yielded $1,458.57 versus the $1,153.93 included in complication costs by the manufacturer. |

| Identified Limitation | Description | Implication |
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| Cost calculations not consistent with stated stopping rule | The manufacturer stated that for the base case costs it was assumed that patients would discontinue treatments after three months of nonresponse (manufacturer's PE submission, page 8). However, the calculations presented (manufacturer's PE submission, Table 6) include three months of treatment for everyone, followed by continuing costs of treatment only for patients who are responding during the currently calculated time point; this in effect assumes that patients who become nonresponsive after the first three months are immediately discontinued from therapy. However, in clinical practice, only patients who had nonresponsive mUFC values at the current measure as well as for the past three (or six for sensitivity analyses) months would be likely to be discontinued; i.e., physicians would be unlikely to discontinue treatment based on a single mUFC result. The clinical expert deemed it likely that patients would receive a dose increase after three months of nonresponse (i.e., from 600 to 900 mcg), making the six-month stopping rule the most likely to reflect clinical practice. | Drug costs are underestimated in the manufacturer's calculations. CDR reanalyses led to higher annual and two-year costs. |
| Cost offsets uncertain and typically transient; incremental costs underestimated | The manufacturer based estimates of cost offsets for alternate second-line therapies on an unpublished burden–of-illness study.[7]<br>The expected cost of pasireotide therapy (based on overall response rate) was compared with the cost of radiotherapy, TSS surgery, and bilateral adrenalectomy (manufacturer's PE submission, Table 8). However, as the other therapies would be offset only as long as a patient was using pasireotide, the incremental one-year costs should be based on the annual cost of pasireotide therapy for those still on drug (i.e., the total cost of therapy for a year, not the expected cost based on response). As the observed response rate for pasireotide is only 15.4% after two years, presumably most patients would have only delayed further surgery, radiotherapy, or alternate medical therapy rather than avoiding it.<br><br>Table 9 of the manufacturer's PE submission should include the cost of two years of the offset therapies, not the cost of just the second year after the offset therapy. | Assuming the burden-of-illness study is accurate and generalizable, CDR reanalyses using the total two-year costs for comparators and the total cost of one or two years of pasireotide yielded much higher incremental costs. |

A1C = glycated hemoglobin; BMI = body mass index; CDR = CADTH Common Drug Review; mUFC = mean urinary free cortisol; PE = pharmacoeconomic; TSS = transsphenoidal surgery; UFC = urinary free cortisol; ULN = upper limit normal.

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