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Reimbursement Recommendation

Osilodrostat (Isturisa)

Indication: For the treatment of adult patients with Cushing's disease who have persistent or recurrent hypercortisolism after primary pituitary surgery and/or irradiation, or for whom pituitary surgery is not an option

Sponsor: Recordati Rare Diseases Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Isturisa?

Canada's Drug Agency (CDA-AMC) recommends that Isturisa should be reimbursed by public drug plans for the treatment of adult patients with Cushing disease who have persistent or recurrent hypercortisolism after primary pituitary surgery and/or irradiation or for whom pituitary surgery is not an option if certain conditions are met.

Which Patients Are Eligible for Coverage?

Isturisa should only be covered for adults with Cushing disease who still have the disease after pituitary gland surgery or radiation or who cannot have surgery. These patients must have confirmed high cortisol levels, elevated adrenocorticotropic hormone (ACTH) levels, and a confirmed pituitary source of the excess ACTH.

What Are the Conditions for Reimbursement?

Isturisa should only be reimbursed if it is prescribed by an endocrinologist or a clinician with expertise in managing Cushing disease and the cost of Isturisa does not exceed the drug program cost of treatment with the least costly alternative treatment reimbursed for the treatment of Cushing disease.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 clinical trials showed that Isturisa helped adults with Cushing disease (whose disease returned after surgery or who could not have surgery) achieve better control of their cortisol levels compared with placebo. Patients in the studies also showed improvements in symptoms related to excess cortisol, which may help support better quality of life.
- Isturisa addresses some of the needs identified by patients because it has improved response to treatment and more manageable side effects when compared with placebo. However, the comparative efficacy and safety of Isturisa versus other available treatments, such as ketoconazole with or without cabergoline, remains uncertain.
- Based on the CDA-AMC assessment of the health economic evidence, Isturisa does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Isturisa compared with the most relevant comparators (e.g., ketoconazole, ketoconazole-cabergoline) for the treatment of Cushing disease.

Summary

- Based on public list prices, Isturisa is estimated to cost the public drug plans approximately $30.5 million over the next 3 years. At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption. The actual budget impact of reimbursing Isturisa will depend on the number of patients eligible.

Additional Information

What Is Cushing Disease?

Cushing disease is a rare condition in which a small tumour in the pituitary gland causes the body to make too much cortisol. High cortisol may be associated with significant physical and psychological symptoms and can lead to long-term health problems, such as heart disease, diabetes, and bone weakness. It affects approximately 2 of every 100,000 individuals globally. It occurs most often in adults aged between 30 and 50 years, and particularly in females.

Unmet Needs in Cushing Disease

Current treatment options, such as surgery, radiation, and available medications, have limited effectiveness and serious side effects and are not always easy for patients to access. There is a need for better-tolerated and more effective treatments for patients w who cannot undergo surgery or whose Cushing disease does not respond to surgery.

How Much Does Isturisa Cost?

Treatment with Isturisa is expected to cost between $67,407 and $424,745 per patient per year; the range is based on the Health Canada–recommended dosage (2 mg to 30 mg twice daily).

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that osilodrostat be reimbursed for the treatment of adult patients with Cushing disease who have persistent or recurrent hypercortisolism after primary pituitary surgery and/or irradiation, or for whom pituitary surgery is not an option, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 2 phase III trials (LINC 3 [N = 71 for randomized withdrawal period] and LINC 4 [N = 73]) demonstrated that treatment with osilodrostat results in added clinical benefit in adults with Cushing disease that is persistent or recurrent after pituitary surgery and/or irradiation or those who are not candidates for surgery. A greater proportion of patients in the osilodrostat group than in the placebo group had a complete response (defined as mean urinary free cortisol [mUFC] ≤ upper limit of normal [ULN]) at the end of the 8-week randomized withdrawal period in the LINC 3 trial (odds ratio [OR] = 13.71; 95% confidence interval [CI], 3.73 to 53.44; P < 0.001) and at 12 weeks in the LINC 4 trial (OR = 43.40; 95% CI, 7.10 to 343.20; P < 0.0001). Results from the trials also showed that osilodrostat likely increases overall response rate compared with placebo. No notable safety concerns were identified during the study period in the LINC 3 and LINC 4 studies.

In the absence of head-to-head trials of osilodrostat against relevant active comparators, the sponsor submitted a naive (i.e., unadjusted) indirect comparison comparing osilodrostat with ketoconazole based on osilodrostat data from the LINC 4 trial and ketoconazole data from 4 published studies. However, CDEC was unable to draw definitive conclusion from its results due to the significant methodological limitations of naive comparisons (e.g., lack of adjustment for the prognostic factors and heterogeneity across the studies). No indirect treatment comparison was included in this submission to compare osilodrostat versus ketoconazole-cabergoline combination.

Patients identified a need for effective treatment options that are better tolerated and more accessible than the current treatments for Cushing disease, including surgery, radiation, and available medications. Patient group input highlighted the need for alternatives to surgery and treatment options suitable for individuals who cannot undergo surgical procedures or who have an intolerance to existing therapies, such as ketoconazole. CDEC concluded that osilodrostat met some of the needs identified by patients by improving response to treatment when compared with placebo, although the comparative efficacy of osilodrostat versus ketoconazole with or without cabergoline remains uncertain. CDEC also agreed with the clinical experts that osilodrostat offers a manageable safety profile. However, comparative safety versus alternative treatments was highly uncertain.

At the sponsor-submitted price for osilodrostat and publicly listed price for the relevant comparator treatments (e.g., ketoconazole, ketoconazole-cabergoline), osilodrostat is more costly than the relevant comparators. Because no appropriate comparison was provided to compare osilodrostat with ketoconazole

or ketoconazole-cabergoline, CDEC considered the total drug cost of osilodrostat should not exceed the total drug cost of any relevant comparator treatment.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients (≥ 18 years) must have a confirmed diagnosis of Cushing disease that is persistent or recurrent after primary pituitary surgery and/or irradiation or for whom pituitary surgery is not an option, as evidenced by all the following: 1.1. mUFC > 1.3 × ULN with at least 2 values collected on consecutive days 1.2. morning plasma ACTH level greater than lower limit of normal 1.3. confirmation of pituitary source of excess ACTH.	Evidence from the LINC 3 and LINC 4 trials demonstrated that, when compared to placebo, osilodrostat resulted in a clinically meaningful improvement in complete response (as determined by mUFC) in patients with these characteristics. This condition is per the inclusion criteria in the LINC 3 and LINC 4 trials. In these 2 trials, patients with de novo Cushing disease could be included only if they were not considered candidates for surgery (e.g., due to comorbidities, inoperable tumours)	Patients with newly diagnosed (de novo) Cushing disease may be considered for osilodrostat treatment, if they are not eligible for surgery (e.g., due to comorbidities or inoperable tumours) and meet the criteria listed in this reimbursement condition. CDEC noted that patients who are currently receiving other medications, such as ketoconazole, would be eligible to switch to osilodrostat if they otherwise meet the initiation criteria. The clinical experts consulted by CDA-AMC noted to CDEC that, in clinical practice, it is anticipated that osilodrostat would be used after documented failure of or intolerance to prior medical therapies, such as ketoconazole. For condition 1.3, any of the following 3 criteria were used in the trials to confirm pituitary source of excess ACTH: • MRI confirmation of pituitary adenoma > 6 mm • BIPSS with either CRH or desmopressin stimulation for patients with a tumour ≤ 6 mm • histopathologic confirmation of an ACTH-staining adenoma in patients who have had prior pituitary surgery.
2. The maximum duration of initial authorization is 12 weeks.	The initial treatment response was assessed after 8 weeks (of the randomized withdrawal period) in the LINC 3 trial and 12 weeks (placebo-controlled period) in the LINC 4 trial. The clinical experts consulted by CDA-AMC noted that an initial 12-week (approximately 3 months) approval would be reasonable to assess the treatment response.	—

Reimbursement condition	Reason	Implementation guidance
Renewal		
3. For renewal after initial authorization and each subsequent renewal, patients must maintain a clinical response to therapy (i.e., mUFC ≤ ULN) accompanied by improvement in patient symptoms and control of comorbidities (e.g., cardiovascular events, diabetes, osteoporosis).	The primary efficacy end point in the LINC 3 and LINC 4 trials was the proportion of randomized patients with a complete response, defined as mUFC ≤ ULN.	Monitoring patients' symptoms and comorbidities should be based on the clinician assessment at regular intervals. Renewal of treatment should be re-evaluated by the treating physician after successful surgery and/or irradiation.
4. Subsequent renewals should be assessed annually to ensure clinical benefit, as defined in condition 3, is maintained.	This is to ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment. The trials evaluated the sustainability of efficacy over a 48-week (approximately 1 year) study period.	Clinical experts noted that more frequent evaluations may be required to monitor signs and symptoms of hypocortisolism in patients who receive osilodrostat.
Prescribing		
5. Osilodrostat should be prescribed by endocrinologists or clinicians with expertise in managing Cushing disease.	This is meant to ensure that osilodrostat is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. Osilodrostat should be negotiated so that it does not exceed the drug program cost of treatment with the least costly alternative treatment reimbursed for the treatment of Cushing disease.	While osilodrostat demonstrates added clinical benefit compared to placebo, the evidence comparing osilodrostat with the most relevant comparators (e.g., ketoconazole, ketoconazole-cabergoline) is uncertain or unavailable. As such, there is insufficient evidence to justify a cost premium for osilodrostat over the least expensive alternative treatment reimbursed for Cushing disease.	—
Feasibility of adoption		
7. The feasibility of adoption of osilodrostat must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption because of the difference between the sponsor's estimate and the CDA-AMC estimate(s).	—

ACTH = adrenocorticotropic hormone; BIPSS = bilateral inferior petrosal sinus sampling; CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; CRH = corticotropic-releasing hormone; mUFC = mean urinary free cortisol; UFC = urinary free cortisol; ULN = upper limit of normal.

Discussion Points

- **Significant unmet need:** CDEC acknowledged that there was uncertainty with the clinical evidence; therefore, the committee deliberated on osilodrostat considering the criteria for significant unmet

need described in the Procedures for CDA-AMC Reimbursement Reviews. It was noted that Cushing disease is a rare and serious condition associated with significant morbidity and mortality. The committee heard from the clinical experts that the current treatment options, including pituitary surgery, irradiation, and medical therapy, are often partially effective, associated with serious side effects, and have limited accessibility. Patients expressed a need for more effective therapies that are better tolerated and more accessible, particularly for those who cannot undergo surgery. The clinicians who were consulted echoed these concerns, highlighting modest efficacy, poor tolerability, and restricted availability of existing medical treatments. CDEC agreed that there is a need for effective, well-tolerated, and accessible nonsurgical options to address these gaps.

- **Comparators:** CDEC discussed appropriate comparators for osilodrostat. The clinical experts indicated that for patients with Cushing disease for whom surgery is not feasible or has been ineffective, alternative options include repeat surgery, medical therapy, radiotherapy, or bilateral adrenalectomy. Pharmacotherapy options may include ketoconazole with or without cabergoline, metyrapone, and pasireotide. CDEC noted that ketoconazole and metyrapone are not approved by Health Canada for this indication, and metyrapone is only available through the Special Access Program. The clinical experts noted that the current treatment options for patients described in the indication under review include the off-label use of ketoconazole monotherapy or ketoconazole-cabergoline combination, or active surveillance.
- **Certainty of evidence:** The Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty of evidence assessment results in a rating of moderate for complete response rate. For overall response rate, CushingQoL total score, and Beck Depression Inventory-II total score, the GRADE assessment indicated a rating of low to moderate. CDEC discussed that osilodrostat demonstrates added clinical benefit compared to placebo; however, evidence comparing osilodrostat with other comparators (e.g., ketoconazole and ketoconazole-cabergoline) remains uncertain or unavailable. CDEC additionally discussed that the primary end point in the pivotal trials (i.e., complete response defined based on mUFC normalization) was a dichotomous surrogate marker with uncertain validity for predicting outcomes most important to patients, such as comorbidities, quality of life, and mortality.
- **Adverse effects:** CDEC discussed the safety profile of osilodrostat based on findings from the LINC 3 and LINC 4 trials and noted that it was generally consistent with expectations for steroidogenesis inhibitors. The most commonly reported adverse events (AEs) included gastrointestinal symptoms, musculoskeletal complaints, and fatigue. Serious AEs (SAEs) were infrequent, and treatment discontinuations due to AEs were rare across both trials. One death occurred during the extension phase of the LINC 3 trial, which was not considered related to study treatment. CDEC highlighted AEs of special interest, including hypocortisolism and adrenal hormone precursor accumulation, which were more frequently observed in patients receiving osilodrostat. CDEC noted that appropriate monitoring and management strategies would be required in clinical practice to mitigate these risks.

Background

Cushing disease is a rare but serious condition caused by a pituitary tumour that leads to excessive production of ACTH and, consequently, cortisol. It represents the most common cause of endogenous Cushing syndrome. Cushing disease causes significant physical and psychological symptoms and increases the risk of long-term complications, such as cardiovascular disease, diabetes, and osteoporosis. Even after treatment, many patients experience persistent health issues and diminished quality of life.

Globally, the estimated prevalence of Cushing disease is approximately 2.2 per 100,000 people, with an annual incidence of approximately 2.4 per million. No Canadian-specific epidemiological data are available, but estimates from other regions are often extrapolated to Canada. Cushing disease occurs most frequently in adults aged between 30 to 50 years. It also occurs more frequently in females than males.

Osilodrostat has been approved by Health Canada for the treatment of adult patients with Cushing disease who have persistent or recurrent hypercortisolism after primary pituitary surgery and/or irradiation or for whom pituitary surgery is not an option. Osilodrostat is a cortisol synthesis inhibitor which blocks cortisol synthesis via 11-beta-hydroxylase inhibition. It is available as a 1 mg, 5 mg, or 10 mg oral tablet. The product monograph recommends a starting dosage of 2 mg twice daily (can be gradually titrated by increments of 1 mg or 2 mg twice daily, no more frequently than once every 2 to 3 weeks), and a maximum dosage of 30 mg twice daily.

Sources of Information Used by the Committee

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

- a review of 2 pivotal studies — LINC 3 (randomized withdrawal study) and LINC 4 (randomized controlled trial) — in adult patients with Cushing disease, 2 long-term extension studies, and 1 unadjusted (naive) indirect comparison of osilodrostat versus ketoconazole
- patients' perspectives gathered by 1 patient group, the Canadian Organization for Rare Disorders (CORD)
- input from public drug plans that participate in the reimbursement review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with Cushing disease
- 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

Input From Patients and Clinicians

One patient group submission from CORD and 1 clinician group submission from the CSEM were received. Patient group input was gathered through online questionnaires and interviews with 21 patients (12

from Canada and 9 from the US), including 18 individuals (86%) diagnosed with Cushing disease and 3 individuals (14%) with Cushing syndrome. Clinician group input was gathered through iterative review and discussion among all 12 CSEM clinician members, who were experts in the treatment of Cushing syndrome. Additionally, 2 clinical specialists with expertise in the diagnosis and management of Cushing disease participated as part of the review team.

Unmet Needs and Existing Challenges

The patient group input indicated that many found current treatments (surgery, radiation, and medications) only partially effective and are often associated with severe side effects, highlighting the need for more tolerable and accessible therapies.

According to the clinician group providing input, treatment options for Cushing syndrome are constrained by suboptimal efficacy, serious side effects, limited accessibility, and a lack of long-term data. The clinician group noted that commonly used medical therapies, such as ketoconazole, cabergoline, metyrapone, and pasireotide, present various challenges, including off-label use, hepatotoxicity, modest efficacy, poor tolerability, and restricted availability or funding. Radiotherapy is slow to achieve remission and carries significant risks, while bilateral adrenalectomy is typically reserved as a last-resort option due to its high-risk profile and lifelong consequences. The clinician group indicated that these limitations prevent current treatments from achieving an optimal balance between efficacy and safety, underscoring the need for better-tolerated and effective therapies such as osilodrostat.

The clinical experts consulted for this review further noted that some patients may be unable to undergo surgery due to poor health condition or technical constraints that make surgery unfeasible; for these patients, effective and well-tolerated nonsurgical treatments are needed.

Considerations for Using the Drug Under Review

Contents within this section have been informed by input from the clinical experts consulted for the purpose of this review and from clinician groups.

Place in Therapy

The clinical experts consulted for this review noted that osilodrostat selectively inhibits cortisol synthesis, effectively lowering hormone levels without removing the underlying tumour. They emphasized that its selectivity offers an advantage over other therapies, which are often associated with more side effects due to broader mechanisms of action. Input from the clinician group further supported use of osilodrostat as a first-line medical treatment, citing its consistent cortisol-lowering effects, improvements in metabolic and psychological parameters, and a manageable safety profile.

Patient Population

The clinical experts indicated that patients with active disease who are not candidates for surgery or who have had unsuccessful prior surgery due to feasibility, ineffectiveness, or significant comorbidities, should be prioritized for medical treatment with osilodrostat. The clinical experts emphasized the importance of early and accurate diagnosis; Cushing disease is often underdiagnosed due to its clinical overlap with metabolic

syndrome. The clinical experts also noted that diagnosis is frequently delayed by months or years, leading to complications that may limit the success or feasibility of surgery.

Assessing the Response to Treatment

The clinical experts consulted for this review indicated that key measures of treatment response include improvement in patient symptoms, control or reversal of comorbidities, and reduction in life-threatening complications, such as myocardial infarction and serious infections or sepsis. Consistent with input from the clinician group, the clinical experts noted that assessing treatment response can be challenging in patients with prolonged exposure to elevated cortisol levels, which results in a wide range of clinical manifestations.

Discontinuing Treatment

According to the clinical experts consulted for this review, discontinuation of osilodrostat may be considered when the drug is poorly tolerated due to severity of clinical symptoms or documented adverse effects (e.g., liver dysfunction) or when the treatment fails to reduce cortisol levels and associated complications to a clinically satisfactory level.

The clinical experts emphasized that monitoring liver parameters during treatment with osilodrostat is important because liver dysfunction is common in patients with Cushing disease and may reflect disease-treatment interactions. They also emphasized the need to regularly assess drug effectiveness to ensure continued use is clinically justified.

Prescribing Considerations

The clinical experts consulted for this review indicated that a specialist is required to diagnose and manage patients who may be treated with osilodrostat because Cushing disease is an uncommon condition that typically falls outside the scope of general practitioners or internists.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for osilodrostat:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- system and economic issues.

The clinical experts consulted for this review provided advice on the potential implementation issues raised by the drug programs (Table 2).

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
Were all relevant comparators considered?	The clinical experts noted that the current treatment options for patients described in the indication under review include the off-label use of ketoconazole monotherapy or ketoconazole-cabergoline combination, or active surveillance. CDEC agreed with the clinical experts that ketoconazole with or without cabergoline is a relevant comparator for this review. The clinical experts consulted for this review also indicated that, in Canada, ketoconazole-cabergoline combination therapy may be used for patients who do not respond to ketoconazole monotherapy. Therefore, combination therapy with ketoconazole-cabergoline could be considered a potential comparator in this subgroup of patients. No ITC was provided by the sponsor to compare osilodrostat vs. ketoconazole-cabergoline combination therapy.
Considerations for initiation of therapy	
What would be the criteria for starting therapy? Where does osilodrostat fit in relation to other nonmedication therapies? (For example: LINC 3 included confirmed persistent or recurrent Cushing disease after pituitary surgery or irradiation or both if they had not had previous surgery or radiotherapy and refused surgery or were not deemed to be surgical candidates. Patients were required to have evidence of a pituitary origin [based on specific criteria]. Patients could be receiving other medical therapies if specified washout was achieved. LINC 4 included specific values for mUFC — greater than 1.3 × ULN and plasma ACTH above the lower limit of normal.)	CDEC agreed that the initiation criteria listed in Table 1 (condition 1) should be used for starting osilodrostat. According to the clinical experts consulted for this review, patients with active Cushing disease for whom surgery is not possible, feasible, or effective would be eligible for starting therapy with osilodrostat. The clinical experts pointed out that although osilodrostat can reduce production of cortisol, it may not eliminate the structural presence of the tumour. For patients with inoperable Cushing disease, a medication that works through selective enzyme inhibition to limit cortisol production (such as osilodrostat) may be of significant advantage.
Would there be a requirement to have any previous therapies before starting osilodrostat?	CDEC agreed with the clinical experts that surgical resection of the primary lesion(s) underlying the disease is considered the first-line treatment option for Cushing disease. For patients for whom surgery is not feasible, medications that reduce cortisol production are available. According to the clinical experts, aside from surgery, most patients with persistently active Cushing disease would typically have received ketoconazole, with or without cabergoline, as part of their prior pharmacological management. Although osilodrostat fits as a treatment option in the persistent or recurrent disease setting after pituitary surgery and/or irradiation, CDEC agreed with the clinical experts that initiation of osilodrostat may also be considered after documented failure or intolerance to prior medical therapies, such as ketoconazole (with or without cabergoline).
Considerations for continuation or renewal of therapy	
What would the guidance be around continuing therapy? What is the marker for treatment success? The 2 studies (LINC 3 and LINC 4) used mUFC ≤ ULN.	The clinical experts noted that the criteria for continuing therapy would depend on patients' response to osilodrostat. Some measures that are generally used by clinicians include patient

Drug program implementation questions	Clinical expert response
	symptoms, extent to which comorbidities are controlled or reversed, and reduced incidence of life-threatening complications such as myocardial infarcts and/or serious infections or sepsis. The clinical experts emphasized that the liver function parameters should be closely monitored among patients with Cushing disease because they are indicative of tolerance to the medication and reflective of disease-treatment interactions. The clinical experts noted that mUFC is commonly used in practice to monitor biochemical control, and mUFC ≤ ULN is regarded as a practical and appropriate marker in both trials and clinical settings. However, decisions regarding continuation of therapy require a comprehensive evaluation encompassing clinical improvement and safety, rather than reliance on mUFC alone.
Considerations for discontinuation of therapy	
How would response to therapy be quantified? Is this a standard measure or would this depend on other individual patient factors? What parameters should be considered related to improvement of comorbid conditions?	The clinical experts noted that response to therapy in Cushing disease is typically quantified using normalization of mUFC, which is the primary end point in most clinical trials. However, they noted that mUFC alone is not considered sufficient to define treatment success in the clinical practice. Instead, a broader evaluation that includes patient-important outcomes, such as the incidence of cardiovascular disease, incidence of diabetes, physical function (for example, patient mobility, and ECOG performance status), as well as mortality, is more reflective of meaningful clinical benefit. The clinical experts noted that although mUFC is a standard measure in trials, its interpretation in clinical practice depends on individual patient factors. For example, changes in BMD at the lumbar spine can be a valuable indicator of treatment impact, particularly in relation to physical function. BMD can be measured precisely using validated techniques and normative values. However, the extent of BMD improvement may vary depending on the degree of cortisol reduction and the patient's baseline condition, making it a context-dependent marker. In assessing improvement of comorbid conditions, clinical experts emphasized the importance of monitoring cardiovascular events, metabolic parameters, osteoporosis, and physical performance.
System and economic issues	
The primary comparison is vs. ketoconazole, which is not indicated in this population and is covered in most (but not all) formularies as a full benefit. Is this the most appropriate comparison or should other medications or surgery/radiation also be considered?	Clinical experts' feedback suggested that osilodrostat was more likely to be used in patients for whom surgery was ineffective or not possible. Although it is unlikely to replace a currently available treatment, it may be preferred over currently available treatments. In addition to ketoconazole (as a potential first-line pharmacotherapy treatment comparator), the clinical experts expressed that the combination therapy of ketoconazole-cabergoline and active surveillance are the most relevant comparators in patients in whom surgery was ineffective or not possible.

ACTH = adrenocorticotropic hormone; BMD = bone mineral density; CDEC = Canadian Drug Expert Committee; ECOG = Eastern Cooperative Oncology Group; mUFC = mean urinary free cortisol; ULN = upper limit of normal.

Clinical Evidence

Systematic Review

Description of Studies

Two multicentre, phase III, double-blind (DB), placebo-controlled studies — LINC 3 (randomized withdrawal trial) and LINC 4 (randomized controlled trial) — provided evidence comparing osilodrostat with placebo in adult patients with Cushing disease. The LINC 3 study enrolled 137 patients. The study included a dose titration period of osilodrostat (2 mg to 30 mg twice daily based on the mean of three 24-hour mUFC) from week 0 to week 12, followed by a maintenance period from week 12 to week 26. From week 26 to week 34, patients entered a DB, randomized withdrawal phase (osilodrostat [1 mg to 30 mg, oral, twice daily] or placebo at a 1:1 ratio), involving 71 patients with complete response at week 24 who did not require up-titration between weeks 13 and 24. Finally, all patients received osilodrostat in an open-label period from week 34 to week 48. The LINC 4 study randomized 74 patients to receive osilodrostat (2 mg to 30 mg, oral, twice daily) or placebo at a 2:1 ratio from week 0 to week 12. Thereafter, all patients received open-label treatment with osilodrostat until week 48 or the end of the optional extension phase (week 96). The maximum dosage of osilodrostat in the LINC 3 and LINC 4 studies was 30 mg twice daily. The primary end point, in both studies, was the complete response rate (proportion of randomized patients with mUFC ≤ ULN [i.e., 138 nmol per 24 hours]) at the end of placebo-controlled period. Secondary end points included overall response rate (proportion of patients with mUFC ≤ ULN or at least 50% reduction from baseline), cardiovascular-related metabolic parameters, BMD, Cushing's quality-of-life (CushingQoL) questionnaire, Beck Depression Inventory-II (BDI-II), as well as harms.

At baseline in the LINC 3 study (randomized withdrawal period including patients whose Cushing disease responded with no up-titration in the preceding weeks), the mean age of participants was 44.3 years (SD = 11.3 years) in the osilodrostat arm and 42.0 years (SD = 13.5 years) in the placebo withdrawal arm. There was a higher proportion of females in the osilodrostat arm (83%) than in the placebo withdrawal arm (63%). Time since diagnosis of Cushing disease was shorter in the osilodrostat group (mean = 71.4 months) than in the placebo withdrawal group (mean = 88.3 months). Most patients had persistent or recurrent disease (89% in the osilodrostat arm and 94% in the placebo withdrawal arm). Adenoma size was not reported. At the baseline of the placebo-controlled period, mUFC was higher in the osilodrostat arm (mean =6.4 × ULN, equivalent to 890 nmol per 24 hours; SD =1,276 nmol per 24 hour) compared with the placebo withdrawal arm (mean = 4.1 × ULN; equivalent to 560 nmol/24 hour; SD =549 nmol per 24 hour) in the placebo arm, respectively. Most patients in both the osilodrostat and placebo arms had prior pituitary surgery (89% and 94%) or irradiation (17% and 14%), and the majority had also received medical therapy (97% and 94%).

At baseline in the LINC 4 study, the mean age of participants was 42.3 years (SD =13.8 years) in the osilodrostat arm and 38.9 years (SD =12.3 years) in the placebo arm. There was a higher proportion of females in the osilodrostat arm (90%) than in the placebo arm (72%). Adenoma classification showed a lower proportion of microadenomas in the osilodrostat arm (62.5%) compared to the placebo arm (80%), while macroadenomas were more frequent in the osilodrostat arm (35% versus 16%). Baseline mUFC levels were similar between groups (osilodrostat: mean = 3.1 × ULN, equivalent to 421 nmol per 24 hours

[SD =291 nmol per 24 hours]; placebo: mean = 3.3 × ULN, equivalent to 451.5 nmol per 24 hours [SD =535 nmol per 24 hours]). Most patients had prior pituitary surgery (osilodrostat: 85%; placebo: 92%) or irradiation (osilodrostat:12.5%; placebo: 12%). Prior medical therapy was more frequent in the placebo group (76%) than in the osilodrostat group (54%).

Efficacy Results

The key efficacy results from the LINC 3 and LINC 4 studies are summarized in Table 3 and Table 4.

mUFC Response

Complete Response Rate

In the LINC 3 study, at the end of the 8-week randomized withdrawal period (week 34), a higher proportion of patients in the osilodrostat arm (86.1%) had a complete response than in the placebo arm (29.4%; OR = 13.71; 95% CI, 3.73 to 53.44; P < 0.001). Absolute between-group differences were not available.

In the LINC 4 study, at the end of DB randomized period (week 12), a higher proportion of patients in the osilodrostat arm (77.1%) had a complete response than in the placebo arm (8.0%; OR = 43.40; 95% CI, 7.10 to 343.20; P < 0.0001). Absolute between-group differences were not available.

Overall Response Rate

The overall response rate in the osilodrostat arm compared to the placebo arm in the LINC 3 study was [redacted]% versus [redacted]% and in the LINC 4 study was [redacted]% versus [redacted]% at the end of DB period. Between-group differences were not available and were not tested statistically.

Bone Mineral Density

The BMD outcomes were measured at study baseline and week 48 in both the LINC 3 and LINC 4 studies, as specified in the study protocols. In the LINC 3 study, data were available for the all-patients population (N = 137), whereas in the LINC 4 study, BMD assessments at week 48 were available for 49 patients with at least 1 BMD assessment.

In the LINC 3 study, among patients with available data (n = [redacted]), the mean percentage change from baseline in BMD of L1 to L4 lumbar spine at week 48 was [redacted]% (SD = [redacted]), with mean change in the actual value of [redacted] g/cm^2 (SD = [redacted]).

In the LINC 4 study, among patients with available data (n = [redacted]), the mean percentage change from baseline in BMD of L1 to L4 lumbar spine at week 48 was [redacted]% (SD = [redacted]), with mean change in the actual value of [redacted] g/cm^2 (SD = [redacted]).

Cardiovascular-Related Metabolic Parameters Associated With Cushing Disease

In the LINC 3 study at week 34 (end of randomized withdrawal period), the mean change from study baseline for hemoglobin A1C was [redacted]% (SD = [redacted]) in the osilodrostat arm (n = [redacted]) and [redacted]% (SD = [redacted]) in the placebo withdrawal arm (n = [redacted]), for low-density lipoprotein cholesterol was [redacted] mmol/L (SD = [redacted], n = [redacted]) versus [redacted] mmol/L (SD = [redacted], n = [redacted]), for diastolic blood pressure was [redacted] mm Hg (SD = [redacted], n = [redacted]) versus [redacted] mm Hg (SD =[redacted], n = [redacted]), and for weight was [redacted]

kg (SD = , n =) versus kg (SD = , n =). Between-group differences were not reported for the randomized withdrawal period. The adjusted mean changes from baseline to week 48 in the all-patients population ranged from % to % for hemoglobin A1C, mmol/L to mmol/L for LDL cholesterol, mm Hg to mm Hg for diastolic blood pressure, and kg to kg for weight.

In the LINC 4 study, during the placebo-controlled period, there were greater improvements in all the cardiovascular-related metabolic parameters in the osilodrostat arm than the placebo arm, except for triglycerides. However, there was an overall improvement in triglycerides value during the core phase. the mean change from study baseline in the following parameters was: hemoglobin A1C % (SD =) in the osilodrostat arm (n =) and (SD =) in the placebo withdrawal arm (n =); LDL cholesterol mmol/L (SD, , n =) versus mmol/L (SD = , n =); standing diastolic blood pressure mm Hg (SD = , n =) versus mm Hg (SD = , n =); and weight kg (SD = , n =) versus kg (SD = , n =). Between-group differences were not available and were not tested statistically.

Liver Function Biochemical Parameters

In the LINC 3 study, most abnormal liver parameters occurred during the dose titration period of the trial. During the placebo-controlled, randomized withdrawal period, patients (%,) in the osilodrostat arm versus no patients in the placebo withdrawal arm had alanine transaminase (ALT) or aspartate transaminase (AST) levels greater than ULN but less than or equal to times ULN. During the 48-week core study period of the LINC 3 study, among the patients in the all-patients population, (%) had an increase in ALT or AST levels greater than ULN but less than or equal to times of ULN. Specifically, patients (%) had ALT or AST increases exceeding times the ULN, patients (%) exceeded times ULN, patients (%) exceeded || times ULN, and patient (%) exceeded times ULN. In patient with liver metastases, ALT and AST levels did not normalize. No patients had ALT or AST levels greater than times ULN in the LINC 3 study.

In the LINC 4 study, liver enzyme abnormalities were infrequent, mild, and reversed spontaneously. During the placebo-controlled period (12 weeks), patients (%,) in the osilodrostat arm versus no patients in the placebo arm had an increase in ALT level greater than times of ULN. During the overall 48-week core study period, a total of patients (%,) had an increase in ALT greater than times of ULN. In LINC 4, no patients had ALT or greater times ULN; and no patients had an increase in AST or greater times ULN during the overall study period. No patient had concurrent increases in AST, ALT, and total bilirubin and/or alkaline phosphatase (ALP) levels. No patient met Hy's Law criteria.

No patients discontinued the study drug due to abnormal liver biochemical parameters in the LINC 3 and LINC 4 studies.

Patient-Reported Outcomes

CushingQoL Total Score (Range: 0 [Worst] to 100 [Best])

In the LINC 3 study, at week 34 (end of the randomized withdrawal period), the mean change from study baseline in CushingQoL total score was [redacted] points (SD = [redacted]) in the osilodrostat arm (n = [redacted]) and [redacted] points (SD = [redacted]) in the placebo withdrawal arm (n = [redacted]). A between-group difference was not reported.

In the LINC 4 study at week 12, the mean change from baseline in CushingQoL total score was [redacted] points (95% CI, [redacted]) in the osilodrostat arm (n = [redacted]) and [redacted] points (95% CI, [redacted]) in the placebo arm (n = [redacted]). The adjusted mean difference between the 2 treatment arms was [redacted] points (95% CI, [redacted]).

BDI-II Total Score (Range: 0 [Best] to 63 [Worst])

In the LINC 3 study at week 34 (end of the randomized withdrawal period), the mean change from study baseline in BDI-II total score was [redacted] points (SD = [redacted]) in the osilodrostat arm (n = [redacted]) and [redacted] points (SD = [redacted]) in the placebo withdrawal arm (n = [redacted]). A between-group difference was not reported.

In the LINC 4 study at week 12, the mean change from baseline in BDI-II total score was [redacted] points (95% CI, [redacted]) in the osilodrostat arm (n = [redacted]) and [redacted] points (95% CI, [redacted]) in the placebo arm (n = [redacted]). The adjusted mean difference between the 2 treatment arms in the BDI-II total score was [redacted] points (95% CI, [redacted]), favouring [redacted].

Harms Results

During the DB randomized withdrawal period in the LINC 3 study, AEs were reported in 26 patients (72.2%) in the osilodrostat arm and 23 patients (65.7%) in the placebo arm. The most commonly reported AEs in the osilodrostat and placebo arms were nausea (11.1% and 0), anemia (8.3% and 8.6%), arthralgia (8.3% and 0), and headache (8.3% and 0). In the LINC 4 study, during the placebo-controlled period of the first 12 weeks, AEs were reported in 46 patients (95.8%) in the osilodrostat arm and 23 patients (92.0%) in the placebo arm. The most commonly reported AEs in the osilodrostat and placebo arms were arthralgia (35.4% and 8.0%), decreased appetite (37.5% and 16.0%), and fatigue (25.0% and 16.0%).

During the DB randomized withdrawal period in the LINC 3 study, SAEs were reported in 3 patients: 2 in the osilodrostat arm (cholelithiasis and neutropenia were each reported by 1 patient) and 1 in the placebo arm (increased blood corticotrophin). During the placebo-controlled period in the LINC 4 study, SAEs were reported in 3 patients: 2 in the osilodrostat arm (3 events in 2 patients: dengue fever, electrocardiogram T-wave inversion, and erosive duodenitis) and 1 in the placebo arm (pneumonia).

During the DB randomized withdrawal period in the LINC 3 study, no patients in the osilodrostat arm and 2 patients in the placebo arm discontinued the study due to AEs. During the placebo-controlled period in the LINC 4 study, 1 patient in the osilodrostat arm and no patients in the placebo arm discontinued the study drug due to AEs.

In the LINC 3 study, 1 patient (who was randomized to the placebo arm during the DB randomized withdrawal period) died by suicide during the extension period. No deaths were reported during the study period in the LINC 4 study.

AEs of special interest in the LINC 3 and LINC 4 studies included the following: hypocortisolism-related AEs (51.1% and 27.4% of patients), adrenal hormone precursor accumulation-related AEs (42.3% of patients and 61.6% of patients), pituitary tumour enlargement-related AEs (2.2% and 5.5%), and arrhythmogenic potential and QT prolongation-related AEs (4.4% and 4.1%).

During the DB randomized period of the LINC 4 study, a higher proportion of patients in the osilodrostat arm reported adrenal hormone precursor accumulation-related AEs compared to the placebo arm (osilodrostat: 43.8%; placebo: 36.0%), as well as hypocortisolism-related AEs (osilodrostat 14.6%; placebo: 0).

Critical Appraisal

The LINC 3 and LINC 4 studies used appropriate randomization and allocation concealment, maintained blinding throughout placebo-controlled periods, and applied robust methods for measuring UFC. Baseline characteristics were generally balanced, and missing data for most outcomes were minimal during placebo-controlled phases, supporting overall internal validity. In the LINC 3 study, the randomized withdrawal design exposed all patients to osilodrostat before randomization, creating potential carry-over effects in the placebo group, although these were considered limited but not empirically confirmed. Concomitant therapies and prior pituitary irradiation in both trials may have confounded outcomes such as mUFC, BMD, and metabolic measures, making attribution to osilodrostat uncertain. Formal statistical testing was largely restricted to primary end points, with most other outcomes reported descriptively without between-group differences or CIs, limiting interpretation and increasing risk of type I error. Missing data were substantial for BMD at 48 weeks, and handling of these data was not described, introducing potential bias. Furthermore, the primary end point (cortisol normalization based on mUFC) is not universally accepted as a validated surrogate for long-term outcomes, and evidence demonstrating its predictive validity was lacking.

Patients in the LINC 3 and LINC 4 studies were recruited from multiple countries, including Canada, and eligibility criteria generally aligned with Canadian practice. Demographics were comparable to those typically seen in Canada, and dosing strategies were considered reasonable. However, enrolled patients appeared to have milder disease than those most in need of treatment, raising uncertainty about generalizability to more severe cases. The LINC 3 study used an enriched randomized withdrawal design that excluded patients with harder-to-control Cushing disease, potentially overstating efficacy and understating harms, while the LINC 4 study employed a more conventional DB design. Both trials used placebo comparators rather than active treatments common in Canada, and the placebo-controlled periods were relatively short, limiting assessment of long-term outcomes and AEs. Much of the study duration involved single-arm treatment, reducing ability to draw causal inferences. Overall, although the trials were well-designed and aligned with regulatory standards, these factors may affect applicability to real-world practice.

GRADE Summary of Findings and Certainty of the Evidence

Literature-based minimal important difference estimates were used as the thresholds for CushingQoL total score (10.1 points based on within-group data); within-group estimates were used in the absence of available between-group estimates. Refer to the summary of outcome measures in Appendix 3 of the Supplemental Material document. In the absence of a known threshold, the certainty in the presence of a non-null effect was rated for complete response rate. For all other outcomes, a specific threshold for a clinically important effect could not be established. However, with the input from clinical experts, the review team assessed whether the point estimates and corresponding CI bounds represented clinically important effects. According to the GRADE guidance, noncomparative evidence starts at very low.

Table 3: Summary of Findings for Osilodrostat vs. Placebo Withdrawal in Adult Patients With Cushing Disease With a Complete Response at Week 24 (mUFC ≤ ULN) and No Up-Titration Between Weeks 13 and 24 in the LINC 3 Study

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo withdrawal	Osilodrostat	Difference		
mUFC response							
Complete response rate (proportion of patients with mUFC ≤ ULN) Follow-up: 8 weeks (RW period from week 26 to week 34)	70 (1 randomized withdrawal study)	OR = 13.71 (3.73 to 53.44)	294 per 1,000	861 per 1,000 (705 to 953 per 1,000)	NR	Moderate[a] (serious imprecision)	Osilodrostat likely results in an increase in complete response rate when compared with placebo withdrawal. The clinical importance of the increase is uncertain.
Overall response rate (proportion of patients with mUFC ≤ ULN or ≥ 50% reduction from baseline) Follow-up: 8 weeks (RW period from week 26 to week 34)	71 (1 randomized withdrawal study)	NR	[redacted]	[redacted]	[redacted]	Low[b] (very serious imprecision)	Osilodrostat may result in an increase in overall response rate when compared with placebo withdrawal. The clinical importance of the increase is uncertain.
Patient-reported outcomes (HRQoL and depression)							
CushingQoL total score (0 [worst] to 100 [best]), change from baseline, points Follow-up: 34 weeks	70 (1 randomized withdrawal study)	NR	Mean (SD), [redacted]	Mean (SD), [redacted]	[redacted]	Low[b] (very serious imprecision)	Osilodrostat may result in little to no difference in CushingQoL total score when compared with placebo withdrawal.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo withdrawal	Osilodrostat	Difference		
Beck Depression Inventory-II total score (0 [best] to 63 [worst]), change from baseline, points Follow-up: 34 weeks	70 (1 randomized withdrawal study)	NR	Mean (SD), [redacted]	Mean (SD), [redacted]	[redacted]	Low[b] (very serious imprecision)	Osilodrostat may result in little to no difference in BDI-II total score when compared with placebo withdrawal.
Treatment discontinuation							
Treatment discontinuation due to AEs[c] Follow-up: 8 weeks (RW period from week 26 to week 34)	71 (1 randomized withdrawal study)	NR	57 per 1,000	0	NR	Low[b] (very serious imprecision)	Osilodrostat may result in a decrease in discontinuation due to AEs when compared with placebo withdrawal. The clinical importance of the decrease is uncertain.

AE = adverse event; BDI-II = Beck Depression Inventory-II; CI = confidence interval; CushingQoL = Cushing's quality-of-life questionnaire; HRQoL = health-related quality of life; MID = minimal important difference; mUFC = mean urinary free cortisol; NR = not reported; OR = odds ratio; RW = randomized withdrawal; SD = standard deviation; ULN = upper limit of normal.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. The clinical experts consulted for this review commented that the patients in this study had relatively mild disease and might have relatively low risk of developing the patient-important outcomes.

[a]No literature-based MID was available and, in consultation with clinical experts, a MID estimate could not be determined; therefore, the null was used as the threshold for "any" effect. No absolute between-group difference or CI was available; therefore, the relative effect was appraised. The level of evidence was rated down 1 level for serious imprecision; the sample size and number of events was small, raising concern for prognostic imbalance and that the estimated magnitude of effect and its CI may be unstable. The large size of the effect was considered when rating down only once.

[b]No literature-based MID was available and, in consultation with clinical experts, a MID estimate could not be determined; therefore, the null was used as the threshold for "any" effect. No absolute between-group difference or CI was available; therefore, rating of imprecision required consideration of the sample size and/or number of events. The level of evidence was rated down 2 levels for very serious imprecision; the sample size and number of events was small, raising concern for prognostic imbalance and that the estimated magnitude of effect and its CI may be unstable.

[c]At 48 weeks, a total of 18 (13.1%) patients discontinued the study due to an AE.

Table 4: Summary of Findings for Osilodrostat vs. Placebo for Adult Patients With Cushing Disease With mUFC Greater Than 1.3 Times ULN in the LINC 4 Study

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Osilodrostat	Difference		
mUFC response							
Complete response rate (proportion of patients with mUFC ≤ ULN) Follow-up: 12 weeks	73 (1 RCT)	OR = 43.4 (7.06 to 343.19)	80 per 1,000	771 per 1,000 (627 to 880 per 1,000)	NR	Moderate[a] (serious imprecision)	Osilodrostat likely results in an increase in complete response rate when compared with placebo. The clinical importance of the increase is uncertain.
Overall response rate (proportion of patients with mUFC ≤ ULN or ≥ 50% reduction from baseline) Follow-up: 12 weeks	73 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[b] (serious imprecision)	Osilodrostat likely results in an increase in overall response rate when compared with placebo. The clinical importance of the increase is uncertain.
Patient-reported outcomes (HRQoL and depression)							
CushingQoL total score (0 [worst] to 100 [best]), change from baseline, points Follow-up: 12 weeks	70 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Low[c] (very serious imprecision)	Osilodrostat may result in little to no difference in CushingQoL total score when compared with placebo.
Beck Depression Inventory-II total score (0 [best] to 63 [worst]), change from	70 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[d,e] (serious imprecision)	Osilodrostat likely results in a smaller improvement in BDI-II total score

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Osilodrostat	Difference		
baseline, points Follow-up: 12 weeks							compared with placebo. The clinical importance of the difference is uncertain.
Treatment discontinuation							
Treatment discontinuation due to AEs Follow-up: 12 weeks	74 (1 RCT)	NR	0	21 per 1,000 (NR)	NR	Low[a,f] (very serious imprecision)	Osilodrostat may result in little to no difference in treatment discontinuation due to AEs when compared with placebo.

AE = adverse event; CI = confidence interval; CushingQoL = Cushing's quality-of-life questionnaire; HRQoL = health-related quality of life; MID = minimal important difference; mUFC = mean urinary free cortisol; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; SD = standard deviation; ULN = upper limit of normal.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. The clinical experts consulted for this review commented that the patients in this study had relatively mild disease and might have relatively low risk of developing the patient-important outcomes.

[a]No literature-based MID was available and, in consultation with clinical experts, a MID estimate could not be determined; therefore, the null was used as the threshold for "any" effect. No absolute between-group difference or CI was available; therefore, the relative effect was appraised. The level of evidence was rated down 1 level for serious imprecision; the sample size and number of events is small, raising concern for prognostic imbalance and that the estimated magnitude of effect and its CI may be unstable. The large size of the effect was considered when rating down only once.

[b]No literature-based MID was available and, in consultation with clinical experts, a MID estimate could not be determined; therefore, the null was used as the threshold for "any" effect. No absolute between-group difference or CI was available; therefore, rating of imprecision required consideration of the sample size and/or number of events. The level of evidence was rated down 1 level for serious imprecision; the sample size and number of events is small. The large size of the effect was considered when rating down only once.

[c]Rated down 2 levels for very serious imprecision. Only a within-group literature-based MID was available; therefore, the null was used to assess certainty. The point estimate and the lower bound of 95% CI suggested a decrease, while the upper bound of 95% CI suggested an increase compared to placebo.

[d]Not controlled for multiple comparisons, there is an increased risk of type I error.

[e]Rated down 1 level for serious imprecision. No MID was available; therefore, the null was used to assess certainty. The point estimate and the lower bound of 95% CI suggested little to no differences, while the upper bound of 95% CI suggested a smaller decrease from baseline compared to placebo.

[f]No literature-based MID was available and, in consultation with clinical experts, a MID estimate could not be determined; therefore, the null was used as the threshold for "any" effect. No absolute between-group difference or CI was available; therefore, rating of imprecision required consideration of the sample size and/or number of events. The level of evidence was rated down 2 levels for very serious imprecision; the sample size and number of events is small, raising concern for prognostic imbalance and that the estimated magnitude of effect and its CI may be unstable.

Long-Term Extension Studies

Description of Studies

The LINC 3 extension study was a single-arm, open-label continuation of the LINC 3 study for patients who continued to benefit and consented at week 48. Of 137 enrolled patients, 106 (77.4%) entered the extension, 72 (52.6%) completed it, and 34 (24.8%) discontinued, mainly due to AEs (8.8%) or patient decision (8.8%). The extension ended 16 months after all patients completed week 72 or earlier if treatment was discontinued; patients who continued to benefit could join a separate long-term safety follow-up study.

The LINC 4 extension study was also a single-arm, open-label continuation starting at week 48. Of 73 treated patients, 65 (89.0%) completed the core phase, 60 (82.2%) entered the extension, and 53 (72.6%) completed it. During the extension, osilodrostat dosing was maintained at the effective dose unless adjusted based on mUFC results at scheduled visits. Patients who benefited could enter a separate long-term safety follow-up study or discontinue treatment with a posttreatment visit after 30 days.

Efficacy Results

LINC 3 Extension

At the end of the core period (week 48), 75.9% of patients (104 of 137; 95% CI, 67.9% to 82.8%) met the predefined response criteria. Among patients whose Cushing disease responded, 66.4% was a complete response and [redacted]% was a partial response.

By week 72, of the 106 patients who entered extension period, 88.7% of patients (95% CI, 81.1% to 94.0%) met the response criteria, with 81.1% (86 of 106) had Cushing disease classified as a complete response and [redacted]% ([redacted] of 106) as a partial response.

LINC 4 Extension

At the end of the core period (week 48), the overall response rate among all patients was 79.5% (58 of 73), with 68.5% (50 of 73) of patients with Cushing disease classified as a complete response and [redacted]% ([redacted] of 73) as a partial response.

At week 72, in the all-patients population, 65 patients had data available for the response outcome, including those who discontinued during the core phase. Among these patients, the overall response rate was 69.2% (45 of 65), with 61.5% (40 of 65) of patients with Cushing disease classified as a complete response and [redacted]% ([redacted] of 65) as a partial response.

At the end of the extension phase, 58 patients were evaluable for overall response, based on the longest available data for each individual. Among these patients, the overall response rate was 81.0% (47 of 58), with 72.4% (42 of 58) of patients with Cushing disease classified as a complete response and [redacted]% ([redacted] of 58) as a partial response.

Harms Results

All patients (100%) in the LINC 3 extension study and almost all patients in the LINC 4 extension study (98.6% of the 73 patients) reported at least 1 AE. The most frequently observed AEs (≥ 20%) in the LINC 3 and LINC 4 extension studies included nausea (45.3% and 37.0%), headache (36.5% and 34.2%), fatigue

(32.8% and 39.7%), adrenal insufficiency (29.2% and 26.0%), and arthralgia (21.2% and 45.2%). Additional AEs reported among 20% of patients or more in the LINC 3 extension study included vomiting (24.8%), nasopharyngitis (24.1%), back pain (21.2%), increased blood corticotrophin (20.4%), and glucocorticoid deficiency (20.4%). In the LINC 4 extension study, other frequently reported AEs were decreased appetite (46.6%), dizziness (30.1%), increased blood testosterone (24.7%), myalgia (24.7%), asthenia (23.3%), diarrhea (23.3%), hypertension (21.9%), and upper respiratory tract infection (21.9%).

Grade 3 or 4 AEs were reported in 60.6% of patients in the LINC 3 extension study and in 38.4% of patients in the LINC 4 extension study. The most commonly reported grade 3 or 4 AE (≥ 5%) in both the LINC 3 and LINC 4 extension studies was hypertension, occurring in 11.7% and 12.3% of patients, respectively. In addition, myalgia was reported as a grade 3 or 4 event in 6.8% of patients in the LINC 4 extension study.

In the LINC 3 extension study, 55 patients (40.1%) experienced at least 1 SAE. The most commonly reported SAEs (≥ 2%) were adrenal insufficiency (5.8%), pituitary tumour (4.4%), adrenocortical insufficiency and gastroenteritis (2.9% each), and abdominal pain, headache, influenza, benign pituitary tumour, and sixth cranial nerve paralysis (2.2% each). All other SAEs occurred in no more than 2 patients. In the LINC 4 extension study, 10 patients (13.7%) experienced at least 1 SAE, with adrenal insufficiency being the only commonly reported SAE (≥ 2%), occurring in 4.1% of patients.

AEs leading to study drug discontinuation occurred in fewer than 20% of patients across both studies. In the LINC 3 extension study, 25 patients (18.2%) discontinued treatment due to an AE. The most commonly reported AEs leading to discontinuation were adrenal insufficiency, pituitary tumour, and benign pituitary tumour, each affecting 3.6% of patients. All other AEs leading to discontinuation occurred in no more than 2 patients. In the LINC 4 extension study, 9 patients (12.3%) discontinued treatment due to an AE. Adrenal insufficiency was the most frequent cause, reported in 4.1% of patients, while all other AEs leading to discontinuation were reported in a single patient each.

No additional deaths were reported during the open-label extension phases in LINC 3 and LINC 4.

AEs of special interest in the LINC 3 and LINC 4 extension studies included hypocortisolism-related AEs (54.0% of patients and 28.8% of patients), adrenal hormone precursor accumulation-related AEs (58.4% and 61.6%), pituitary tumour enlargement-related AEs (16.1% and 5.5%), and arrhythmogenic potential and QT prolongation-related AEs (4.4% and 4.1%).

Critical Appraisal

Both the LINC 3 and LINC 4 extension studies were limited by their open-label and noncomparative design. Because there was no comparator, it is not possible to draw causal inferences about the longer-term effect of osilodrostat. The open-label design risks introducing bias in the collection of subjective outcomes (e.g., harms). There were large reductions in sample size over time resulting in risk of bias due to missing outcome data.

Both the LINC 3 and LINC 4 extension studies included patients who rolled over from core study with characteristics consistent to that at entry into the core study. It is reasonable to expect that similar limitations to generalizability of the study results are relevant to the open-label, long-term safety extension phases

of the LINC 3 and LINC 4 studies. The long-term extension of the LINC 3 study included all patients with continued clinical benefit, not only the enriched population from the randomized withdrawal phase. The patient population in both studies may have become more selected over time to preferentially include patients who were deriving benefit from the treatment without intolerable AEs. Information on patient-important outcomes, such as HRQoL and depression, were unavailable in the long-term extension studies.

Indirect Comparisons

Description of Studies

This section summarizes and critically appraises the sponsor-submitted indirect treatment comparison (ITC) comparing osilodrostat with ketoconazole and ketoconazole-cabergoline for treating endogenous Cushing syndrome. On July 3, 2025, Health Canada approved a narrower indication for osilodrostat in adults with Cushing disease who have persistent or recurrent hypercortisolism after pituitary surgery and/or irradiation or for whom surgery is not an option. This differs from the broader population used in the original ITC evidence submitted in 2023; no updated ITC reflecting the revised indication was provided.

For this review, the sponsor submitted an unadjusted (naive) indirect comparison estimating the relative efficacy and safety of osilodrostat, based on LINC 4 study data, versus ketoconazole using aggregate data from 4 published studies.

Efficacy and Harms Results

Between the comparison of osilodrostat and ketoconazole:

- The results for complete response are inconclusive, [redacted].
- No HRQoL was assessed in the naive comparison.

No ITC was provided by the sponsor to compare osilodrostat versus ketoconazole-cabergoline combination therapy.

Critical Appraisal

The sponsor's naive indirect comparison was based on a systematic literature review, but no protocol, statistical analysis plan, or details of the search and review process were reported, which introduces risk of bias and the omission of relevant studies. No feasibility assessment for a conventional ITC was provided, and naive comparisons, which do not adjust for differences in populations, designs, or outcomes, are at critical risk of confounding. Major differences existed across the 5 included studies in design, baseline characteristics, and outcome definitions, with some studies enrolling broader populations than the Health

Canada–approved indication. Small sample sizes, limited events, and assumptions underlying hazard ratio calculations further increase imprecision and potential bias. Patient-important outcomes, such as HRQoL, were not assessed; long-term effects were not evaluated; and no ITC was provided for osilodrostat versus ketoconazole-cabergoline, limiting conclusions on comparative clinical value.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps in the pivotal and RCT evidence were submitted for this review.

Economic Evidence

Cost and Cost-Effectiveness

- Osilodrostat is available as 1 mg, 5 mg, and 10 mg tablets. The median average dosage was 4.6 mg and 7.4 mg per day for the LINC 4 and LINC 3 studies, respectively. At the submitted price of $46.14 per 1 mg tablet, $184.58 per 5 mg tablet, and $193.81 per 10 mg tablet, the annual cost of Isturisa is expected to range from $67,407 to $424,745 per patient, based on the Health Canada–recommended dosage (2 mg to 30 mg twice daily).
- Key clinical efficacy data (complete response rate, overall response rate) used to inform the economic model were derived from the LINC 4 trial, which compared Isturisa with placebo, and published literature for ketoconazole. Evidence submitted by the sponsor indicates that Isturisa is likely to improve complete response rate and overall response rate compared with placebo among adult patients with Cushing disease who have persistent or recurrent hypercortisolism after primary surgery and/or irradiation, or for whom pituitary surgery is not an option. No conclusions can be drawn from the naive comparison regarding the comparative efficacy and safety of Isturisa versus ketoconazole in the treatment of Cushing disease in adults due to critical risk of bias.
- The results of the CDA-AMC base case suggest:
  - Isturisa is predicted to be associated with higher costs to the health care system than ketoconazole (incremental costs = $340,490), primarily driven by increased costs associated with drug acquisition.
  - Isturisa is predicted to be associated with a gain of 0.05 life-years compared to ketoconazole and may result in a gain of 0.44 quality-adjusted life-years (QALYs) compared to ketoconazole.
  - The incremental cost-effectiveness ratio (ICER) of Isturisa compared to ketoconazole was $742,689 per QALY gained in the CDA-AMC base case. The estimated ICER was highly sensitive to the long-term mortality benefits of Isturisa, approximately 95% of benefit was predicted to be accrued after the treatment duration of the LINC 4 trial (trial period = 11 months [48 weeks]).
- CDA-AMC estimates that the budget impact of reimbursing Isturisa for the treatment of for the indicated population will be approximately $30.5 million over the first 3 years of reimbursement compared to the amount currently spent on ketoconazole, with an estimated expenditure of $31

million on Isturisa over this period. The actual budget impact of reimbursing Isturisa will depend on the number of patients eligible.

CDEC Information

Members of the Committee

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

Meeting date: November 26, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

Questions or requests for information about this report can be directed to Requests@cda-amc.ca.