

An addendum to the March 2024 minutes has been included at the end of the document.

7.06 OSILODROSTAT, Tablet 1 mg, Tablet 5 mg, Isturisa[®], Recordati Rare Diseases Australia Pty. Ltd.

1 Purpose of submission

- 1.1 The Standard Re-entry submission requested General Schedule Authority Required (Telephone/Online) listing for osilodrostat for the treatment of endogenous Cushing's syndrome (CS).
- 1.2 Listing was requested on the basis of a cost-utility analysis versus placebo.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the resubmission)

Component	Description
Population	Adult patients with endogenous Cushing's syndrome who are not candidates for surgery or for whom surgery was not curative
Intervention	Osilodrostat \leq 2 mg orally bid, with dose titration permitted up to 30 mg bid
Comparator	<u>Main comparator</u> <ul style="list-style-type: none">• Placebo <u>Supplementary comparators</u> <ul style="list-style-type: none">• Metyrapone: 500-3000 mg/day*• Ketoconazole: 400-2400 mg/day*
Outcomes	Complete response rate, defined as the proportion of patients achieving normalisation of mean urinary free cortisol Overall response rate, defined as patients who achieved either a complete or partial response**
Clinical claim	In adults with endogenous Cushing's Syndrome, osilodrostat is more effective than placebo at improving the proportion of patients achieving complete response

Source: Table 1.1-2 of the submission

*Typical maintenance doses according to clinicians experienced in the treatment of endogenous CS in Australia

** partial response was defined as patients with a mUFC > ULN but who achieved \geq 50% improvement from baseline

Bid = twice daily; mUFC = mean urinary free cortisol; ULN = upper limit of normal

Blue shade indicates data previously seen by the PBAC

2 Background

Registration status

- 2.1 Osilodrostat was registered by the TGA on 12 May 2022 for the treatment of endogenous CS in adults.

Previous PBAC consideration

- 2.2 The key matters of concern from the previous submission from March 2023 are presented in Table 2 below.

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Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Comparator	The placebo comparator was the most relevant given that ketoconazole was deregistered by the TGA and metyrapone was used as an off-label therapy (Para 7.5, March 2023 PSD)	Placebo was the primary comparator and metyrapone and ketoconazole were only included as supplementary comparators. While the submission noted that metyrapone and ketoconazole were supplementary comparators, these were only included in the economic evaluation as a sensitivity analysis for patients who received them as subsequent therapies after osilodrostat or placebo. The ESC considered that placebo remained the relevant comparator.
Effectiveness data	The PBAC considered that despite the limitations of the evidence, it was biologically plausible that if a patient is tolerating and responding to osilodrostat, that the response would be maintained (Para. 7.7, March 2023, PSD). The PBAC accepted the clinical claim of superior comparative effectiveness of osilodrostat to placebo for the surrogate outcome of complete response of UFC. However, it was noted that there was still uncertainty with translating this into the longer-term mortality and morbidity improvements. The PBAC considered that it was not uncommon for patients with CS to have a gradual improvement in symptoms after treatment, with clinical benefits usually seen after a year or so, requiring considerable amount of time to adapt to the normal cortisol level (Para 7.8, March 2023, PSD).	The ESC considered that this was partially addressed. Longer-term efficacy data was provided as well as the following additional analyses based on LINC 4 and LINC 3: <ul style="list-style-type: none"> Swimmer plots of response and dose over time Analysis of responders (including response rates, duration of response, and quality of life [QoL]) However, data was limited to 120 weeks and treatment was expected to be potentially lifelong. There was also no additional mortality data provided, and information regarding QoL improvements in the longer term were limited. Evidence from the literature provided suggested sustained remission from hypercortisolism irrespective of treatment received could improve CS comorbidities (Mondin 2023) however this was not incorporated in the consideration of the clinical evidence or the economic evaluation.
Safety data	It was considered that adverse events relating to pituitary tumour enlargement should be monitored and required further investigation to better understand the impact of this phenomenon (Para 7.9, March 2023 PSD)	The ESC considered that this was adequately addressed. The resubmission presented patient narratives for patients who experience pituitary tumour enlargement in LINC 4 and LINC 3.
Economic evaluation	The 12-week trial-based incremental cost per responder analyses did not allow for long-term assessment of osilodrostat's cost-effectiveness. The PBAC considered there would be important long-term benefits not captured by the trial period and the surrogate outcome measured, and an alternative cost-effectiveness or cost utility analysis would need to be considered in any future resubmission. The economic analysis should incorporate longer durations of therapy and quality of life data, using literature and natural history data to supplement the available trial evidence. The PBAC considered that it is highly likely that responding patients would continue with treatment beyond three years (mean duration of treatment of 169.5 weeks as per the LINC trials). (Para 7.11, March 2023 PSD)	The ESC considered that the submitted model was not suitable for decision making because it did not include the important long-term benefits expected with durable cortisol control. (See ESC advice in Section 6-Economic analysis).

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Component	Matter of concern	How the resubmission addresses it
Financial estimates	The usage in the latter years was underestimated and that ongoing lifelong treatment for responding patients was more appropriate. The uptake rates were also underestimated and considered █████% uptake in Year 1, █████% in Year 2, and █████% in Year 3+ was reasonable (Para 7.12, March 2023 PSD)	Partially addressed. While the resubmission assumed that patients would continue treatment into subsequent years, the estimated usage was still likely underestimated since uptake rates were only assumed to be █████% in Year 1.
MBS costs	The DUSC noted costs associated with dose titration and ongoing monitoring were not included in the financial estimates (Para 6.46, March 2023 PSD)	Addressed. MBS items for UFC testing and endocrinologist visits were included.

Source: osilodrostat, PSD, March 2023 PBAC meeting; Sections 2.5.1; 2.5.2; 2.6.2; 2.6.3; Section 3; Table 4.2-5 and 4.2-7; and Tables 4.5-2 and 4.5-3 of the submission

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OSILODROSTAT						
Osilodrostat 1 mg tablet, 60	\$2,400 published \$█████ effective	New	1	60	5 6	Isturisa, Recordati Rare Diseases Australia Pty Ltd.
Osilodrostat 5 mg tablet, 60	\$9,660 published \$█████ effective	New	1	60	5 6	Isturisa, Recordati Rare Diseases Australia Pty Ltd.
Restriction Summary [new1] / Treatment of Concept: [new2]						
Concept ID (for internal Dept. use)	Category / Program: Section 85 – General Schedule					
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
	Restriction Type <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)					
PR level	Caution: <i>The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period:</i>					
	<ul style="list-style-type: none"> • QTc prolongation via an electrocardiogram • Hypocortisolism • Corticotroph tumour growth 					
	Administrative advice: <i>Cortisol levels should be monitored at regular intervals, since hypocortisolism-related events can occur at any time during treatment.</i>					
	Administrative advice: <i>No increase in the maximum number of repeats may be authorised.</i>					
	Administrative Advice: <i>Special Pricing Arrangements apply.</i>					
	Episodicity: Chronic					
	Severity: NA					
	Condition: Endogenous Cushing's Syndrome					
	Indication: Endogenous Cushing's syndrome					

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	Treatment Phase: Initial treatment
	Clinical criteria:
	Patients must have failed surgery for the removal of the primary tumour The condition must be, at least one of: (i) persistent hypercortisolism after surgery OR (ii) recurrent hypercortisolism after surgery, OR (iii) inappropriate for surgery.
	OR
	Patients must not be considered candidates for surgery
	AND
	Clinical criteria:
	Patient must have active endogenous Cushing's Syndrome as determined by a mean urinary free cortisol (UFC) level greater than 1.3 times the upper limit of normal (ULN). OR
	Patient must have undergone treatment for this condition with <i>conventional therapies to control cortisol production resulting in an improved UFC level</i> prior to applying for the initial authority application of this drug.
	AND
	Treatment criteria:
	Patients must be treated and supervised by a physician experienced in endocrinology or internal medicine. <i>Must be treated by an endocrinologist.</i>
	Population criteria:
	Patients must be aged 18 years or older at least 18 years of age.
	Prescribing Instructions: To assess patients eligible for initial treatment, the mean UFC should be the average of two values being 1.3 times greater than the ULN. <i>For the purposes of administering this restriction, the mean UFC is the average of at least two values being 1.3 times greater than the ULN.</i> Patients must undergo a dose titration period whereby doses are gradually titrated (initially by dose increments of 1 or 2 mg). Increases in dose should not occur more frequently than once every 1-2 weeks and should be guided by the results of cortisol assessments and by the individual clinical response. Only patients who demonstrate either a complete response (mean UFC \leq ULN) or a partial response (mean UFC $>$ ULN but a 50% reduction from the baseline value) after 6 months of treatment are eligible for continuing treatment. At the time of authority application, medical practitioners should request the appropriate number of packs to provide sufficient drug, based on the prescribed dose of the patient, for one month of treatment. The dose must not exceed 30 mg twice daily. Up to a maximum of 5 repeats will be authorised. Patients must not exceed more than 6 months of treatment under this restriction. Treatment should be discontinued, or the dose reduced, if mean UFC levels fall below the lower limit of normal (LLN) or there are signs of adrenal insufficiency.
	Prescribing Instructions: Patient must undergo a dose titration period whereby responses must be assessed every 1-2 weeks until the mean UFC levels are within the normal range.
	Prescribing Instructions: At the time of authority application, medical practitioners must should request the appropriate number of packs to provide sufficient drug, based on the prescribed dose of the patient, for 4 weeks one month of treatment. A separate authority prescription form must be completed for each strength requested. The dose must not exceed 30 mg twice daily. Up to a maximum of 5 repeats will be authorised. Patients must not exceed more than 6 months of treatment under this restriction.
	Prescribing Instructions: <i>Where there is a current, approved PBS prescription with valid repeat prescriptions specified (i.e., where the dose is changing), mark the prescription that is intended for no further supply as 'Cancelled'.</i>

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	<p>Prescribing Instructions: Patients who failed surgery are defined as those with recurrent or persistent hypercortisolism (UFC > 1.3x ULN). Patients who are not candidates for surgery are defined as: The condition is inappropriate for surgery if the patient:</p> <ul style="list-style-type: none"> • those with has a medical contraindication for surgery • those with has inoperable tumours • has been determined that surgery is unlikely to reduce hypercortisolism • those who refuses surgery • can't access surgical treatment being unavailable to the patient
	<p>Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</p>
	<p>Notes: Patients who failed surgery are defined as those with recurrent or persistent hypercortisolism (UFC > 1.3x ULN). Patients who are not candidates for surgery are defined as:</p> <ul style="list-style-type: none"> • those with a medical contraindication for surgery • those with inoperable tumours • surgery unlikely to reduce hypercortisolism • those who refuse surgery • surgical treatment being unavailable to the patient
	<p>Administrative advice: No increase in the maximum number of repeats may be authorised.</p>
	<p>Administrative Advice: Special Pricing Arrangements apply.</p>
	<p>Caution: The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period:</p> <ul style="list-style-type: none"> • QTc prolongation via an electrocardiogram • Hypocortisolism Corticotroph tumour growth <p>Inhibition of cortisol synthesis by osilodrostat has led to hypocortisolism related events such as cortisol withdrawal syndrome (symptomatic decrease of cortisol levels, but still above the lower limit of the normal range) and adrenal insufficiency (cortisol levels below the normal range). Cortisol levels should be monitored at regular intervals, since hypocortisolism related events can occur at any time during treatment</p>

The requested restriction for continuing treatment is presented below.

Proposed listing of medicine – Continuing Treatment

MEDICINAL PRODUCT	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
medicinal product pack					
OSILODROSTAT					
Osilodrostat, 1 mg oral tablet	New	1	60	5	ISTURISA
Osilodrostat, 5 mg oral tablet	New	1	60	5	ISTURISA
Restriction Summary [new3] / Treatment of Concept: [new4]					
Concept ID	Category / Program:				
(for internal Dept. use)	Section 85 – General Schedule				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction Type – <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)				
PR level	Caution:				
	The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period:				
	<ul style="list-style-type: none"> • QTc prolongation via an electrocardiogram • Hypocortisolism 				

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	<ul style="list-style-type: none"> Corticotroph tumour growth
	<p>Administrative advice: Cortisol levels should be monitored at regular intervals, since hypocortisolism-related events can occur at any time during treatment.</p>
	<p>Administrative advice: No increase in the maximum number of repeats may be authorised.</p>
	<p>Administrative Advice: Special Pricing Arrangements apply.</p>
	Episodicity: Chronic
	Severity: NA
	Condition: Endogenous Cushing's Syndrome
	Indication: Patients with Chronic Endogenous Cushing's syndrome
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patients Patient must have demonstrated a complete response or a partial response after at least 6 months 26 weeks of treatment with this drug OR
	Patient must have demonstrated a partial response after at least 6 months 26 weeks of treatment with this drug
	Treatment criteria:
	Patients must be treated and supervised by a physician experienced in endocrinology or internal medicine. Must be treated by an endocrinologist.
	Population criteria:
	Patients must be at least aged 18 years of age or older
	Prescribing Instructions: For the purposes of administering this restriction, a complete response is defined as a mean urinary free cortisol (UFC) level of less than or equal to the upper limit of normal (ULN). A partial response is defined as mean UFC level of greater than ULN but with at least 50% reduction from the baseline value. The mean UFC should be the average of at least two urine samples.
	Prescribing Instructions: At the time of authority application, medical practitioners must should request the appropriate number of packs to provide sufficient drug, based on the prescribed dose of the patient, for 4 weeks one month of treatment. A separate authority prescription form must be completed for each strength requested. The dose must not exceed 30 mg twice daily. Up to a maximum of 5 6 repeats will be authorised.
	Prescribing Instructions: Where there is a current, approved PBS prescription with valid repeat prescriptions specified (i.e., where the dose is changing), mark the prescription that is intended for no further supply as 'Cancelled'.
	Prescribing Instructions: An application for the continuing treatment must be accompanied with the assessment of response conducted up to after 26 weeks after from the first dose of osilodrostat and no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for patients who meet the continuing restriction for PBS-subsidised treatment.
	Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Prescribing Instructions: For the first authority application for continuing treatment, a patient must have demonstrated a complete or overall response to osilodrostat 6 months after commencing initial treatment.

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	<p>For subsequent authority applications for continuing treatment, a patient must have demonstrated a complete or partial response prior to applying for further continuing treatment.</p> <p>A complete response is defined as a mean urinary free cortisol (UFC) less than or equal to the upper limit of normal (ULN). A partial response is defined as mean UFC greater than ULN but a 50% reduction from the baseline value. The mean UFC should be the average of two urine samples.</p> <p>At the time of authority application, medical practitioners should request the appropriate number of packs to provide sufficient drug, based on the prescribed dose of the patient, for one month of treatment. Up to a maximum of 5 repeats will be authorised. The dose must not exceed 30 mg twice daily</p>
	<p>Caution: The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period:</p> <ul style="list-style-type: none"> • QTc prolongation via an electrocardiogram • Hypocortisolism <p>Inhibition of cortisol synthesis by osilodrostat has led to hypocortisolism-related events such as cortisol withdrawal syndrome (symptomatic decrease of cortisol levels, but still above the lower limit of the normal range) and adrenal insufficiency (cortisol levels below the normal range). Cortisol levels should be monitored at regular intervals, since hypocortisolism-related events can occur at any time during treatment.</p>

The requested restriction for grandfather patients is presented below.

Proposed restriction – Grandfather patients

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OSILODROSTAT					
Osilodrostat, 1 mg oral tablet	New	1	60	5 6	ISTURISA
Osilodrostat, 5 mg oral tablet	New	1	60	5 6	ISTURISA
Restriction Summary [new5] / Treatment of Concept: [new6]					

Concept ID (for internal Dept. use)	Category / Program: Section 85 – General Schedule
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners Restriction Type– <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)
PR level	Caution: The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period: <ul style="list-style-type: none"> • QTc prolongation via an electrocardiogram • Hypocortisolism • Corticotroph tumour growth
	Administrative advice: Cortisol levels should be monitored at regular intervals, since hypocortisolism-related events can occur at any time during treatment.
	Administrative advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Episodicity: Chronic
	Severity: NA
	Condition: Endogenous Cushing's Syndrome

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	Indication: Patients with Endogenous Cushing's syndrome
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment – 'grandfather' arrangements
	Clinical criteria:
	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
	AND
	Clinical criteria:
	Patients must have failed surgery for the removal of the primary tumour. The condition must have been, at least one of: (i) persistent hypercortisolism after surgery OR (ii) recurrent hypercortisolism after surgery, OR (iii) inappropriate for surgery, prior to commencing non-PBS subsidised treatment with this drug
	AND
	Clinical criteria:
	Patients have had active endogenous Cushing's Syndrome determined by a mean urinary free cortisol (UFC) level greater than 1.3 times the upper limit of normal (ULN) prior to commencing non-PBS subsidised treatment with this drug.
	AND
	Clinical criteria:
	Patient must have demonstrated a complete response after at least 6 months 26 weeks of treatment with this drug OR
	Patient must have demonstrated a partial response after at least 6 months 26 weeks of treatment with this drug.
	OR
	Patients must not be considered candidates for surgery
	Treatment criteria:
	Patients must be treated and supervised by a physicians experienced in endocrinology or internal medicine by an endocrinologist or a general medicine physician Must be treated by an endocrinologist
	Population criteria:
	Patients must be at least 18 years of age. aged 18 years or older
	Prescribing Instructions:
	Only patients who demonstrate a complete or partial response at 6 months are eligible for continuing treatment.
	Prescribing Instructions:
	For the purposes of administering this restriction, a complete response is defined as a mean urinary free cortisol (UFC) level of less than or equal to the upper limit of normal (ULN). A partial response is defined as mean UFC level of greater than ULN but with at least 50% reduction from the baseline value. The mean UFC should be the average of at least two urine samples.
	Prescribing Instructions:
	Patient must undergo a dose titration period whereby responses must be assessed every 1-2 weeks until the mean UFC levels are within the normal range.
	Prescribing Instructions:
	At the time of authority application, medical practitioners must should request the appropriate number of packs to provide sufficient drug, based on the prescribed dose of the patient, for 4 weeks of treatment. A separate authority prescription form must be completed for each strength requested. The dose must not exceed 30 mg twice daily. Up to a maximum of 5 repeats will be authorised.
	Prescribing Instructions:
	Where there is a current, approved PBS prescription with valid repeat prescriptions specified (i.e., where the dose is changing), mark the prescription that is intended for no further supply as 'Cancelled'.
	Prescribing Instructions:
	Patients who failed surgery are defined as those with recurrent or persistent hypercortisolism (UFC > 1.3x ULN). Patients who are not candidates for surgery are defined as: The condition is inappropriate for surgery if the patient: <ul style="list-style-type: none"> • these with has a medical contraindication for surgery • these with has inoperable tumours

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	<ul style="list-style-type: none"> has been determined that surgery is unlikely to reduce hypercortisolism those who refuses surgery can't access surgical treatment being unavailable to the patient
	<p>Prescribing Instructions: An application for the continuing treatment must be accompanied with the assessment of response conducted up to after 26 weeks after from the first dose of osilodrostat and no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for patients who meet the continuing restriction for PBS-subsidised treatment.</p>
	<p>Prescribing Instructions: A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the continuing treatment criteria.</p>
	<p>Administrative Advice: This Grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria</p>
	<p>Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</p>
	<p>Prescribing Instructions: Only patients who demonstrate a complete or partial response at 6 months are eligible for continuing treatment.</p> <p>At the time of authority application, medical practitioners should request the appropriate number of packs to provide sufficient drug, based on the prescribed dose of the patient, for one month of treatment. The dose must not exceed 30 mg twice daily. Up to a maximum of 5 repeats will be authorised. Patients must not exceed more than 6 months of treatment under this restriction.</p> <p>Treatment should be discontinued, or the dose reduced, if mean UFC levels fall below the lower limit of normal (LLN) or there are signs of adrenal insufficiency.</p>
	<p>Notes: Patients who failed surgery are defined as those with recurrent or persistent hypercortisolism (UFC > 1.3x ULN).</p> <p>Patients who are not candidates for surgery are defined as:</p> <ul style="list-style-type: none"> those with a medical contraindication for surgery those with inoperable tumours surgery unlikely to reduce hypercortisolism those who refuse surgery surgical treatment being unavailable to the patient
	<p>Caution: The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period:</p> <ul style="list-style-type: none"> QTc prolongation via an electrocardiogram Hypocortisolism <p>Inhibition of cortisol synthesis by osilodrostat has led to hypocortisolism related events such as cortisol withdrawal syndrome (symptomatic decrease of cortisol levels, but still above the lower limit of the normal range) and adrenal insufficiency (cortisol levels below the normal range). Cortisol levels should be monitored at regular intervals, since hypocortisolism related events can occur at any time during treatment.</p>

3.2 Compared to the March 2023 submission, the resubmission did not request listing of the 10 mg tablet and the PBAC noted that there was a price reduction compared to the previous submission for both the 1 mg (effective: \$| vs \$| [|% decrease]) and 5 mg tablets (effective: \$| vs \$| [|% decrease]).

3.3 The resubmission included a number of changes to the requested restriction criteria to align with advice from Australian clinicians:

- Patients must have a mean urinary free cortisol (mUFC) $>1.3 \times$ upper limit of normal (ULN) based on an average of at least two urine samples (the previous submission was based on three samples);
 - The initial treatment period is now six months (increased from 12 weeks from the previous submission);
 - Eligibility for continuing treatment was based on patients who either achieve a complete response (CR) i.e., $mUFC \leq ULN$ or partial response (PR) i.e., $mUFC > ULN$ but $\geq 50\%$ reduction from the baseline value after six months of treatment. The previous submission required that patients achieve a CR after 12 weeks of treatment. The outcome of CR and PR was also referred to as overall response. The PBAC had previously noted that clinicians considered a PR could lead to clinically important outcomes (paragraph 6.1, osilodrostat, Public Summary Document [PSD], March 2023 Pharmaceutical Benefits Advisory Committee [PBAC] meeting).
 - The ESC considered that these changes to the restriction were reasonable, aligning better with clinical practice, although may lead to a larger treatment population.
- 3.4 The proposed initial treatment criteria did not limit the number of times a patient may be treated under the initial criteria or the amount of time that must lapse before retreatment or specification of any clinically relevant circumstances in which a patient may continue treatment despite not achieving response. As such, a patient who failed to achieve CR or PR could continue (or restart) treatment under the initial criteria without delay. This may be against the spirit of the requested restrictions and consideration to account for this should be made in the restriction. However, there may be some cases where the failure to achieve CR or PR was not related to lack of efficacy (e.g. due to comorbidities or baseline fluctuations in mUFC) and consideration to allow patients to reinitiate treatment may need to be included. Further, it was unclear whether the type of assay or the value of ULN would need to be specified. The DUSC has previously noted that mUFC can be volatile, with Giraldi 2015¹ noting that ULN range reported by direct urine assays are roughly twice as high as those reported in extracted urine (approx. $150 \mu\text{g}/24 \text{ h}$ or $410 \text{ nmol}/24 \text{ h}$ vs $80 \mu\text{g}/24 \text{ h}$ or $220 \text{ nmol}/24 \text{ h}$, respectively). The pre-sub-committee response (PSCR) suggested that if osilodrostat is listed on PBS, the sponsor is amenable to revisions in the restrictions to resolve these issues.
- 3.5 At the March 2023 meeting, the addition of the following clinical criterion to grandfathered patients was noted to be important for consistency with the initial treatment restriction but was not included in this resubmission:

¹ Giraldi, F, Ambrogio, A (2015) Variability in laboratory parameters used for management of Cushing's syndrome, *Endocrine Methods and Techniques*, 50,580-589, <https://link.springer.com/article/10.1007/s12020-015-0676-9>

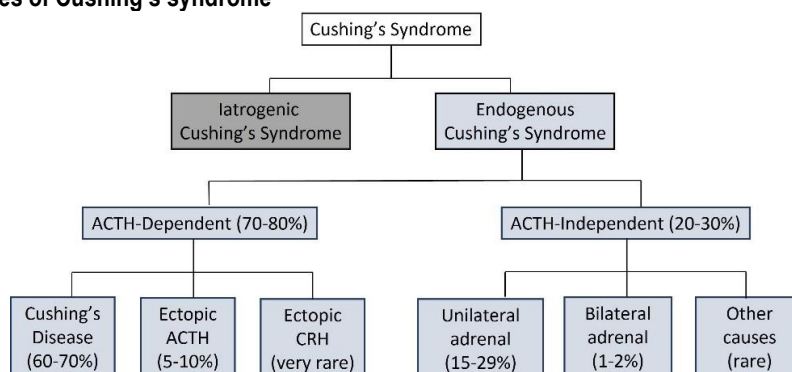
“Patient must have had active endogenous Cushing’s Syndrome determined by a mean urinary free cortisol (UFC) level greater than 1.3 times the upper limit of normal (ULN) at the time non-PBS subsidised treatment was commenced with this drug” (paragraph 3.3, osilodrostat, PSD, March 2023 PBAC meeting). The PBAC noted from consumer comments that there may also be patients who had been treated with other non-PBS therapies (ketoconazole or metyrapone) and they would need to be able to transition to osilodrostat.

For more detail on PBAC’s view, see section 7 PBAC outcome.

4 Population and disease

4.1 Endogenous CS is a rare endocrine disorder which is characterised by excessive levels of blood cortisol levels. The different causes of CS are shown in Figure 1.

Figure 1: The causes of Cushing’s syndrome



Source: Figure 1.1-2 of the submission.

ACTH = adrenocorticotropic hormone; CRH=Corticotrophin-releasing hormone

4.2 The most common cause of adrenocorticotropic hormone (ACTH) dependent CS is a pituitary adenoma (approximately 70%), also known as Cushing’s disease (CD). Ectopic ACTH syndromes represent a small portion of patients where the excessive release of ACTH arises from malignant or benign neuroendocrine tumours outside of the pituitary glands. The most common cause of ACTH-independent CS is a unilateral adrenal adenoma (10% - 22%) or carcinoma (5% - 7%). Bilateral adrenal causes of CS are rare. Irrespective of the origin, the result is hypersecretion of cortisol from the adrenal gland.

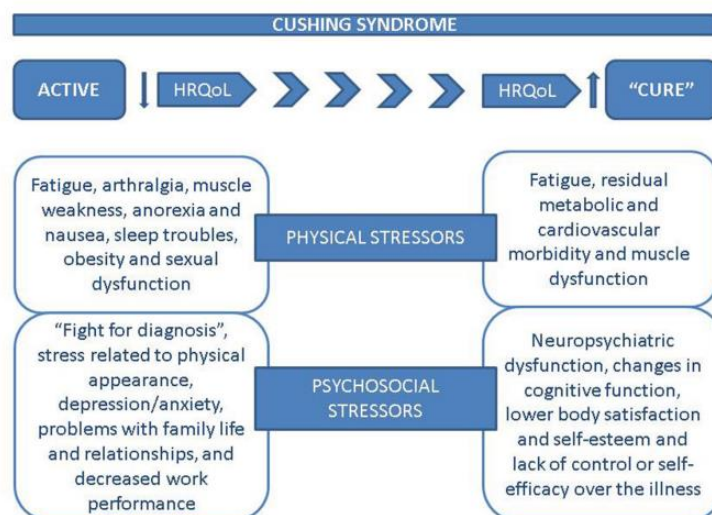
4.3 The resubmission indicated that the most common clinical features include obesity or weight gain, hypertension, as well as neuropsychiatric symptoms. The main comorbidities include cardiovascular disease, diabetes, infection and osteoporosis and impact on quality of life (QoL).

4.4 The clinical features of CD are due to excess cortisol secretion and are indistinguishable from other causes of CS (ectopic ACTH production and adrenal tumours). The diagnostic process therefore begins with establishing that there is excess cortisol secretion, and then proceeds to distinguish the various specific causes. ACTH measurement distinguishes ACTH-dependent (CD or ectopic ACTH production)

- from ACTH-independent disease (adrenal tumour), and pituitary MRI and further biochemical testing establish the diagnosis of Cushing's disease.
- 4.5 The treatment of choice for CD in adults is surgical removal of the pituitary adenoma. Case series by neurosurgeons specialising in pituitary surgery report control of hypercortisolism immediately after surgery in about 80% of patients. Recurrence is not uncommon: up to 25% after 10 years. Patients who are not initially cured by surgery, or who have recurrence, can have repeat surgery, pituitary irradiation, or medical treatment. Pituitary irradiation may be used as primary treatment, especially in children, in whom it results in cure in about 80%. Response is often delayed, especially in adults, and, while awaiting a response, medical treatment is necessary to control hypercortisolism. A trial of medical treatment to establish that hypercortisolism can be controlled may be undertaken before irradiation.
- 4.6 The manifestations of hypercortisolism improve over months to years after successful treatment. Hypertension, obesity, impaired glucose tolerance, osteoporosis and neuropsychiatric symptoms improve but are often not cured. The PBAC noted that the resubmission provided two additional retrospective, observational studies (Mondin 2023 (conducted in Padova, Italy) and Chihaoui 2023 (conducted in Tunis, Tunisia)) to address uncertainties with translating CR into longer-term mortality and morbidity improvements (paragraph 7.8, osilodrostat, PSD, March 2023 PBAC meeting). Mondin 2023 (N=126) showed that over a median follow-up of 130.5 months, 78 (61.9%) patients who were in biochemical remission (defined as normal cortisol levels for at least 12 months) regardless of treatment received had significant improvements from baseline in hypertension, dyslipidaemia, diabetes, and obesity and comparatively for patients with persistent disease these comorbidities remained elevated. Furthermore, patients in biochemical remission showed lower standardised mortality ratios (SMR) (SMR=1.66, 95% CI 0.34, 4.85) compared to patients with active disease (SMR=4.99, 95% CI 2.15, 9.83). Similarly, the retrospective study by Chihaoui 2023 (N=75) reported that after one year of follow-up, 38 (51%) patients achieved remission and had significant reductions in hypertension and diabetes. Based on these studies, the ESC acknowledged that ongoing remission from hypercortisolism can lead to improvements in cardiovascular and metabolic comorbidities from CS and mortality in the longer term. The ESC considered these studies supported the value of cortisol control and the high unmet clinical need for new and effective therapies in CS that PBAC had previously acknowledged (paragraph 7.2, osilodrostat, PSD, March 2023 PBAC meeting).
- 4.7 While QoL can improve with treatment, physical and psychosocial stressors impacting a patient's QoL can remain (Figure 2) where patients still exhibit poorer QoL compared to the general population even years after normalisation of hypercortisolism due to residual metabolic, cardiovascular, and cognitive morbidity from the hypercortisolism

previously (McBride 2021; Santos 2019; and Broersen 2019).^{2,3,4} The resubmission provided a perspective from the Executive Director at the World Alliance of Pituitary Organization (WAPO), who described the experiences of patients after bilateral adrenalectomy (BLA). The common consequences of BLA included lack of energy which negatively impacts the patients’ social and work life as well as anxiety and depression due to social withdrawal, mobility associated tiredness, self-care due to a lack of energy, and sleep disturbances.

Figure 2: Physical and psychological stressors affecting HRQoL before and after treatment of Cushing’s syndrome



Source: Figure 1, p5 from McBride 2021
 HRQoL = health related quality of life

For more detail on PBAC’s view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The resubmission reasonably nominated placebo as the PBAC previously considered this most relevant comparator given that ketoconazole was deregistered by the TGA (for treatment of fungal infections due to hepatotoxicity) and metyrapone was used as an off-label therapy (paragraph 7.5, osilodrostat, PSD, March 2023 PBAC meeting). The ESC reaffirmed that placebo was the appropriate comparator.
- 5.2 The resubmission included metyrapone and ketoconazole as supplementary comparators, but they were only included as subsequent therapies in a sensitivity analysis in the economic model.

² McBride, M, et al. (2021) Quality of life in Cushing’s syndrome, Best Practice & Research Clinical Endocrinology & Metabolism, 35:1. 101505. <https://doi.org/10.1016/j.beem.2021.101505>

³ Santos A, et al. (2019). Quality of Life in Patients With Cushing's Disease. Front Endocrinol (Lausanne); 10:862. doi: 10.3389/fendo.2019.00862. PMID: 31920973; PMCID: PMC6917662

⁴ Broersen, LHA, et al. (2019). Improvement but No Normalization of Quality of Life and Cognitive Functioning After Treatment of Cushing Syndrome, The Journal of Clinical Endocrinology & Metabolism, 104:11,5325–5337, <https://doi.org/10.1210/jc.2019-01054>

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician stressed the unmet clinical need for treatment of CS as there is currently no PBS listed alternative. The clinician highlighted that CS is one of the most challenging endocrine conditions given the difficulty with diagnosis and limited therapeutic options, and that even partial cortisol response with osilodrostat has clinical benefits. The clinician also emphasised the need for slow up-titration of osilodrostat dose to minimise risk of adrenal insufficiency and patient symptoms (to allow time for patients to re-adapt to the new cortisol level), and the importance of adequate prescriptions to cover up to 6 months of treatment as symptom improvement is gradual and often requires this duration for patients to achieve the maximum therapeutic effect. The clinician also added that one 24-hour urine free cortisol is sufficient for follow-up management in clinical practice, and it is inconvenient for patients to collect 3 urine samples.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (8), health care professionals (6) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits with osilodrostat including high efficacy and safety, improvements in quality of life (including physical, emotional, mental and social wellbeing) and potential survival benefits. The Australian Pituitary Foundation and the Endocrine Society of Australia reiterated the high unmet clinical need and the need for alternative effective therapy. The PBAC noted the patient perspective provided valuable insight, including challenges encountered throughout their journey from diagnosis and management.

Clinical trials

- 6.3 This resubmission was based on one head-to-head randomised trial comparing osilodrostat to placebo: LINC 4 (N=73); and supplemented by one randomised withdrawal trial comparing osilodrostat to placebo: LINC 3 (N=137); and one single-arm study of osilodrostat: C1202 (N=9). The clinical evidence for osilodrostat included the same trials and studies as the previous submission.
- 6.4 The comparative efficacy in LINC 4 and LINC 3 was assessed at week 12, with an open label period where all patients were switched to osilodrostat from week 12 to 48. Following that was an additional optional extension phase from week 48 to last follow up.
- 6.5 The resubmission included additional long-term efficacy data from the optional extension phases of LINC 4 and LINC 3 from Week 48 to until last follow up. Response data reported in the resubmission was up to Week 96 in LINC 4 and Week 120 for

LINC 3, with the LINC 4 data the same as was previously considered by PBAC and the LINC 3 data was previously presented at 72 weeks with additional follow up of mUFC out to 204 weeks (see Table 5, Figure 2 and paragraphs 6.11 and 6.12, of the osilodrostat, PSD, March 2023 PBAC meeting). The PSCR clarified that the resubmission presented additional efficacy data for the optional extension periods for LINC 3 (up to 245.1 weeks) and LINC 4 (up to 126.6 weeks), however, the end of treatment (EOT) extension results for response rates presented in Table 5 below are unchanged from the previous submission.

6.6 Details of the trials and studies presented in the submission are provided in Table 3.

Table 3: Trials/studies and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
LINC 4 NCT02697734	A Phase III, multi-center, randomised, double-blind, 48-week study with an initial 12-week placebo-controlled period to evaluate the safety and efficacy of osilodrostat in patients with Cushing's disease. Gadelha M, Bex M, Feelders RA, Heaney AP et al. Randomized trial of osilodrostat for the treatment of Cushing's disease. Gadelha, M, Snyder, P J, Witek, P, Bex, M, Belaya, Z, Turcu, A F, Feelders, R A, Heaney, A P, Paul, M, Pedroncelli, A M, & Auchus, R J. Long-term efficacy and safety of osilodrostat in patients with Cushing's disease: results from the LINC 4 study extension	September 2020; July 2021; August 2023 J Clin Endocrinol Metab 2022; 107(7): e2882-e2895. J Clin Endocrinol Metab 2023; 23 (14):1236465
LINC 3 NCT02180217	A Phase III, multi-center, double-blind, randomised withdrawal study of LCI699 following a 24 week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LCI699 for the treatment of patients with Cushing's disease Pivonello R, Fleseriu M, Newell-Price J, Bertagna X et al 2020. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. Fleseriu M, Newell-Price J, Pivonello R, Shimatu A et al. Long-term outcomes of osilodrostat in Cushing's disease: LINC 3 study extension.	September 2018; May 2020 Lancet Diabetes Endocrinol 2020; 8:748-761. Eur J Endocrinol 2022; 187: 531-541.
C1201 NCT02468193	A Phase II, open-label, dose titration, multi-center study to assess the safety/tolerability and efficacy of osilodrostat in patients with all types of endogenous Cushing's syndrome except Cushing's disease. Tanaka T, Satoh F, Ujihara M, Midorikawa S et al. A multicentre, phase 2 study to evaluate the efficacy and safety of osilodrostat, a new 11β-hydroxylase inhibitor, in Japanese patients with endogenous Cushing's syndrome other than Cushing's disease.	October 2018; June 2019 Endocr J 2020; 67:841-852.

Source: Table 2.2-6 of the submission

Blue shade indicates publications previously considered by the PBAC

6.7 The key features of the included evidence are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in economic model
Osilodrostat vs. placebo						
LINC 4	73	R, DB 12 wks then OL osi wk 12 to 48	Low	Adults with CD with persistent or recurrent hypercortisolism after surgery and/or radiation or patients who were not candidates for surgery mUFC >1.3 × ULN with ≥2 of UFC values being > 1.3 × ULN	Complete, partial, overall response ^a ; time to escape ^b ; QoL; safety	Overall response, time to escape ^c , QoL, safety
LINC 3	137 (OL) 71 (RW)	OL single arm 26 wks then R, DB to 34 wks then OL osi to 48 wks	High	Adults with CD with persistent or recurrent hypercortisolism after surgery and/or radiation or patients who were not candidates for surgery mUFC > 1.5 × ULN		Sensitivity analysis only (overall response)
C1201	9	OL single arm 48 wks	High	Adult Japanese patients with endogenous CS other than CD	Response rate; QoL	Not included.

Source: Table 3, osilodrostat, PSD, March 2023 PBAC meeting

CD = Cushing's disease; CS = Cushing's syndrome; DB = double-blind; mUFC = mean urinary free cortisol; OL = open-label; osi = osilodrostat; R = randomised; RW = randomised withdrawal; QoL = quality of life; ULN = upper limit of normal; wks = weeks

a Complete response was defined as mUFC ≤ ULN; partial response was defined as patients with a mUFC > ULN but who achieved ≥50% improvement from baseline; and overall response was defined as patients who achieved either a complete or partial response.

b Time to escape defined as the time (in days) between the first normalisation of UFC (mUFC ≤ ULN) and either the UFC assessment of escape (loss of UFC control after dose titration period, defined as at least two individual values contributing to that mUFC were >1.3xULN (LINC 4) or >1.5xULN (LINC 3), unrelated to dose interruption or reduction due to safety/tolerability reasons) or last UFC assessment before permanent discontinuation of osilodrostat treatment (censored), whichever occurred earlier.

c time to escape was used to inform duration of response in the post-hoc analysis of LINC 4 which was then used in the economic model

Blue shade indicates data previously seen by the PBAC

6.8 At the March 2023 PBAC meeting, LINC 4 was considered to have a low risk of bias during the double-blinded, placebo-controlled period (12 weeks) after which during the open-label (OL) period, outcomes were subject to a higher risk of performance bias, particularly for patient-reported outcomes (PROs; paragraph 6.6, osilodrostat, PSD, March 2023 PBAC meeting). LINC 3 was considered to have a high risk of bias given the initial OL period of 26 weeks (N=137) and only patients responding to osilodrostat were randomised at that point (N=71; paragraph 6.6, osilodrostat, PSD, March 2023 PBAC meeting), leading to selection bias. The selection bias in LINC 3 meant that any estimate of effect size was likely overestimated (paragraph 7.6, osilodrostat PSD, March 2023 PBAC meeting). Both LINC 4 and LINC 3 extension periods only enrolled patients who demonstrated a response to osilodrostat which likely led to overestimated response rates in the extension period. C1201 was a non-randomised, single-arm OL study of nine patients and was considered to have a high risk of bias.

Comparative effectiveness

6.9 The comparative evidence between osilodrostat and placebo (full analysis set [FAS]) in LINC 4 and LINC 3 were the same as the previous submission. The PBAC had previously noted that osilodrostat demonstrated a statistically significant improvement in CR at week 12 (risk difference [RD] = 0.69 [95% CI 0.47, 0.80]; odds

ratio [OR] = 43.4 [95% CI 7.06, 343.19]; paragraph 7.7, osilodrostat, PSD, March 2023 PBAC meeting) and has accepted the clinical claim of superior comparative effectiveness of osilodrostat to placebo for the surrogate outcome of CR of UFC (paragraph 7.8, osilodrostat, PSD, March 2023 PBAC meeting). The overall response rate (ORR), defined as CR plus PR, also favoured osilodrostat over placebo (RD = 0.65 [95% CI 0.47, 0.83]; OR = 22.75 [95% CI 6.25, 82.79]).

- 6.10 The decrease in response at week 96 in LINC 4 (CR = 4/19, 21% from 34/48, 70.8% at Week 48, see Table 5) called into question the durability of response to osilodrostat, however, the previous submission considered data up to week 72 in LINC 3 better reflected the durability of response (paragraph 6.11, osilodrostat, PSD, March 2023 PBAC meeting) and that mUFC levels were consistently below the ULN (138 nmol/24h) up to week 204 (Figure 2, p19, osilodrostat, PSD, March 2023 PBAC meeting). However, the additional data from LINC 3 indicated that response at week 120 reduced considerably when the denominator was based on the FAS population (CR = 62/137, 45.3% a decrease from 91/137, 66.4% at Week 48; ORR = 73/137, 53.3% a decrease from 104/137, 75.9% at Week 48). Further, only patients who demonstrated response to osilodrostat enrolled in the extension periods which potentially led to overestimated response rates for the EOT extension. The response rate results for LINC 4 and LINC 3 at different time points are presented in Table 5.

Table 5: Response rates during in the overall study periods of LINC 4 and LINC 3 (FAS)

	LINC 4			LINC 3
	Osilodrostat N = 48	Placebo + Osilodrostat ^a N = 25	All patients N = 73	All patients, N=137
Complete response rate				
Week 12, n/N (%)	37/48 (77.1)	2/25 (8.0) ^b	NE	98/137 (71.5)
Week 24, n/N (%)	-	-	-	93/137 (67.9)
Week 26, n/N (%) ^e	38/48 (79.2)	22/25 (88.0)	60/73 (82.2)	89/137 (65.0)
Week 36, n/N (%)	38/48 (79.2)	21/25 (84.0)	59/73 (80.8)	80/137 (58.4)
Week 48, n/N (%) ^c	34/48 (70.8)	16/25 (64.0)	50/73 (68.5)	91/137 (66.4)
Week 72, n/N (%)	25/41 (61.0)	15/24 (62.5)	40/65 (61.5)	86/106 (81.1)
Week 96, n/N (%)	4/19 (21.1)	6/13 (46.2)	10/32 (31.3)	66/105 (62.9)
Week 120, n/N (%)	-	-	-	62/100 (62.0)
Week 120 among all enrolled, n/N (%) ^{d, e}	-	-	-	62/137 (45.3)
EOT Extension, n/N (%)	28/38 (73.7)	14/20 (70.0)	42/58 (72.4)	86/137 (62.8)
Overall response rate				
Week 12, n/N (%)	39/48 (81.3)	4/25 (16.0%) ^b	NE	117/137 (85.4)
Week 24, n/N (%)	-	-	-	113/137 (82.5)
Week 26, n/N (%) ^e	38/48 (79.2)	24/25 (96.0)	62/73 (84.9)	107/137 (78.1)
Week 36, n/N (%)	40/48 (83.3)	24/25 (96.0)	64/73 (87.7)	97/137 (70.8)
Week 48, n/N (%) ^c	39/48 (81.3)	19/25 (76.0)	58/73 (79.5)	104/137 (75.9)
Week 72, n/N (%)	29/41 (70.7)	16/24 (66.7)	45/65 (69.2)	94/106 (88.7)
Week 96, n/N (%)	5/19 (26.3)	6/13 (46.2)	11/32 (34.4)	77/105 (73.3)
Week 120, n/N (%)	-	-	-	73/100 (73.0)
Week 120 among all enrolled, n/N (%) ^{d, e}	-	-	-	73/137 (53.3)
EOT Extension, n/N (%)	31/38 (81.6)	16/20 (80.0)	47/58 (81.0)	113/137 (82.5)

Source: Table 2.5-9; Table 2.5-18; Table 2.5-28; Table 2.5-29; Table 2.5-37, of the submission; Table 14-2-2.1, and LINC 3 Final CSR
 CI = confidence interval; EOT = end of treatment; FAS = full analysis set; mUFC = Mean Urinary free cortisol; ULN = Upper Limit of Normal

^a LINC 4: Patients randomised to placebo switched to open-label osilodrostat at Week 12

^b LINC 4: Week 12 estimate is based on placebo patients only (have not received osilodrostat)

^c the denominator rules after Week 48 (extension period) were as follows:

LINC 3: 1) patients who declined to enter optional extension period after completion of the core phase were excluded and 2) patients who discontinued prior to the December 2019 data cut off were included up to the furthest scheduled visit they could have completed if they had not discontinued early based on data cut off and last completed based on the date of last completed schedule visit and analyses cut-off date.

LINC 4: Patients who completed the extension phase were only included in the denominator until their individual EOT visit. Beyond Week 48, patients who completed the extension phase will only be included in the denominator until their individual EOT visit. Patients who discontinued prior to the data cutoff date were included for visits they could have completed if they had continued until week 96 or data cut off for the analysis (whatever occurs earlier) but excluded for further visits.

^d Using all patients as denominator, as in an intention to treat analysis

^e Additional information included during the evaluation

Complete responder: mUFC ≤ ULN, Partial responder: mUFC > ULN but ≥ 50% reduction from baseline, Overall responder: either a complete or partial responder

Blue shaded text indicates data previously seen by the PBAC

6.11 Results for QoL outcomes showed no statistically significant advantages for osilodrostat compared to placebo, although there was greater improvement on the Beck Depression Inventory (BDI-II) for placebo-treated patients (paragraph 6.14, osilodrostat, PSD, March 2023 PBAC meeting). The extension data of LINC 4 and LINC 3 in the resubmission suggested that improvements in QoL could be maintained to the EOT visits. Notably, the baseline QoL scores for all patients in LINC 4 appeared relatively high, particularly for EuroQoL-5 Dimension (EQ-5D)-5L utility values (0.83 in

osilodrostat and 0.90 in placebo), potentially suggesting that patients were not experiencing substantial deterioration in QoL prior to entering the trial. The economic model however does not rely on any of this data and instead, a post hoc analysis of utilities in overall responders at week 26 in LINC 4 was used to inform the economic model (discussed further in paragraphs 6.59 to 6.61).

- 6.12 The PBAC had previously considered that despite the limitations of the evidence, it was biologically plausible that if a patient is tolerating and responding to osilodrostat, that the response would be maintained. The PBAC suggested that in clinical practice there may be variation in response related to the unintended effects or hormonal changes from the treatment (as a result of blocking cortisol production and increasing the levels of other hormones) requiring patients to take a break from the treatment to allow their hormone levels to return to normal. However, the PBAC further considered that it is unknown what impact this may have on long-term outcomes and quality of life (paragraph 7.7, osilodrostat, PSD, March 2023 PBAC meeting).
- 6.13 To address this issue, the resubmission provided the following analyses:
- an unanchored indirect treatment comparison (ITC) of pooled osilodrostat (LINC 4, LINC 3, and C1201) vs placebo (LINC 4);
 - individual patient swimmer plots of dose and response over time; and
 - a post-hoc analysis of responders from a subgroup of patients from LINC 4 and LINC 3 who met the proposed PBS restriction for initiating (mUFC>1.3xULN based on two values) and continuing treatment (achieved overall response at 26 weeks). This analysis included patients who were initially randomised to placebo but then subsequently crossed over to osilodrostat at week 12.
- 6.14 The resubmission noted the ITC was performed for completeness, however, given the pooled trials/studies presented transitivity issues and that LINC 4 already provided direct randomised evidence for osilodrostat vs placebo, the evaluators considered the ITC had limited value. The response rates for osilodrostat in the ITC at week 12 (CR = 141/194, 72.7%; ORR = 163/194, 84%) were similar to LINC 4 (CR = 37/48, 77.1%; ORR = 39/48, 81.3%). The submission claimed the swimmer plots suggested that patients who maintained their therapeutic dose could maintain their response and patients with appropriately titrated doses could improve their response (from PR to CR; Figures 2.6-1, and 2.6-2 from the resubmission). The ESC advised the swimmer plots provide a descriptive plot of individual patient data, but they cannot be relied on to infer anything about maintenance of response.
- 6.15 The post-hoc analysis of the subgroup of patients in LINC 4 treated with osilodrostat who met the proposed PBS restriction for initiating (mUFC>1.3xULN based on two values) and continuing treatment (achieved overall response at 26 weeks) was used to inform the economic model. Specifically, the ORR at Week 26, the duration of response (DoR) among patients who achieved response at Week 26, and the EQ-5D-

5L utility scores using the Australian tariff for responders and non-responders were used to inform the model. These results are presented in Table 6.

Table 6: Response, DoR, and QoL (EQ-5D-5L utility score) results from the LINC 4 post-hoc analysis of the proposed PBS population (baseline mUFC>1.3xULN and Week 26 ORR) and LINC 4 FAS population

Response	LINC 4 post-hoc analysis, N=60 ^a		LINC 4 FAS, N=73
Complete response at Week 26, n (%)	47/60 (78)		60/73 (82.2)
Overall response at Week 26, n (%)	52/60 (87)		62/73 (84.9)
Median time to response (95% CI)	5 weeks		5 weeks (4.9, 7.4)
Median duration of response	1.34 years		NR
EQ-5D-5L utility score	Responders, n=35 ^b	Non-responders, n=7 ^b	All patients, N=73
Baseline, mean (SD)	0.713 (0.227)	0.658 (0.257)	0.85 (0.14)
Mean change from baseline: dose titration period up to Week 12 (95% CI)	0.012 (-0.065, 0.088)	-0.065 (-0.214, 0.085)	-
Mean change from baseline: after dose titration period for continuing responders (95% CI)	0.086 (0.026, 0.146)	-	0.037 (-0.004, 0.078) at week 72 (n=47)

Source: Table 2.5-4; Table 2.5-25; Tables 2.6-9 to 2.6-11; Table 2.6-28; Table 2.6-34; Table 2.6-38 of the submission

CI = confidence interval; CR = complete response; DoR = duration of response; EQ-5D = EuroQol 5 Dimension; FAS = full analysis set; mUFC = Mean Urinary Free Cortisol; OL = open label; ORR = overall response rate; QoL = quality of life; SD = standard deviation; ULN = Upper limit of normal

^a Included patients had baseline mUFC>1.3xULN based on two daily values from the osilodrostat arm (at Week 0) and from the placebo arm for those who crossed over (at Week 12). Patients randomised to placebo treatment for the first 12 weeks have had their response to open-label osilodrostat analysed after Week 12. For these patients, the baseline mUFC is the mUFC value at week 12, the 'week 12' response is based on the mUFC at Week 23 and the 'Week 26' response is based on the mUFC at Week 36. The resubmission reported that 60 patients received osilodrostat when including the placebo patients who switched to osilodrostat, however, there were only 59 patients who met the PBS restriction criteria (42 in osilodrostat arm and 17 in placebo arm at Week 0). It is possible that at Week 12 given this was the 'baseline mUFC' for placebo switchers, a total of 18 patients in the placebo arm could have met the eligibility criteria and therefore were included.

^b only used QoL data from patients randomised to osilodrostat at baseline and while in response (n=42)

Notes: mUFC was calculated from the first two daily values at each visit in the post-hoc analysis and based on three (or two when only available) in the LINC 4 FAS population; ULN defined as 138 nmol/day; Overall response is defined as a complete response (mUFC ≤ 1 x ULN) or partial response (mUFC > ULN but ≥ 50% reduction from baseline)

6.16 In the LINC 4 post-hoc analysis, there were 60/73 (82%) patients who met the proposed PBS restriction criteria for initiating osilodrostat treatment (baseline mUFC>1.3xULN based on two values). 52/60 (87%) patients subsequently achieved an overall response at Week 26 and therefore met the continuing treatment criterion. The median time to first overall response was five weeks, and the median DoR was 1.34 years. This pattern was consistently reflected in mUFC levels which sharply decreased in the first 12 weeks of treatment and remained steadily below the ULN (138 nmol/day) through to 96 weeks.

6.17 The resubmission reported QoL of responders compared to non-responders based on patients randomised to osilodrostat who met the proposed PBS restriction criteria (n=42). The resubmission reported that patients who achieved response (n= 35) had a better QoL at baseline compared to non-responders (n=7). For example, as shown in Table 6, baseline EQ-5D utility score was higher in responders (0.713) than non-responders (0.658). Inappropriately, these differences in baseline scores were carried through to the economic evaluation, implying that patients who will become 'responders' inherently have a higher QoL at baseline compared to those who will become 'non-responders' prior to and without any treatment being administered.

- 6.18 No justification or statistical tests were conducted to support the assumption that baseline utilities should be different between responders and non-responders. The baseline differences highlighted by the resubmission suggest that the populations being analysed were inherently different, though this was likely due to the results being derived from a selective subgroup from an already small sample size of patients (35 responders vs seven non-responders). It was unclear whether any subsequent improvements in QoL would be attributed to osilodrostat or if any differences observed were simply due to unobserved confounding factors beyond the treatment administered.
- 6.19 Additionally, it was unclear why the baseline utility in this subgroup of patients (0.713 for responders and 0.658 for non-responders) was so much lower than the FAS population of LINC 4 (0.83 in osilodrostat, 0.90 in placebo, and 0.85 in all patients). While potentially attributed to the use of different tariffs, the magnitude of the difference raised concerns regarding the validity of the values. For example, a patient assumed to have overall response at week 26 in the subgroup of patients with baseline $mUFC > 1.3 \times ULN$ would have a utility of 0.799 [0.713 + 0.086], which was lower than the baseline value in the FAS population of LINC 4.
- 6.20 While there were improvements from baseline QoL (Cushing's QoL, BDI-II, and EQ-5D-5L utility scores) for the Week 26 responders who maintained osilodrostat treatment, the sample sizes were small, the baseline utility values differed substantially from the FAS population in LINC 4 and also differed between responders and non-responders and as such the utility results in the proposed PBS subgroup in LINC 4 were highly uncertain. The mean change in the Cushing's QoL (10.4-point, 95% CI 5.7, 15.1), BDI-II (-3.7%, 95% CI -4.6, -1.8), and EQ-5D-5L utility scores (0.086, 95% CI 0.026, 0.146) after week 12 up to week 96 for responders in the LINC 4 post-hoc analysis favoured osilodrostat, however, the lower confidence intervals were not regarded as clinically meaningful.⁵ This may be related to the limited follow-up and/or the capacity of these instruments to capture improvements in CS symptoms and comorbidities given the gradual improvements in CS patients. The PBAC has previously noted that "it was not uncommon for patients with CS to have a gradual improvement in symptoms after treatment, with clinical benefits usually seen after a year or so, requiring considerable amount of time to adapt to the normal cortisol level" (paragraph 7.8, osilodrostat, PSD, March 2023 PBAC meeting). Given that osilodrostat was expected to be a lifelong treatment, the PBAC was interested to consider the important long-term benefits of cortisol control from the literature or natural history data (paragraph 7.11, osilodrostat, PSD, March 2023 PBAC meeting). The resubmission provided some evidence from the literature that suggested sustained remission from hypercortisolism regardless of treatment strategy could lead to improvements in CS comorbidities and QoL (see paragraphs 4.6 and 4.7), but were not incorporated in the

⁵ Minimal clinically important difference (MCID) thresholds described in the resubmission:
EQ-5D-5L utility scores = 0.037-0.069 change from baseline; Cushing's QoL = 10.1-point change from baseline;
BDI-II = 17.5% reduction from baseline

economic model. The PSCR suggested osilodrostat is more accurately described as a chronic therapy and for some patients this may be long term, rather than as a lifelong treatment, and as such the clinical evidence presented in the resubmission is adequate. The ESC considered the long-term benefits from improvements in cardiovascular and metabolic outcomes (as noted in paragraph 4.6) were highly relevant to considering the value of achieving a sustained complete or partial response in normalisation of mUFC.

Comparative harms

- 6.21 The safety evidence presented was the same as the previous submission. A summary of adverse events (AEs) from the randomised periods of LINC 4 and LINC 3 are presented in Table 7.

Table 7: Summary of key adverse events in LINC 4 and LINC 3 randomised periods

Adverse event	Osilodrostat (N=48)	Placebo (N=25)	RD (95% CI)	RR (95% CI)	OR (95% CI)
LINC 4 at Week 12					
Any AE	46 (95.8%)	23 (92.0%)	0.04 (-0.08, 0.16)	1.04 (0.91, 1.19)	2.00 (0.26, 15.12)
Treatment-related AE	30 (62.5%)	11 (44.0%)	0.18 (-0.05, 0.42)	1.42 (0.87, 2.33)	2.12 (0.79, 5.67)
Treatment-related Grade ≥3 AE	4 (8.3%)	1 (4.0%)	0.04 (-0.07, 0.15)	2.08 (0.25, 17.66)	2.18 (0.23, 20.64)
Treatment-related SAE	0 ^a	0 ^a	0.00 (-0.06, 0.06)	NE	NE
Treatment-related discontinuation due to AE	1 (2.1%)	0	0.02 (-0.05, 0.09)	1.58 (0.07, 37.35)	1.61 (0.06, 40.98)
AEs requiring additional therapy	37 (77.1%)	11 (44.0%)	0.33 (0.10, 0.56)	1.75 (1.10, 2.80)	4.28 (1.52, 12.08)
Death	0 ^a	0 ^a	0.00 (-0.06, 0.06)	NE	NE
AEs of special interest					
Adrenal hormone precursor accumulation	21 (43.8%)	9 (36.0%)	0.08 (-0.16, 0.31)	1.22 (0.66, 2.24)	1.38 (0.51, 3.74)
Hypocortisolism-related AEs	7 (14.6)	0	0.15 (0.03, 0.26)	7.89 (0.47, 132.61)	9.22 (0.50, 168.33)
Pituitary tumour enlargement-related AEs	0	0	0.00 (-0.06, 0.06)	NE	NE
Arrhythmogenic potential and QT prolongation	0	0	0.00 (-0.06, 0.06)	NE	NE
Adverse event	Osilodrostat (N=36)	Placebo (N=35)	RD (95% CI)	RR (95% CI)	OR (95% CI)
LINC 3 at Week 26-34					
Any AE	26 (72%)	23 (66%)	0.07 (-0.15, 0.28)	1.10 (0.80, 1.50)	1.36 (0.49, 3.72)
Treatment-related AE	15 (41.7%)	11 (31.4%)	0.10 (-0.12, 0.33)	1.33 (0.71, 2.47)	1.56 (0.59, 4.13)
Any SAE	2 (6%)	1 (3%)	0.03 (-0.07, 0.12)	1.94 (0.18, 20.49)	2.00 (0.17, 23.11)
Discontinuation due to AE	0	2 (5.7%)	-0.06 (-0.15, 0.03)	0.19 (0.01, 3.91)	0.18 (0.01, 3.96)
Death	0 ^a	0 ^a	0.00 (-0.05, 0.05)	NE	NE
AEs of special interest					
Adrenal hormone precursor accumulation	2 (6%)	1 (3%)	0.03 (-0.07, 0.12)	1.94 (0.18, 20.49)	2.00 (0.17, 23.11)
Hypocortisolism related AEs	3 (8%)	1 (3%)	0.05 (-0.05, 0.16)	2.92 (0.32, 26.72)	3.09 (0.31, 31.24)
Pituitary tumour enlargement-related AEs	0	0	0.00 (-0.05, 0.05)	NE	NE
Related to QT prolongation	0	0	0.00 (-0.05, 0.05)	NE	NE
Arrhythmogenic potential	0	0	0.00 (-0.05, 0.05)	NE	NE

Source: Table 10, osilodrostat, PSD, March 2023 PBAC meeting cross-referenced from Table 2.5-54; Table 2.5-55; Table 2.5-59; Table 2.5-60 of the resubmission.

AE = adverse event; CI = confidence interval; NE = not evaluable; OR = odds ratio; RD = risk difference; RR = relative risk

Bold values indicate a difference in which the 95% confidence interval does not include no difference.

Blue shade indicates data previously seen by the PBAC

6.22 Despite the higher proportion of hypocortisolism in patients randomised to osilodrostat in LINC 4 and even higher proportions in the overall study period, the PBAC had previously accepted the Sponsor’s pre-PBAC response that hypocortisolism occurred more frequently during dose titration and there was low level of QTc

prolongation throughout the treatment period. Therefore, the PBAC accepted that the claim of non-inferiority safety to placebo was reasonable noting regular monitoring of side effects of hypocortisolism was required (paragraph 7.9, osilodrostat, PSD, March 2023 PBAC meeting).

- 6.23 The PBAC noted that “adverse events relating to pituitary tumour enlargement should be monitored and required further investigation to better understand the impact of this phenomenon” (paragraph 7.9, osilodrostat, PSD, March 2023 PBAC meeting). The resubmission provided additional detail around pituitary tumour enlargement in LINC 4 and LINC 3 in the form of patient narratives.
- 6.24 Generally, pituitary tumour enlargement AEs were low in LINC 4 (four patients, 5.5%) and these patients discontinued osilodrostat without medical treatment for the AE. In LINC 3, 22 patients (16.1%) experienced at least one pituitary tumour enlargement-related AE with 12 (8.8%) suspected of being osilodrostat-related. Most pituitary tumour enlargement-related AEs occurred during the extension phase from Week 48 onwards. Generally, the serious AEs were Grade ≥ 3 and patients were treated with pituitary surgery or radiotherapy and or received various medical therapies. Patients had recovered from treatment and the primary tumour was resolved, generally in the same day. Most of these patients discontinued during the extension phase.

Benefits/harms

- 6.25 A summary of the comparative benefits and harms for osilodrostat versus placebo is presented in Table 8.

Table 8: Summary of comparative benefits and harms for osilodrostat and placebo

Trial	Osilodrostat	Placebo	OR (95% CI)	Event rate/100 patients		RD ^a (95% CI)
				Osilodrostat	Placebo	
Benefits						
Overall response^b						
LINC 4	39/48	4/25	22.8 (6.25,82.79)	81.3	16.0	0.65 (0.47, 0.83)
Harms						
	Osilodrostat	Placebo	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Osilodrostat	Placebo	
AEs requiring additional therapy						
LINC 4	37/48	11/25	1.75 (1.10, 2.80)	77.1	44.0	0.33 (0.10, 0.56)
Hypocortisolism-related AEs						
LINC 4	7/48	0	7.89 (0.47, 132.61)	14.6	-	0.15 (0.03, 0.26)

Source: Table 2.5-2; Table 2.5-55 of the resubmission

AE = adverse events; OR = odds ratio; RD = risk difference; RR = risk ratio

^a For the comparison of osilodrostat and placebo the resubmission calculated RD, RR, and OR *post hoc* using R(v.4.1.0) with the Meta package (v.4.18.2)

^b Overall response defined as either normalisation of mean urinary free cortisol (complete response) or $\geq 50\%$ reduction in mean urinary free cortisol from baseline but mean urinary free cortisol is still higher than upper limit of normal (partial response)

Bold indicates a difference in which the 95% confidence interval does not include no difference.

Blue shade indicates information previously considered by the PBAC

- 6.26 On the basis of direct evidence presented by the submission, for every 100 patients treated with osilodrostat in comparison with placebo over a 12-week treatment period:

- Approximately 65 additional patients would have either a complete response (normalisation of mean urinary free cortisol) or partial response ($\geq 50\%$ reduction in mean urinary free cortisol from baseline but mean urinary free cortisol is still higher than upper limit of normal);
- Approximately 33 additional patients would experience AEs requiring additional therapy; and
- Approximately 15 additional patients would experience hypocortisolism-related AEs.

Clinical claim

- 6.27 The resubmission described osilodrostat as superior in terms of effectiveness compared with placebo and non-inferior in terms of safety compared to placebo. The therapeutic conclusion presented in the resubmission was adequately supported by the evidence. The PBAC has previously “accepted the clinical claim of superior comparative effectiveness of osilodrostat to placebo for the surrogate outcome of complete response of UFC [at 12 weeks]” (paragraph 7.8, osilodrostat, PSD, March 2023 PBAC meeting) and “...accepted that the claim of non-inferiority safety to placebo was reasonable” (paragraph 7.9, osilodrostat, PSD, March 2023 PBAC meeting). The restriction in the resubmission proposed complete or partial response (overall response) be used to qualify for continuing therapy beyond the initial 6 months phase. The overall response data also supports the clinical claim, with 2 additional patients in each arm with an overall response at 12 weeks in LINC 4 compared to complete response.
- 6.28 The PBAC had previously considered that despite the limitations of the evidence, it was biologically plausible that if a patient is tolerating and responding to osilodrostat, that the response would be maintained (paragraph 7.9, osilodrostat, PSD, March 2023 PBAC meeting). The economic analysis uses the EOT extension data to support this.
- 6.29 The EOT extension data suggested that improvements in effectiveness and QoL outcomes could potentially be maintained but were possibly confounded by selection bias in the extension periods. Consistently, the resubmission’s analyses of responders suggested that for patients treated with osilodrostat, response could be achieved and maintained in the longer-term with the median DoR being 1.34 years among patients who achieved CR or PR after 26 weeks of treatment in LINC 4 post-hoc analysis. However, the QoL analysis from the subgroup of patients with a baseline $mUFC > 1.3 \times ULN$ who were randomised to osilodrostat in LINC 4 should be interpreted with caution due to the small sample size and the difference in baseline utility between the subgroup analysis with the FAS population as well as between responder and non-responders.
- 6.30 Overall, the limitations of the evidence (e.g., short randomised periods, high risk of bias in OL phases, small sample sizes, reliance on post-hoc analyses) created uncertainty around the duration and magnitude of the long-term incremental benefit

of osilodrostat over placebo which the resubmission was not able to fully address. However, the ESC agreed with the prior PBAC consideration that patients who tolerate and respond to osilodrostat would likely achieve and maintain improvements in CS symptoms and comorbidities, acknowledging that improvements are gradual with clinical benefit usually observed after a year of treatment given the considerable amount of time to adapt to normal cortisol levels (paragraph 7.8, osilodrostat, PSD, March 2023 PBAC meeting).

- 6.31 The evidence supporting the claim of non-inferior safety of osilodrostat compared to placebo was consistent with the previous submission and was appropriate. Additional details of the patient experience with pituitary tumour enlargement-related AEs suggested that at least half of these events were serious and of Grade \geq 3, and patients were treated with pituitary surgery or radiotherapy which were resolved soon after.
- 6.32 Despite the obvious limitations of the data, given the rarity of endogenous CS and the high unmet clinical need, the ESC considered that the claim of superiority in terms of effectiveness and non-inferiority in terms of safety compared to placebo was reasonable, and that additional retrospective studies detailing the impact of long-term sustained remission from hypercortisolism on cardiovascular and metabolic outcomes supported the clinical benefit of effective chronic therapy.
- 6.33 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.34 The PBAC considered that the claim of non-inferior comparative safety was reasonable, noting regular monitoring of side effects of hypocortisolism was required.

Economic analysis

- 6.35 The PBAC previously considered that the 12-week trial-based incremental cost per responder analyses in the previous submission did not allow for assessment of cost-effectiveness of long-term use of osilodrostat in this chronic condition (paragraph 7.11, osilodrostat, PSD, March 2023 PBAC meeting).
- 6.36 In response, the resubmission presented a stepped cost-utility analysis based on one direct randomised trial, LINC 4, and implementing a modelled evaluation using microsimulation. The resubmission stated that due to the limited available clinical data to model treatment effect, the impacts of comorbidities associated with CS were not considered. The PBAC had previously considered the economic analysis should incorporate longer durations of therapy and quality of life data, using literature and natural history data to supplement the available trial evidence. The PBAC considered that it is highly likely that responding patients would continue with treatment beyond three years (mean duration of treatment of 169.5 weeks as per the LINC trials) (paragraph 7.11, osilodrostat, PSD, March 2023 PBAC meeting).
- 6.37 The resubmission discussed the impacts of longer-term remission from the literature (see paragraphs 4.6 and 4.7), noting that in Mondin 2023, there were improvements in cardiovascular and metabolic comorbidities with sustained remission which was

achieved irrespective of the treatment strategy, but these were not incorporated in the model. Hence, the evaluation advised the cost-utility analysis presented in the resubmission does not fully consider important long-term benefits of durable cortisol control and is therefore unlikely to adequately reflect the cost-effectiveness of treatment. The PSCR (pg 3) argued that, to minimise the complexity of the model, additional health states (e.g., diabetes, hypertension, body weight) and events (e.g., myocardial infarction, stroke) were not included. The ESC noted that the resubmission adopted a complex, 50 year, microsimulation model informed by a small sample size of LINC 4 without incorporating the long-term benefits of durable cortisol control or improvement in comorbidities. The ESC considered that this resulted in an inflated ICER despite the price reduction of 1% from the previous submission. Noting the tangible health benefits of osilodrostat on the comorbidities documented in the literature, the ESC advised that a Markov model incorporating the impacts of osilodrostat on comorbidities would have better captured the long-term benefits on quality of life.

- 6.38 Overall, the ESC acknowledged the attempt to address the PBAC request by modelling long-term costs and benefits, but essentially considered the modelled economic evaluation was not informative for decision-making. The ESC considered the literature quantifying the disease burden of CS and the improvements in comorbidities from sustained remission from hypercortisolism could be considered alongside the previously presented incremental cost per responder analysis over 12 weeks, including the lower proposed price in this resubmission.
- 6.39 The pre-PBAC response provided updated cost per responder analyses for PBAC consideration. In the March 2023 submission, the proportion of patients who achieved a complete response (CR) at week 12 resulted in an incremental cost per CR of \$25,000 to < \$35,000. This changes to \$15,000 to < \$25,000 per CR when the analysis is updated to reflect the revised proposed AEMP and the removal of the 10 mg strength which was no longer proposed for listing on the PBS. The resubmission requested an initiation period of 26 weeks and response was defined as achieving at least a partial response (PR). The cost per responder for this analysis, which corresponds to the Step 1 analysis of the stepped economic evaluation presented in the resubmission, is \$35,000 to < \$45,000 per patient achieving at least a partial response (see Table 9).

Table 9: Economic evaluation: cost per responder analysis – pre-PBAC response

	Cost			Response			ICER
	Osilodrostat	Placebo	Incr.	Osilodrostat	Placebo	Incr.	
ORR at 26 weeks	\$█	\$0	\$█	86.66%	17.66%	69.0%	\$█ ¹ /ORR
CR at 12 weeks (March 2023)	\$█	\$0	\$█	77.1%	8.0%	69.1%	\$█ ² /CR
CR at 12 weeks (March 2024) [^]	\$█	\$0	\$█	77.1%	8.0%	69.1%	\$█ ³ /CR

Source: 7.01.ESC ADV.33 Table 11; Isturisa (osilodrostat) - CEA - March 2023 - pre PBAC.xlsx

Abbreviations: CR = complete response; ICER = incremental cost effectiveness ratio; Incr. = Incremental; LYG = life years gained; QALY = quality adjusted life year gained; ORR = overall responder (i.e., partial or complete response)

[^]The March 2023 submission analysis updated to consider the new proposed AEMP and excluding the 10 mg strength which is no longer proposed for listing on the PBS. All other variables from the March 2023 analysis were for the purposes of this response unchanged.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$25,000 to < \$35,000

³ \$15,000 to < \$25,000

6.40 The PBAC noted previous decisions it had made using an incremental cost per responder analysis.

Table 10: Incremental cost per responder analyses - precedents

Drug & condition (PBAC meeting)	Cost per responder
Bevacizumab for relapsed or refractory glioblastoma (May 2019)	The cost per responder (ORR) was between \$█ and \$█. (Redacted as per PSD)
Brentuximab vedotin for refractory or relapsed CD30 positive cutaneous T-cell lymphomas (CTCL). (Nov 2018)	The cost per responder (ORR) was \$45,000 - \$75,000 and the cost per additional year without progression was \$15,000 - \$45,000
Vorinostat for refractory or relapsed cutaneous T-cell lymphoma (CTCL) March 2017	Cost per responder: \$█ (Redacted as per PSD)
Clostridium botulinum type A toxin-haemagglutinin complex (Dysport®) for focal spasticity of the upper limb following a stroke, to also include spasticity following acute events other than stroke (March 2019)	Cost per responder: less than \$15,000
Denosumab giant cell tumour of bone (November 2013)	Incremental cost per responder: less than \$15,000
Etanercept severe chronic plaque psoriasis in patients under the age of 18 years (March 2012)	incremental cost per PASI 75 response: less than \$15,000
Tiotropium severe asthma in children and adolescents aged 6-17 years who have not achieved adequate asthma control. (November 2018)	Incremental cost per symptomatic exacerbation avoided: less than \$15,000

Source: constructed from PSDs

6.41 The economic evaluation in the resubmission was primarily informed by the post-hoc analysis of LINC 4 which was based on the subgroup of patients who met the proposed PBS restriction criteria for:

- Initiating treatment i.e., patients with baseline mUFC>1.3xULN based on two UFC values (60/73 [82%] patients met the initial treatment criteria. Data from this cohort was used to inform the response at week 26); and
- Continuing treatment i.e., patients who achieve an overall response (mUFC≤ULN or ≥50% improvement in mUFC from baseline) at 26 weeks and every 26 weeks thereafter (52/60 [87%] patients who met the initial treatment criteria achieved an overall response at Week 26. Data from this cohort was used to inform the DoR curves). Results for this post-hoc analysis were described in Table 6.

6.42 The key components of the economic model are presented in Table 11. This economic evaluation has not been previously considered by the PBAC.

Table 11: Summary of model structure, key inputs, and rationale

Component	Summary
Treatments	Osilodrostat vs placebo. A sensitivity analysis that included metyrapone and ketoconazole as subsequent therapies for patients who do not respond was included.
Time horizon	50 years in the model base case vs 15 months in the trial (ORR at 26 weeks followed by DoR up to 15 months)
Outcomes	ORR at 26 weeks, LYG, and QALYs gained
Methods used to generate results	Microsimulation of 5,000 iterations
Health states	Responders (mUFC≤ULN or ≥50% improvement in mUFC from baseline), non-responder, and dead
Cycle length	3 months
Transition probabilities	<p>ORR at 26 weeks based on week 26 results from LINC 4 post hoc analysis</p> <ul style="list-style-type: none"> • 86.67% for osilodrostat • 17.65% for placebo. <p>DoR (time to escape data from LINC 4 post-hoc analysis) informed by KM estimates up to 15 months then a log normal distribution was fitted to 50-years.</p> <p>OS was informed by Ragnarsson 2019. A SMR of 1.9 for responders and 6.9 for non-responders was applied to the general population mortality in Australia.</p> <p>Grade≥3 AE incidences in the initial titration period of 12 weeks in LINC 4 were used to inform AEs. (events per patient in cycle 1: osilodrostat = 0.23 (10/43) and placebo= 0.24 (4/17) and incidence of AEs in subsequent cycles (cycle probability=0.0399)</p>
Extrapolation method	<p>Parametric models (exponential, Weibull, Gompertz, log normal, and log logistic) were fitted to the DoR data in the osilodrostat arm and the log normal was selected in the base case. This selection was primarily based on external validation against the DoR curves from LINC 3. The DoR extrapolation for placebo was assumed the same.</p> <p>Osilodrostat arm, 91% of total QALYs (93% and 98% of responder and non-responder QALYs) and 74% of total costs occurred in the extrapolated period.</p> <p>Placebo arm, 90% of total QALYs (70% and 93% of responder and non-responder QALYs) and 90% of total costs occurred in the extrapolated period.</p>
Health related quality of life	<p>Informed by the EQ-5D-5L utility values from the LINC 4 post-hoc analysis.</p> <p><u>Responders:</u> Baseline responders = 0.713 Change from baseline in initial 12 weeks = +0.012 Change from baseline in after 12 weeks = +0.086</p> <p><u>Non-responders:</u></p>

Component	Summary
	Baseline non-responders = 0.658 Change from baseline in initial 12 weeks = -0.065
Healthcare resource use and costs	<u>Drug costs</u> Osilodrostat: 1 mg = eff. \$ [REDACTED] and 5 mg = eff. \$ [REDACTED] Placebo: nil cost Average doses in the initial (responders and non-responders) and continuing treatment periods were based on patients in the LINC 4 post-hoc analysis. <u>Routine disease monitoring (ongoing on treatment)</u> HCP: responders = \$62.58 per cycle; non-responders = \$219.40 per cycle Investigation–scans: responders = \$131.10 per cycle; non-responders=\$262.20 per cycle Investigation–tests: responders = \$118.08 per cycle; non-responders = \$305.60 per cycle <u>Routine disease monitoring – osilodrostat dose titration (only incurred in the first cycle)</u> Endocrinologist visits = \$545.68 per cycle Investigational tests (ACTH, 24hr UFC, serum cortisol, testosterone, estrogen IGF-1) = \$1,083.55 per cycle <u>AE management costs</u> Weighted average cost for various AEs according to number of separations and the DRG costs

Source: Table 3.1-2 of the resubmission

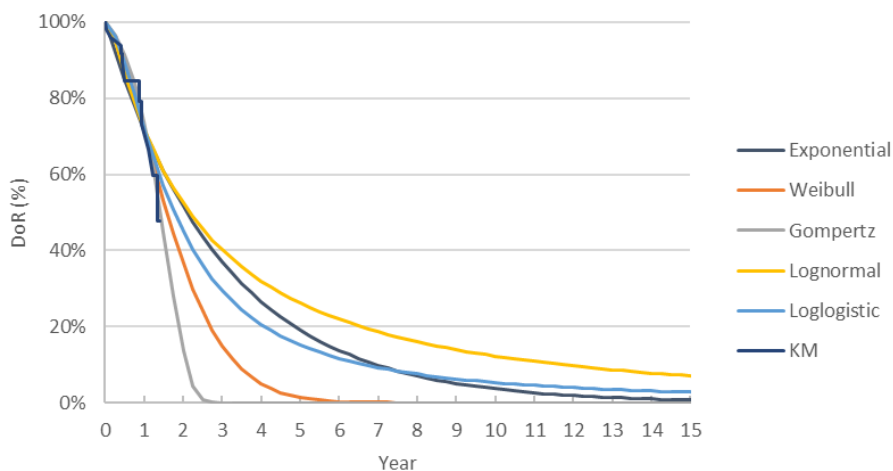
AE = adverse events; ACTH = adrenocorticotrophic hormone; DoR = duration of response; DRG = diagnosis-related group; HCP = healthcare practitioners; ICER = incremental cost-effectiveness ratio; IGF-1 = insulin growth factor-1; KM = Kaplan-Meier; mUFC = mean urinary free cortisol; ORR = overall response rate; OS = overall survival; QALYs = quality adjusted life years; SMR = standardised mortality ratio; ULN = upper limit of normal

- 6.43 Patients entered the model as either a responder or non-responder to osilodrostat or placebo based on ORR at week 26 in the LINC 4 post-hoc analysis. After week 26 (cycle 2), the likelihood of a responder becoming a non-responder was informed by the DoR curves from the LINC 4 post hoc analysis, extrapolated over the full 50-year time horizon. Survival was based on the Australian life tables (adjusted for age and gender) with a SMR for responders and non-responders applied as adjustments. According to these transitions, responders will either remain a responder, transition to a non-responder, or die. Non-responders either remain a non-responder or die. Medical treatment costs are incurred every cycle for responders (reflects ongoing treatment) and for only two cycles in non-responders who survive (reflects the continuing treatment criteria).
- 6.44 The resubmission adopted a microsimulation approach with 5,000 simulations. The resubmission acknowledged the use of a Markov model for the base case analysis but stated that a microsimulation model would better handle the sensitivity analysis that included patients who receive ketoconazole or metyrapone as subsequent therapies after failing osilodrostat or placebo. However, it was unclear if there were sufficient patients who would receive either ketoconazole or metyrapone in Australia to justify the microsimulation approach. In addition, there were limitations in the LINC 4 trial (e.g., small sample sizes and lack of data to inform time-varying covariates) which may have limited its value in informing a microsimulation model. This was acknowledged by the resubmission noting that data to inform the time-varying covariates (e.g., demographics, disease characteristics, prior treatments etc.) was not available to inform the risk of events occurring. Therefore, a complex modelling method such as a microsimulation model may not be appropriate, and a Markov model may be more reasonable. The PSCR argued that a microsimulation model was chosen as it was

better suited for tracking the number of subsequent treatments, as in the case of sensitivity analyses where patients were modelled to receive subsequent treatments with metyrapone and ketoconazole. The PSCR further argued that although the microsimulation was developed to better capture the long-term impact of improved cortisol levels on QoL and survival, it was done using assumptions that did not favour osilodrostat, resulting in an overestimated base case ICER. The ESC acknowledged that the microsimulation model could accommodate subsequent treatments better, however, the small sample size of the input data and the rarity of the condition rendered it less suitable compared to the Markov model.

- 6.45 The ORR for osilodrostat at week 26 (86.67%) reflected the ORR of all patients after they received 26 weeks of osilodrostat (i.e., included the placebo patients who switched to osilodrostat OL at Week 12, with their response at week 38 being reported as week 26 results). Comparatively, the resubmission assumed the Week 26 ORR for placebo was equal to the week 12 ORR (17.65%) since this was the placebo-controlled period (and all patients crossed over to osilodrostat after week 12).
- 6.46 Using the osilodrostat ORR estimate that included patients who switched from placebo while assuming the placebo arm stayed the same as the ORR in week 12 favoured osilodrostat. The ORR at week 12 for patients who had a baseline mUFC > 1.3xULN and were randomised to osilodrostat was 78.57% (33/42) and 17.65% (3/17) in those randomised to placebo. Using the week 12 placebo-controlled period of LINC 4 ORR results led to a 1% increase in the incremental cost-effectiveness ratio (ICER).
- 6.47 The resubmission additionally conducted a sensitivity analysis using results from LINC 3 to inform the response rate of osilodrostat. This increased the ICER by 1%, indicating that the model was sensitive to changes around the response rate as well as highlighting the uncertainty regarding the source of data.
- 6.48 The resubmission used the DoR Kaplan Meier (KM) data for Week 26 responders up to 15 months (1.25 years; ~20% of patients were at risk) and then fitted the log normal parametric model to extrapolate DoR to 50 years (Figure 3). The DoR for placebo was reasonably assumed to be the same as osilodrostat. It was unclear why the gamma or generalised gamma functions were not tested in the extrapolation.

Figure 3: Extrapolations of DoR for osilodrostat



Source: Figure 3.4-2 of the resubmission
DoR = duration of response

- 6.49 According to the Akaike information criterion (AIC) and Bayesian information criterion (BIC) values, the Gompertz distribution was regarded the best fitting distribution followed by the Weibull function. These distributions indicated that the DoR would reach zero (i.e., all patients are no longer responding to treatment) after approximately 2.5 years for the Gompertz and five years for the Weibull.
- 6.50 However, the resubmission selected the log normal function in the base case as it was the best fitting curve against the DoR in LINC 3 post-hoc analysis with the exponential and log logistic being other plausible distributions. The evaluation considered that resubmissions' approach may not be reasonable. If LINC 3 was to be the basis for the DoR, then the LINC 3 data should have informed the extrapolation. Comparisons of the parametric distributions of the LINC 4 extrapolations against LINC 3 were not presented for further assessment. Notably, the log normal distribution was the most optimistic function despite it being the lowest ranking according to AIC and BIC values among the tested functions. The PSCR argued that the log normal function together with the loglogistic and exponential distributions provided the most clinically plausible long-term duration of response, as some patients may receive treatment with osilodrostat for a prolonged period (modelled mean DoR: 4.35 years; duration of treatment: 4.62 years) as previously noted by the PBAC. The ESC noted the justification on the selection of log normal function but considered it was not appropriate to ignore the visually better fitting function, with the lowest AIC and BIC values. However, the ESC noted that the ICER was not overly sensitive to the use of the log logistic and exponential distributions (<1% increase in the ICER), and that the extrapolation function had a relatively minor impact on the economic analysis.
- 6.51 The log normal extrapolation, which was the most optimistic of all the extrapolations, generated a mean treatment duration 4.62 years over a 50-year time horizon. As noted by the resubmission, most of the modelled cohort were in the non-responder health state after around 10 years and given the occupancy of responder vs non-

responder health states drove the incremental difference between treatment, this would suggest that any incremental benefit between osilodrostat and placebo were accrued within the initial 10 years after which there would be minimal to no incremental difference (i.e., both osilodrostat and placebo patients occupied the non-responder health state for the remaining ~40 years).

- 6.52 The PBAC had considered that it was highly likely that responding patients would continue treatment beyond three years (paragraph 7.11, osilodrostat, PSD, March 2023 PBAC meeting) and it would be appropriate to expect lifelong treatment (paragraph 7.12, osilodrostat, PSD, March 2023 PBAC meeting). Therefore, the model did not adequately capture the full extent of the cost and benefit of osilodrostat. It was suspected that DoR was a key driver of the model, however reflecting what would reasonably occur in clinical practice was constrained by the limited available long-term evidence. Alternatively informing DoR using LINC 3 (to which the resubmission considered to be a valid dataset to inform DoR) may be more informative given its longer follow, however this was not possible based on the evidence provided in the resubmission.
- 6.53 Instead, a ‘best case’ scenario analysis was performed during the evaluation that assumed a 100% response rate in the osilodrostat arm that was maintained over the entire model time horizon (i.e., 100% DoR) while maintaining the base case placebo assumptions. This scenario reported an increased incremental benefit by seven-fold (0.54 in the base case to 3.90 incremental QALYs gained) and led to a 100% decrease in the base case ICER (\$155,000 to < \$255,000 per QALY gained). However, the ICER still remained substantially high.
- 6.54 Though there was no mortality benefit for osilodrostat demonstrated in LINC 3 and LINC 4, the submission assumed that there was a difference in mortality based on response which implied that there was a survival benefit associated with osilodrostat.
- 6.55 The resubmission estimated OS by applying SMR for responders and non-responders to the gender- and age-specific mortality rate of the Australian general population. The base case SMR was informed by Ragnarsson 2019 (responders = 1.9, 95% CI 1.5, 2.3; non-responders = 6.9, 95% CI 4.3, 10.4) and a sensitivity analysis was informed by Graversen 2012 (responders = 1.2, 95% CI 0.5, 3; non-responders = 3.7, 95% CI 2.3, 6). Ragnarsson 2019 included 502 patients (77% females), of whom 419 (83%) were confirmed to be in remission after receiving treatment with pituitary surgery, pituitary radiotherapy, bilateral adrenalectomy, or medical therapy. The mean age at diagnosis was 43 years, which was similar to LINC 4 (mean age 41.2 years). An alternative study, Graversen 2012, was proposed by the resubmission. Graversen 2012 was a meta-analysis of seven mortality studies in patients with CD or CS secondary to benign adrenal adenoma after patients received treatment with surgery or irradiation.
- 6.56 The resubmission considered Ragnarsson 2019 was a more applicable study given it was not limited to remission from only surgery or irradiation. This may not be reasonable unless it was expected that different treatments that led to remission

would lead to different mortality, for example this would imply a patient who achieved remission via surgery would have different mortality compared to a patient who achieved remission via medical therapy. This was not justified in the resubmission nor was it evident in Ragnarsson 2019. The ICER was moderately sensitive to changes in the non-responder SMR, where applying the SMR lower (4.3) and upper (10.4) 95% CI from Ragnarsson 2019 led to a 1% increase and 1% decrease in the ICER, respectively. Given the majority of time spent in the model was in the non-responder health state, changes to survival in this health state were expectedly more pronounced compared to the responder health state. Widening the survival difference between responders and non-responders made the ICER more favourable to osilodrostat, which was reasonable given more patients in the placebo arm occupied the non-responder health state. The ESC noted the evidence from Mondin (2023) showed patients in biochemical remission had lower standardised mortality ratios (SMR) (SMR=1.66, 95% CI 0.34, 4.85) compared to patients with active disease (SMR=4.99, 95% CI 2.15, 9.83).

- 6.57 The resubmission assumed a fixed number of AEs Grade ≥ 3 in the first cycle based on treatment with osilodrostat at week 12, then estimated a cycle probability of experiencing an AE based on the incidence of AEs in the overall study period of LINC 4 post-hoc analysis. Given the small sample size and relatively short duration of follow up in LINC 4 (compared to the 50-year time horizon) the rates for AE used in the model should be considered uncertain.
- 6.58 The utility values applied in the model were based on the EQ-5D-5L data from patients randomised to osilodrostat (n=42) who had a baseline mUFC > 1.3 ULN from the LINC 4 post-hoc analysis (see Table 6). The same utilities were applied regardless of treatment received. The resubmission stated that week 12 was selected for the change from baseline analysis because this represented the end of the dose titration period in LINC 4 and thus captures the impact of any AEs that may have occurred in that time.
- 6.59 As discussed in paragraphs 6.17 to 6.20, the post-hoc analysis of the EQ-5D-5L utility scores of responders and non-responders should be interpreted with caution. The resubmission suggested that the baseline health related QoL of responders was better than non-responders according to differences in EQ-5D-5L utility scores at baseline. However, the application of a differential baseline utility was not justified, and the difference may have been due to the small sample size in the post hoc subgroup analysis. The PSCR asserted the difference in the baseline utility was attributed to responders' more optimistic outlook on life, higher compliance, enhanced well-being, and increased motivation, justifying the use in the economic model. The ESC did accept this argument and considered that differential baseline values was inappropriate. It was noted the ICER was sensitive to the difference at baseline, that it was confounded by the small study sample, and therefore it was not appropriate to have applied these values to the economic model.
- 6.60 It would be more appropriate that patients begin with the same baseline utility. As such, informing the utility scores of all patients at baseline using a weighted value by

number of responders and non-responders may be a more reasonable approach. Alternatively, the baseline utility from the FAS in LINC 4 could be used.

- 6.61 The ICER was sensitive to the assumption that baseline utilities were equal between responders and non-responders, and the subsequent changes to the baseline utility value (leaving the change from baseline unchanged for responder and non-responder). From the LINC 4 FAS population, a baseline utility of 0.851 led to a 1% increase in the ICER. Alternatively, the weighted average baseline utility of responders and non-responders from the LINC 4 post-hoc analysis, resulted in a baseline value of 0.708⁶ and increased the ICER by 1%.
- 6.62 The ICER was also sensitive to varying the 'Change after Week 12' utility value in responders. Applying the upper (0.146) and lower (0.026) 95% CIs led to a 1% decrease to 1% increase in the ICER, respectively. The ICER was not sensitive to varying the 'Changes in the initial 12 week' utility values given this was applied only for a short time period.
- 6.63 The model assumed the mean doses of osilodrostat from the post hoc LINC 4 analysis would apply in the model. A mean dose of 7.53mg and 7.99 mg per day was applied in the initiating period for responders and non-responders, respectively. Continuing responders were assumed to use a mean dose of 9.65mg per day. In Appendix 18 to the resubmission, the daily average doses (for days exposed to osilodrostat) for 26-week responders and non-responders were 7.71 mg/day and 8.09 mg/day, respectively.
- 6.64 The resubmission acknowledged that not all possible distributions of drug doses were considered but did not expect this to have a significant impact on the overall results. This was not reasonable, as the choice of a microsimulation model would have allowed different dosages to have been tested. The usage of a static mean dose for osilodrostat, which requires titration, in a microsimulation model was underutilising the advantages of the modelling method.
- 6.65 Further, the increase from a 12-week initiation (in LINC 4) to a six-month initiation period (in the model) would likely result in a higher dose of osilodrostat use in the non-responders, given that patients will have more time to increase their dose, which they will be incentivised to do as they are not achieving response. Using the 12-week dose titration period from LINC 4 to inform a 26-week titration period likely underestimated the dose of osilodrostat received by non-responders, which favours osilodrostat.
- 6.66 The resubmission assumed patients required regular follow-up visits with endocrinologists and general practitioners and various tests and investigations. The resubmission assumed the non-responders incurred a higher frequency of these visits and tests compared to responder patients and were not assumed to differ between treatment arms (based on clinician advice). The resubmission stated that osilodrostat

⁶ Weighted average baseline utility (LINC 4 post-hoc analysis) calculation: $35/42 \times 0.713 + 7/42 \times 0.658 = 0.70833$

dose titration costs were applied once off in the first cycle and to avoid double counting, the cost per cycle of endocrinologist visits and mUFC assessments as part of routine monitoring were removed. The net cost of healthcare professional visits and investigational tests in the first cycle were \$503.70 and \$1,000.20, respectively.

6.67 The resubmission stated that the average cost of all AEs in the initial 12 weeks was applied in the first cycle to each treatment arm and in subsequent cycles were applied only when the AE occurred. However, the model only applied AE management costs in the first cycle, and not in subsequent cycles. This is likely underestimated AE costs, though the AE management costs had a negligible contribution to overall incremental costs.

6.68 The key drivers of the economic model are summarised in Table 12.

Table 12: Key drivers of the model

Description	Method/Value	Impact Base case \$ ¹ /QALY gained
Trial source data	The resubmission included a sensitivity analysis that informed the trial data using LINC 3. However, it was unclear what parameters were changed exactly, though it appeared that the inputs pertaining to the eligible patient criteria (baseline mUFC ≥ 1.3xULN, response definition (ORR), and timepoint (Week 26)) were changed to reflect LINC 3. This could not be independently verified.	High. Using LINC 4 data favoured osilodrostat. Using LINC 3 data increased the ICER by █████%
Baseline utilities	The base case assumed differential baseline utilities for responders (0.713) and non-responders (0.658).	High. Assuming differential responder and non-responder baseline utilities favoured osilodrostat. Using the same baseline values for responders and non-responders based on a weighted average (0.708) increased the ICER by █████%, while using the FAS LINC 4 baseline value (0.851) increased the ICER by █████%.
Utility values	Point estimate from 'Change from baseline after week 12' utility value based on post-hoc LINC 4 analysis used in base case (0.086, 95% CI 0.026, 0.146).	High. Using the lower and upper 95% CI of the 'change from baseline after week 12' utility changed the ICER by █████% and - █████%, respectively.
Mortality in non-responder	Ragnarsson 2019 reported the SMR in patients who were not in remission was 6.9 (95% CI 4.3, 10.4)	Moderately high. Using the lower and upper 95% CI changed the ICER by - █████% and █████%, respectively.

Source: Table 3.10-1 of the resubmission; tested during the evaluation using the economic model

CI = confidence interval; DoR = duration of response; FAS = full analysis set; mUFC = mean urinary free cortisol; ICER = incremental cost-effectiveness ratio; ORR = overall response rate; ULN = upper limit of normal; QALY = quality adjusted life years; SMR = standardised mortality ratio

The redacted values correspond to the following ranges:

¹ \$355,000 to < \$455,000

6.69 The stepped results of the economic evaluation are presented in Table 13.

Table 13: Results of the stepped economic evaluation

Step and component	Proposed medicine	Comparator	Increment
Step 1: trial-based analysis (ORR at 26 weeks)			
Costs	\$█	\$0	\$█
ORR	86.66%	17.66%	69.00%
Incremental cost/additional overall response gained			\$█ ¹ /Responder
Step 2: Step 1 + transformed to LY and extrapolated time horizon to 50 years			
Costs	\$█	\$0	\$█
LYG	14.46	14.21	0.24
Incremental cost/extra LYG gained			\$█ ² /LYG
Step 3: Step 2 + including all resource use			
Costs	\$█	\$44,458	\$█
LYG	14.46	14.21	0.24
Incremental cost/extra LYG gained			\$█ ³ /LYG
Step 4: Step 3 + transformed to QALYs			
Costs	\$█	\$44,458	\$█
LYG	9.97	9.43	0.54
Incremental cost/extra QALY gained (base case)			\$█ ⁴ /QALY
Previous consideration (March 2023) based on week 12 trial-based evaluation			
Costs	\$█	\$0	\$█
Complete response	77.1%	8.0%	69.1%
Incremental cost/additional complete responder			\$█ ⁵ /Complete responder

Source: Table 3.8-1 of the resubmission; Table 16, osilodrostat, PSD, March 2023 PBAC meeting

ICER = incremental cost effectiveness ratio; Resp = responder; LYG = life years gained; ORR = overall response rate; QALY = quality adjusted life year gained

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$855,000 to < \$955,000

³ \$755,000 to < \$855,000

⁴ \$355,000 to < \$455,000

⁵ \$25,000 to < \$35,000

6.70 The disaggregated costs and outcomes are presented in Table 14.

Table 14: Disaggregated costs and outcomes (discounted and half-cycle corrected)

	Osilodrostat	Placebo	Increment	% of total incremental
Cost				
Drug cost	\$█	\$0	\$█	█
HCP visits	\$10,877	\$12,060	-\$1,184	
Investigations – Scans	\$13,446	\$14,562	-\$1,116	
Investigations – Tests	\$15,711	\$16,880	-\$1,170	
Adverse events	\$767	\$955	-\$188	
Total cost	\$█	\$44,458	\$█	
LYG^a				
Responders	3.37	0.68	2.69	1109%
Non-responders	11.13	13.58	-2.45	-1009%
Total LYG	14.49	14.25	0.24	100%
QALYs gained				
Responders	2.61	0.53	2.08	386.7%
Non-responders	7.36	8.90	-1.54	-286.7%
Total QALYs	9.97	9.43	0.54	100.0%

Source: Tables 3.9-1 and 3.9-2, of the resubmission

HCP = healthcare professional; LYG = life years gained; QALY = quality adjusted life year gained

^a Added during the evaluation

- 6.71 Over a 50-year time horizon, the base case ICER was \$355,000 to < \$455,000 per QALY gained, with the incremental life years (LYs; 0.24) and QALYs (0.54) being relatively small when considering the large difference in ORR. The small magnitude of incremental benefit may not be unexpected given the trials did not support a survival difference between osilodrostat and placebo nor did they adequately capture potential quality of life gains from durable cortisol control. Further, the estimated mean DoR in the model was only 3.37 years (4.62 years undiscounted) in the osilodrostat arm, with an incremental difference of 2.69 years (3.47 years undiscounted) between arms.
- 6.72 Osilodrostat drug costs were the primary driver of incremental costs (█% of total osilodrostat costs and █% of total incremental costs). The majority of the LYs and QALYs accrued in both treatment arms were in the non-responder health state, which suggested that over the 50-year time horizon, the majority of patients were no longer responding to osilodrostat.
- 6.73 The results of key sensitivity analyses conducted by the resubmission and during the evaluation are summarised in Table 15.

Table 15: Key sensitivity analyses

	Cost			Outcomes			ICER (\$/QALY)	% Δ
	Osi(\$)	Placebo	Inc. (\$)	Osi	Placebo	Inc.		
Base case		\$44,458		9.97	9.43	0.54	\$ ¹	-
Trial source data [mUFC≥1.3xULN, ORR, Week 26]								
LINC 3		\$43,693		8.04	7.56	0.48	\$ ²	%
LINC 3&LINC 4 Pooled		\$43,724		9.08	8.48	0.60	\$ ¹	%
DoR parametric distributions								
Exponential		\$44,638		9.79	9.39	0.41	\$ ¹	%
Loglogistic		\$44,666		9.79	9.40	0.39	\$ ¹	%
Other								
Incl. subsequent therapies		\$102,425		11.00	10.57	0.43	\$ ²	%
Discount 0%		\$85,916		19.05	18.20	0.85	\$ ³	- %
Discount 3.5%		\$52,496		11.73	11.13	0.60	\$ ¹	- %
Sensitivity analysis conducted during the evaluation								
SMR non-responder (base case = 6.9)								
95% LCI = 4.3		\$47,751		10.60	10.12	0.48	\$ ¹	%
95% UCI = 10.4		\$41,084		9.38	8.72	0.65	\$ ³	- %
Base utility value (base case: responders = 0.713; non-responders = 0.658)								
0.851 (FAS LINC 4) for both groups		\$44,458		12.57	12.13	0.44	\$ ²	%
0.708 (Weighted average baseline utility)		\$44,458		10.51	10.10	0.41	\$ ²	%
Change from baseline after 12 weeks utilities in responders (base case: responders = 0.086)								
95% LCI = 0.026		\$44,458		9.78	9.39	0.39	\$ ²	%
95% UCI = 0.146		\$44,458		10.16	9.47	0.69	\$ ³	- %
'Best case' scenario analysis assumed 100% response and 100% DoR in the osilodrostat arm								
'Best case' scenario		\$44,458		13.33	9.43	3.90	\$ ⁴	- %

Source: Table 3.10-1 of the resubmission

CR = complete response; DoR = duration of response; FAS = full analysis set; ICER = incremental cost effectiveness ratio; Inc = incremental; LCI = lower confidence interval; Osi = osilodrostat; PR = partial response; QALY = quality adjusted life year gained; UCI = upper confidence interval; ULN = upper limit of normal

The redacted values correspond to the following ranges:

¹ \$355,000 to < \$455,000

² \$455,000 to < \$555,000

³ \$255,000 to < \$355,000

⁴ \$155,000 to < \$255,000

6.74 Overall, despite the resubmission’s attempt to demonstrate long term benefits of osilodrostat, the inputs informing the model, particularly survival and QoL, remained uncertain and the base case ICER was high and unlikely to adequately represent the cost-effectiveness of osilodrostat.

6.75 The resubmission also included metyrapone and ketoconazole as subsequent therapies for a sensitivity analysis (cost for both \$930 per month based on clinician advice). This scenario led to an increase in the ICER by |%.

Drug cost per patient per year

6.76 The drug cost per patient per year (responders and non-responders) is presented in Table 16. For the initial year of treatment (including dose titration) the cost for responders was estimated to be \$|. Ongoing annual cost would then be \$|.

Table 16: Drug cost per patient for osilodrostat (undiscounted, half-cycle corrected for model)

	LINC 4 (post-hoc analysis)	Economic model	Financial estimates
Mean dose			
Initial treatment period – responders	7.53 mg/day	7.53 mg/day	7.53 mg/day
Initial treatment period – non- responders	7.99 mg/day	7.99 mg/day	7.99 mg/day
Continuing treatment period – responders	9.65 mg/day	9.65 mg/day	9.65 mg/day
Mean treatment duration ^a			
Initial treatment period – responders	81.1 weeks ^c	25.99 weeks ^b	25.99 weeks
Initial treatment period – non- responders			
Continuing treatment period – responders		214.41 weeks	22.06 weeks in 1 st continuing cycle, then 52 weeks thereafter
Cost per patient in each treatment period (or total treatment period for continuing patients) ^d			
Initial treatment period – responders	NR		
Initial treatment period – non- responders			
Continuing treatment period – responders			
Cost per patient per year (responder and non-responder)			
Responders (initial + continuing) Year 1	NR	e	e
Responders (continuing) Year 2+		f	f
Non-responders (initial only) Year 1 only		g	g
Previous consideration (March 2023)	LINC 4 FAS	Trial-based evaluation	Financial estimates
Mean dose	8.79 mg/day	8.79 mg/day	8.79 mg/day
Mean duration	81.1 weeks	1 year	1 year
Cost per patient per year	NR	\$ ^h	\$ ⁱ (N = 68 continuing patients only)

Source: Isturisa (osilodrostat) – endogenous CS – CEA.xlsx – ‘Resource use’ and ‘Figures’ worksheets; Appendix 18 – Average dose- LINC 3 LINC 4 LINC 3&4, ‘First assessment (C2302)’ and ‘Later assessments (C2302)’ worksheets; Table 18, osilodrostat, PSD, March 2023 PBAC meeting

FAS = full analysis set; N = number of patients; NR = not reported

^a Derived from the duration of treatment data from “Figures” worksheet of the economic model

^b Treatment duration in the initial period for responders and non-responders assumed the same (i.e., both responders and non-responders trialed the initial treatment period)

^c Mean duration of LINC 4 post-hoc analysis for each period was not reported, hence the mean duration of LINC 4 (FAS population) in the overall study period was reported instead

^d Total cost per treatment period for responder or non-responder was calculated by respectively multiplying the mean duration by the cost of each treatment period. The cost per cycles were converted to weeks by dividing by 13.02 weeks (3 months × 4.34 weeks) and were based on effective prices for osilodrostat:

Initial treatment period – responders = \$ per cycle = \$ per week

Initial treatment period – non-responders = \$ per cycle = \$ per week

Continuing treatment period – responders = \$ per cycle = \$ per week

^e Year 1 cost for eventual responders = cost during initial treatment period (\$) + cost of continuing treatment in 1st subsequent cycle (\$ over a mean duration 22.06 weeks)

^f Year 2+ cost for eventual responders = continuing treatment period cost per week (\$) × 52 weeks

^g Non-responders incurred costs only in the first 26 weeks of treatment as they were not eligible for continuing treatment, therefore the cost is \$ for completing initial treatment as a non-responder

^h Based on the average annual cost for each dose used and the proportion using each dose in LINC 4 for all patients.

Note: the resubmission assumed the drug costs and initial duration of treatment in the financials were assumed the same as the model

Estimated PBS usage & financial implications

6.77 This resubmission was not considered by the DUSC. The March 2023 submission was considered by the DUSC.

6.78 The resubmission adopted an epidemiological approach to estimate the financial impact of osilodrostat. The approach taken to estimate the eligible patient population was the same as the previous submission.

6.79 A summary of the key data sources and parameter values are presented in Table 17.

Table 17: Key inputs for financial estimates

Data	Value and Source	Comment
Eligible population		
Prevalence and incidence of endogenous CS	Prevalence = 67 per million persons Incidence = 2.2 per million persons The resubmission selected four studies from a search of published literature which reported prevalence and/or incidence rates of CS (Bolland 2011; Lindholm 2001; Orphanet 2022; Wengander 2019).	The DUSC considered the prevalence and incidence estimates reasonable, however there might be an underestimation of the incident population. The Bolland 2011 study prevalence period of 45 years is possibly too long for a prevalence estimate. The DUSC noted that the previous submission used a higher end average. (Table 19, osilodrostat, March 2023 PBAC meeting)
Distribution of CS sub-populations	Cushing's Disease (CD) = 70% Other ACTH dependent = 10% ACTH independent = 20% Australian clinicians estimate that endogenous CS is due to CD in 70% of patients, ACTH-dependent ectopic tumours in 10% of patients and ACTH-independent tumours in 20%. Not all clinician surveys reported these values, as the third survey estimated that endogenous CS was due to CD in 45% of patients, ACTH-dependent in 5% and ACTH-independent in 50% of patients.	The DUSC commented that the distribution of CS sub-populations was reasonable. The DUSC noted that several published estimates in the international literature better inform CS epidemiology, but in the specific case of CS sub-populations, expert estimates were reasonable (Table 19, osilodrostat, March 2023 PBAC meeting).

Data	Value and Source	Comment																																								
<p>Total eligible patients</p>	<p>The proportions eligible for surgery and the surgery success rates were sourced from the clinician questionnaires and Palen-Tytko 2020 (single centre study of 24 patients in Poland)</p>	<p>The DUSC considered surgical eligibility and success might be informed by reports in the literature⁷, with many estimates of surgical success substantially higher than those utilised by the submission, which would lead to substantial underestimation. Lower surgical success rates, particularly outside of specialised centres, can be a substantive source of uncertainty in the utilisation and financial estimates, (Table 19, osilodrostat, March 2023 PBAC meeting).</p> <p>The DUSC noted the possibility of leakage to patients before and during radiotherapy and surgery might result in the estimates from the previous submission being underestimated (Table 19, osilodrostat, March 2023 PBAC meeting).</p>																																								
	<table border="1"> <thead> <tr> <th></th> <th>Ineligible for surgery</th> <th>Unsuccessful first surgery</th> <th>Unsuccessful second surgery</th> </tr> </thead> <tbody> <tr> <td>Cushing's disease</td> <td>2%</td> <td>40%^a</td> <td>50%</td> </tr> <tr> <td>ACTH-dependent</td> <td>50%</td> <td>17%</td> <td>-</td> </tr> <tr> <td>ACTH-independent</td> <td>5%</td> <td>5%</td> <td>-</td> </tr> </tbody> </table>			Ineligible for surgery	Unsuccessful first surgery	Unsuccessful second surgery	Cushing's disease	2%	40% ^a	50%	ACTH-dependent	50%	17%	-	ACTH-independent	5%	5%	-																								
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Eligible patients	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Yr 6																																				
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<p>Source: Table 4.3-1 of the resubmission Yr = year a The total eligible patients in Year 4 = █² = █², however, when rounded up the eligible patients = █² = █²</p>																																										
<p>Uptake rate</p>	<p>Based on the number of patients that are currently enrolled in the patient access program and the conservative approach to adopting new medicines by endocrinologist.</p>	<p>Uptake has increased from █% in Year 1 in the previous submission to █% in Year 1 in the prevalent population and from █% to █% in Year 2 onward in the incident population.</p> <p>The DUSC considered that █% uptake in Year 1 was an underestimate and recommended that an initial uptake rate of 60% would be more appropriate (Table 19, osilodrostat, March 2023 PBAC meeting).</p>																																								
	<table border="1"> <thead> <tr> <th></th> <th>Yr 1</th> <th>Yr 2</th> <th>Yr 3</th> <th>Yr 4</th> <th>Yr 5</th> <th>Yr 6</th> </tr> </thead> <tbody> <tr> <td>Prevalent population cumulative uptake (%)</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> </tr> <tr> <td>Incidence population annual uptake (%)</td> <td>-</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> </tr> </tbody> </table> <p>Source: Sponsor estimates</p> <p>Grandfathered patients: From the sponsor's managed access program, the resubmission estimated 16 patients will require grandfathering, and this estimate would be updated as part of the pre-PBAC response. All grandfathered patients were assumed to be incorporated in the estimated prevalent population.</p>			Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Yr 6	Prevalent population cumulative uptake (%)	█	█	█	█	█	█	Incidence population annual uptake (%)	-	█	█	█	█	█																			
	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Yr 6																																				
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⁷ <https://doi.org/10.3171/2008.8.jns08339> and <https://doi.org/10.1056/nejm198301133080216>

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Data	Value and Source	Comment																														
Dosage of osilodrostat	<p>Average doses were based on patients from the LINC 4 post-hoc analysis: Initiating period – responders = 7.53 mg/day Initiating period – non-responders = 7.99 mg/day Continuing period – responders = 9.65 mg/day</p> <p>In Appendix 18 to the resubmission, the average daily doses (for days exposed to osilodrostat) for 26-week responders and non-responders were 7.71 mg/day and 8.09 mg/day, respectively.</p>	<p>As discussed in paragraph 6.65, the dose of osilodrostat for non-response in the initial treatment period was potentially underestimated due to a longer initiation period.</p> <p>The DUSC also noted that wastage was possible, with up titration using tablets of varying strengths and waste due to missed or lost tablets were not considered (Table 19, osilodrostat, March 2023 PBAC meeting)</p>																														
Treatment duration	<p>Treatment duration was informed by the duration of response from the economic model (mean 240.4 weeks/ 4.62 years) and the resubmission estimated the persistence rate each year based on the proportion of patients remaining on treatment in the economic model.</p> <table border="1" data-bbox="389 913 999 1205"> <thead> <tr> <th>Treatment period</th> <th>% on treatment</th> <th>Duration (weeks)</th> </tr> </thead> <tbody> <tr> <td>Year 1</td> <td>-</td> <td>-</td> </tr> <tr> <td>Initiating treatment</td> <td>100.0%</td> <td>25.99</td> </tr> <tr> <td>Continuing treatment</td> <td>84.8%</td> <td>22.06</td> </tr> <tr> <td>Year</td> <td>% on treatment</td> <td>Persistence rate (%)</td> </tr> <tr> <td>Year 2</td> <td>67.0%</td> <td>79.0%</td> </tr> <tr> <td>Year 3</td> <td>47.8%</td> <td>71.3%</td> </tr> <tr> <td>Year 4</td> <td>36.3%</td> <td>76.1%</td> </tr> <tr> <td>Year 5</td> <td>28.2%</td> <td>78.3%</td> </tr> <tr> <td>Year 6</td> <td>23.2%</td> <td>81.4%</td> </tr> </tbody> </table> <p>Source: 'Figures' worksheet from the economic model Note: persistence rate based on previous year</p>	Treatment period	% on treatment	Duration (weeks)	Year 1	-	-	Initiating treatment	100.0%	25.99	Continuing treatment	84.8%	22.06	Year	% on treatment	Persistence rate (%)	Year 2	67.0%	79.0%	Year 3	47.8%	71.3%	Year 4	36.3%	76.1%	Year 5	28.2%	78.3%	Year 6	23.2%	81.4%	<p>The DUSC previously considered treatment duration (169.5 weeks/3.25 years) was underestimated in the prevalent population with some people potentially needing longer or lifetime treatment (Table 19, osilodrostat, March 2023 PBAC meeting). The resubmission applied a persistence rate based on the economic model that extended the duration of use beyond ~3 years as compared to the previous submission. The PBAC previously “considered ongoing use for all responding patients would be more appropriate for what is expected to be lifelong treatment. Some discontinuation that aligns with a future economic evaluation may be considered, but only 50% continuation beyond year 3, ... was not reasonable” (paragraph 7.12, osilodrostat, PSD, March 2023 PBAC meeting). As such, the mean treatment duration of 4.62 years in the model may also be underestimated.</p>
Treatment period	% on treatment	Duration (weeks)																														
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Year 6	23.2%	81.4%																														
Costs																																
Cost of medicines	<p>1 mg tablet, 60 pack = \$2,400 published and \$ [redacted] effective 5 mg tablet, 60 pack = \$9,660 published and \$ [redacted] effective Nil cost for placebo comparator</p>	<p>Osilodrostat price reduced compared to the previous submission (paragraph 3.2)</p>																														

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Data	Value and Source	Comment
MBS costs	The resubmission assumed that patients would require: <ul style="list-style-type: none"> • 26 UFC tests and 13 endocrinologist visits in the dose titration period (initial) and • Two UFC tests and one endocrinologist visit every continuing treatment period The MBS items for UFC testing and endocrinologist visits are: <ul style="list-style-type: none"> • MBS Item 66707 (\$83.35) • MBS Item 116 (\$83.35) 	MBS item 66707 included both UFC and serum cortisol testing and both costing the same, hence it was unclear how conservative the measurements based on urine samples would be in relation to serum cortisol measurements.

Source: Tables 4.2-1 to 4.2-8 of the resubmission

ABS = Australian Bureau of Statistics; ACTH = adrenocorticotrophic hormone; CD = Cushing's disease; CS = Cushing's syndrome; AEMP = approved ex-manufacturer price; DoH = Department of Health; KOL = key opinion leader; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; UFC = urinary free cortisol

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

6.80 The total eligible patients, scripts dispensed, and the net financial implications to the R/PBS is presented in Table 18.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total eligible patients						
Prevalent	█ ¹	-	-	-	-	-
Incident	-	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Uptake of osilodrostat^a						
Prevalent	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Incident	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total initiating	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Newly initiating and continuing treatment patients						
Initiating	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Continuing ^b	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Persistent continuing patients^c						
Continuing	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total scripts^d						
Total R/PBS	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Financial implications (\$) ^e						
R/PBS cost	█ ³	█ ³	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Co-payment	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net R/PBS cost	█ ³	█ ³	█ ⁴	█ ⁴	█ ⁴	█ ⁴
MBS cost	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost health budget	█ ³	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Pre-PBAC response: Net cost health budget	█ ³	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
March 2023 estimates	█ ³	█ ⁴	█ ⁵	█ ⁴	█ ⁴	█ ³
DUSC March 2023 estimates	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴

Source: Tables 4.3-2 and 4.3-3 of the resubmission; Isturisa (osilodrostat) – endogenous CS – UCM, '2d. Patients – DTG' worksheet from the financial workbook and Table 20 and Table 22, osilodrostat PBAC minutes, March 2023

DUSC = Drug Utilisation Sub-Committee; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Blue shaded cells indicate values previously considered by PBAC.

^a Uptake rates of █% in Year 1, █% Year 2, █% Year 3, █% Year 4, █% Year 5, and █% Year 6

^b Continuing patients based on the overall response rate of 87%

^c Persistent patients based on the proportion of patients who are on treatment in each subsequent year (from the economic model)

^d Total scripts were based on the number of initiating and continuing patients, the average doses, and the distribution of doses in the initial (responders and non-responders) and continuing treatment periods from LINC 4 post-hoc analysis and the mean treatment duration in the economic model.

^e Based on effective prices

Note: < 500 grandfathered patients were assumed part of the prevalent population

The redacted values correspond to the following ranges:

¹ <500

² 500 to <5,000

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

⁵ \$20 million to < \$30 million

6.81 The total cost to the PBS/RPBS of listing osilodrostat was estimated to be \$0 to < \$10 million in Year 1 and increases to \$10 million to < \$20 million in Year 6, and a total of \$60 million to < \$70 million in the first 6 years of listing. Including the MBS costs for monitoring patients, the net cost to the health budget is \$0 to < \$10 million

in Year 1 increasing to \$10 million to < \$20 million in Year 6, and the total cost of \$60 million to < \$70 million in the first 6 years of listing. Compared to the previous submission, the cost was higher due to a higher initial uptake rate (starting at █% compared to █% for the prevalent population) as well as the assumption that patients will continue on treatment for longer (4.62 years compared to 3.25 years in previous submission). The ESC considered that given the potential lifelong treatment, the mean duration of 4.62 years remained underestimated. It was also noted DUSC considered an initial uptake rate of 60% would be more appropriate. The pre-PBAC-response acknowledged that the duration of treatment in LINC 4 is lower than that in LINC 3, hence updated the financial implications using mean duration of treatment of 5.3 years from LINC 3. However, the pre-PBAC response maintained that █% uptake rate is reasonable given that <500 out of <500 patients remained on treatment in the patient access program. The revised estimates are presented in Table 18 above and result in \$0 to < \$10 million in Year 1, increasing to a cost of \$10 million to < \$20 million in Year 6.

6.82 At the March 2023 PBAC meeting, the DUSC considered that the estimates in the previous submission were possibly underestimated (paragraphs 6.47-6.48, osilodrostat, PSD, March 2023 PBAC meeting) highlighting that:

- The eligible population who are unable to achieve a surgical cure was at risk of being underestimated;
- The prevalent uptake rate of █% in Year 1 were likely an underestimate; and
- The MBS costs and possible additional endocrinologist consultations were not accounted for.

6.83 To address these concerns, the resubmission:

- Maintained the same the proportion of patients assumed to achieve surgical cure for each sub-population but performed sensitivity analyses to test higher surgical success rates;
- Increased the uptake rate to █% in Year 1 in the prevalent population (despite the DUSC's advice that a 60% uptake rate in Year 1 was appropriate); and
- Included MBS costs for additional UFC testing and endocrinologist visits during the dose titration period as well as the continuing treatment period

The PSCR maintained the surgical success rates from the previous submission given the absence of alternative data. The PSCR further argued that the █% uptake rate was adopted as a conservative approach aligning with the uptake data from the patient access program (From December 2021, of a total of <500 patients enrolled, <500 patients are currently receiving treatment with osilodrostat). However, the ESC considered that the surgical success rates and lower uptake rate (█% in Year 1) remained a source of uncertainty.

- 6.84 The ESC agreed with the previous DUSC’s comments regarding the possibility of use in patients before and during radiotherapy and surgery might result in the estimates from the previous submission being underestimated, which was not considered in the resubmission (Table 19, osilodrostat, PSD, March 2023 PBAC meeting). Further, the ESC agreed with the DUSC that there may be a risk of use outside the restriction due to the high variability of UFC results, noting that prescribers could selectively choose results to qualify for treatment (osilodrostat, DUSC advice, March 2023 PBAC meeting). Given the current proposed PBS restriction criteria for initiating treatment, this risk is likely greater with two tests required instead of three.
- 6.85 The proposed initial treatment criteria do not limit the number of times a patient may be treated under the initial criteria. As such, a patient who failed to achieve CR or PR could restart treatment under the initial criteria. Retreatment was not accounted for in the financial estimates.
- 6.86 The sensitivity analysis performed by the resubmission and additional sensitivity analyses conducted during the evaluation are presented in Table 19.

Table 19: Sensitivity analyses of financial estimates

	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Yr 6	Total	% Δ
Base case (\$)	1	2	2	2	2	2	3	-
Prevalence rates (\$)								
57/million	1	1	1	1	1	1	4	-13%
79/million	2	2	2	2	2	2	5	16%
Surgery rate								
CD 1 st (80%)	2	2	2	2	2	2	5	28%
CD 2 nd (98%)	1	1	1	1	1	1	4	-17%
Surgery success rates (\$)								
CD 1 st success (40%)	2	2	2	2	2	2	6	35%
CD 1 st success (80%)	1	1	1	1	1	1	7	-35%
ACTH independent 1 st success (60%)	2	2	2	2	2	2	5	21%
ACTH independent 1 st success (40%)	2	2	2	2	2	2	6	34%
Uptake rate (\$)								
60% in year 1 ^a	2	2	2	2	2	2	3	8%

Source: Table 4.6.1 of the resubmission

ACTH = adrenocorticotrophic hormone; CD = Cushing’s disease; yr = year

^a cumulative uptake rate = █% Year 1, █% Year 2, █% Year 3+

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

² \$10 million to < \$20 million

³ \$60 million to < \$70 million

⁴ \$50 million to < \$60 million

⁵ \$70 million to < \$80 million

⁶ \$80 million to < \$90 million

⁷ \$30 million to < \$40 million

- 6.87 Similarly noted in the March 2023 meeting (paragraph 6.45, osilodrostat, PSD, March 2023 PBAC meeting), the financial estimates were sensitive to:
- The prevalence rate (upper and lower limits) which led to -13% to +16% change in total costs; and
 - Variations in the surgery rate and surgery success. The resubmission varied the surgery success rate by large magnitudes (>20% from the base case):
 - Changing the 1st surgery success in the CD sub-population from 60% (base case) to 80% and 40% led to -35% and +35% change in total costs. This large impact was expected given the CD sub-population contributed to the majority of the patient population (70%);
 - Decreasing the 1st surgery success rate in the ACTH independent sub-population from 95% (base case) to 60% and 40% led to 21% to 34% increase in total costs, respectively; and
 - Changes in the surgery success rate in Other ACTH dependent sub-population had minimal impacts on total costs given that the initial proportion eligible for surgery was small (50%) compared to the other sub-populations.
- 6.88 Applying the uptake rate suggested by the DUSC (60% in Year 1) led to an 8% increase in total cost but led to substantial changes in individual years (50% increase in Year 1 then a 28% decrease in Year 6 compared to the base case).
- 6.89 Generally, the surgical success rates, particularly in the CD and ACTH-independent sub-populations remains a source of considerable uncertainty. As an uptake rate that was lower than what the DUSC recommended was assumed in the base case, the financial estimates in the initial years remain potentially underestimated. In addition, the resubmission did not consider patients who may require higher doses over the 26-week titration period. There is a potential for use beyond the restriction (e.g., patients who do not achieve CR or PR but are potential candidates to be retreated under the initial treatment restriction and use in patients before and during radiotherapy and surgery).

Quality Use of Medicines

- 6.90 The resubmission did not include a discussion of the quality use of medicines. In regard to the previous submission it was noted that “the submission did not include discussion of the quality use of medicines despite there being risks of hypercortisolism, glucocorticoid withdrawal syndrome, QT prolongation and interaction with enzymes which break down other drugs. The DUSC noted that these risks could be mitigated by keeping the listing as a speciality endocrinology prescriber base” (paragraph 6.48, osilodrostat, March 2023 PBAC meeting).

For more detail on PBAC’s view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend osilodrostat for the treatment of adult patients with endogenous Cushing's syndrome (CS) who are not candidates for surgery or for whom surgery was not curative. The PBAC accepted that osilodrostat represented an effective therapy for a disease where high clinical need exists. However, the PBAC considered that the economic model was not informative for decision-making as it did not capture the important long-term quality of life benefits associated with osilodrostat, resulting in an unreliable and very high and uncertain cost effectiveness ratio. The PBAC noted that the pre-PBAC response provided an alternative economic analysis using an incremental cost per responder. The PBAC noted that responders to osilodrostat may continue on therapy long-term, although it is likely that clinicians will continue to look for a surgical solution and treatment may be ceased for this, or other reasons related to morbidities of CS. As such, it is unclear how long patients will remain on treatment with osilodrostat. The PBAC considered that as osilodrostat may be used as a chronic therapy, the incremental cost per responder should be closer to those previously accepted for longer term treatments. It was also considered the value of a response had been inadequately supported in the resubmission. The PBAC advised that additional justification of the cost per responder approach was required, and a resubmission would need to provide a stronger interpretation of the quality-of-life benefit of cortisol control in the short-term (up to one year), medium-term (2–3 years) and long-term (beyond 3 years).
- 7.2 The PBAC acknowledged that there was a high clinical need for new therapies for CS, due to high morbidity associated with the condition and given there is no PBS listed medicine for this condition. The PBAC recognised the multiple challenges associated with diagnosis and management of CS, which include difficulties in accessing neurosurgeons in certain regions, the risk of surgical failure and recurrence, complications such as Nelson's syndrome following bilateral adrenalectomy, and the challenges in locating ectopic tumours. In addition, the PBAC noted slow return to normal function with radiation therapy and toxicities associated with off-label oral therapies such as metyrapone and ketoconazole. As such, the PBAC highlighted that there is a high clinical need for novel effective medical therapies for CS.
- 7.3 The PBAC further highlighted that the management of CS is complex with the primary aim being surgical clearance of either a pituitary adenoma or an ectopic ACTH producing tumour. In cases where surgical intervention is unsuccessful, medical therapy may be used as an interim measure until repeat surgery is attempted or where further imaging locates an elusive ectopic ACTH producing tumour which may be amenable to surgical resection. As such, the PBAC considered that the duration of treatment with osilodrostat may vary from life-long to time-limited duration if the tumour is identified at a later stage.
- 7.4 The PBAC noted the consumer comments were supportive of making osilodrostat available on the PBS as a treatment option. The PBAC noted that the benefits, as

described by the consumers, included significant improvement in quality of life such as ability to work, ability to participate in family life and maintaining relationships, overall improvement in mental and emotional well-being; significant improvement in associated morbidities such as diabetes, osteoporosis, hypertension, coagulation, skin changes and psychiatric impact. The PBAC acknowledged that the clinician hearing highlighted the challenges associated with diagnosis, limited therapeutic options and the need for effective therapies.

- 7.5 The PBAC noted the changes to the requested restriction in the resubmission presented in paragraph 3.3. These changes include having a mUFC > 1.3 x upper limit of normal (ULN) based on two urine samples instead of three samples; increasing initial treatment period to 6 months from 12 weeks; allowing partial response as an eligibility for continuing treatment. The PBAC noted the rationale for these changes and the support from the clinician in the sponsor hearing (see paragraph 6.1) and considered that these changes were reasonable, aligning better with the clinical practice.
- 7.6 The PBAC noted that the assessment of response should be conducted after 26 weeks from start of therapy, with up to 6 repeats in initial and GF phase to allow adequate supply. The PBAC also considered that a clinical criterion for patients transitioning to osilodrostat after improvement in UFC level with other non-PBS subsidised therapies such as ketoconazole and metyrapone should be added to the initial restriction. Similarly, the PBAC also considered that the grandfather (GF) patients transitioning from non-PBS subsidised treatment to osilodrostat should have had mUFC > 1.3 times ULN at the time non-PBS subsidised osilodrostat was commenced in the GF treatment phase. The PBAC also noted that this criterion should be considered as a balanced approach, allowing for clinical judgement. The PBAC further considered that given the complexity of titration of doses and close monitoring, treatment should be limited to endocrinologists.
- 7.7 The PBAC reaffirmed its previous consideration that the placebo comparator was the most relevant given that ketoconazole was deregistered by the TGA and metyrapone was used as an off-label therapy (paragraph 7.5, osilodrostat, PSD, March 2023 PBAC meeting).
- 7.8 The PBAC noted the comparative evidence between osilodrostat and placebo was the same as the previous submission. This comparison was based on 2 randomised placebo-controlled trials (LINC 3; LINC 4) and one open-label phase II study (C1202). In its previous consideration the PBAC noted the high risk of bias with the LINC 3 trial given the withdrawal study design where only responders (N=71) were randomised to the comparative stage after the 26 weeks open-label period (N=137). In particular, the high risk of selection bias with LINC 3 meant that any estimate of effect size was likely to be overestimated. Based on the LINC 4 outcomes, the PBAC noted that osilodrostat demonstrated a statistically significant improvement in complete response at week 12 (RD = 0.69 (0.47, 0.80); OR = 43.4 (7.06, 343.19)). Overall, the PBAC also reaffirmed that despite the limitations of the evidence, it was biologically plausible that if a

patient is tolerating and responding to osilodrostat, that the response would be maintained (paragraph 7.7, osilodrostat, PSD, March 2023 PBAC meeting).

- 7.9 The PBAC noted that the resubmission presented additional efficacy data for the optional extension periods for LINC 3 (up to 245.1 weeks) and LINC 4 (up to 126.6 weeks). The resubmission also employed different analytical approaches (see paragraph 6.13) including an unanchored ITC of pooled trial data vs the placebo arm from LINC 4; swimmer plots; and post-hoc analyses of a subgroup of responders who met the proposed PBS criteria. The reanalyses and longer-term efficacy data supported the PBAC's previous conclusion that patients who tolerate and respond to osilodrostat would likely achieve and maintain improvements in CS symptoms and comorbidities, acknowledging that improvements are gradual with clinical benefit usually observed after a year of treatment given the considerable amount of time to adapt to normal cortisol levels (paragraph 7.8, osilodrostat, PSD, March 2023 PBAC meeting).
- 7.10 Although there was no new osilodrostat clinical trial evidence, the resubmission included additional retrospective studies (Mondin 2023; and Chihaoui 2023), detailing the impact on cardiovascular and metabolic outcomes of long-term sustained remission from hypercortisolism. This evidence suggested that sustained remission from hypercortisolism could improve CS comorbidities (see paragraph 4.6). However, this was not incorporated in the consideration of clinical evidence or the economic evaluation. Overall, the PBAC considered, that the claim of superior comparative effectiveness to placebo was reasonable for the surrogate outcomes of complete or partial response, and acknowledged the important long-term benefits associated with durable response to cortisol level.
- 7.11 The PBAC noted that the evidence supporting the claim of non-inferior safety of osilodrostat compared to placebo was consistent with the previous submission. Additional details of the patient experience with pituitary tumour enlargement-related AEs suggested that at least half of these events were serious and of Grade \geq 3, and patients were treated with pituitary surgery or radiotherapy which were resolved soon after (see paragraph 6.24). Overall, PBAC considered that adverse events were generally manageable and the claim of non-inferior safety to placebo was acceptable, noting regular monitoring of side effects of hypocortisolism was required.
- 7.12 The PBAC noted that the resubmission presented a stepped cost-utility analysis based on LINC 4 using a microsimulation and incorporating approximately 4 years of therapy. The economic evaluation was a complex, 50-year, microsimulation model informed by a small sample size from LINC 4 without incorporating the long-term QoL benefits of durable cortisol control and reduced costs from improvement in comorbidities. The PBAC agreed the ESC that the economic model was not informative for decision-making. The PBAC considered that despite the resubmission's attempt to model long-term use of osilodrostat, the inputs informing the model, particularly survival and QoL remained uncertain, the base case ICER was too high, and it was unlikely to adequately represent the cost-effectiveness of osilodrostat.

- 7.13 The PBAC acknowledged the ESC had advised that given the high unmet clinical need for treatment of endogenous CS that, with the price reduction, the cost per responder might be a reasonable measure although this would entail separate consideration of the longer-term benefits (see paragraph 6.38). The PBAC noted that the pre-PBAC response estimated a cost per responder of \$35,000 to < \$45,000 based on overall response (at least a partial response) over 26 weeks using the revised effective price.
- 7.14 The PBAC acknowledged previous decisions it had made using an incremental cost per responder approach (see paragraph 6.40) and considered that this approach was more difficult to justify and value for a chronic therapy. The PBAC considered the longer-term treatments denosumab and Dysport® gave the closest representation of what might be an acceptable ICER for this type of analysis. However, in the absence of longer-term benefits and with ambiguity regarding the duration of therapy, uncertainties regarding the appropriate value attached to each additional responder persist. The PBAC advised that, a further price reduction may mitigate residual uncertainties around the cost per responder, but the key issue of how to value the response remained. The PBAC considered that more information on the potential variation in treatment duration and how QoL is impacted over short, medium and long-term cortisol control would be crucial to accepting an ICER for the cost per responder analysis that is consistent with the previous examples for longer-term treatments.
- 7.15 The PBAC noted the uncertainty in the financial estimates (see paragraphs 6.81 and 6.82) and that the pre-PBAC response provided sensitivity analysis using a longer duration of therapy (5.3 years), MBS items for UFC testing and endocrinologists, and the mean dose from LINC 3. This analysis showed that the net financial implication was a cost of \$0 to < \$10 million in Year 1, increasing to a cost of \$10 to < \$20 million in Year 6. The PBAC considered that the financial estimates were uncertain with a key uncertainty being the treatment duration. The PBAC considered the uptake rate in Year 1 for the prevalent pool of patients to be uncertain but noted that increasing this uptake impacted on the distribution of costs over the 6 years with minimal impact on the total cost as the uptake is appropriately applied in a cumulative manner such that the uptake in years 2 onwards is only applied to patients who have not previously initiated treatment.
- 7.16 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for osilodrostat. The PBAC also considered osilodrostat addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy, over placebo. Therefore, the PBAC considered an early resolution pathway would be acceptable. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.
- Provide expected duration of therapy (in years) entailing whether this would be a lifelong treatment or time-limited treatment considering ongoing attempts to

identify the source for surgical removal. This may be drawn from available evidence such as literature, clinical expert opinion or case studies.

- Justify the value proposition of treatment over time, i.e., provide additional context on QoL improvements regarding cost per responder for at least partial response for expected duration of therapy (this may be short-term, medium-term, and/or long-term depending on what the expected duration of therapy is deemed to be). If the majority of use is expected to be long-term, the cost per responder should be provided in the context of precedents for longer-term treatments for comparison.
- Provide revised financial estimates incorporating the estimated duration of therapy. The PBAC noted that it may be possible to address the uncertainty associated with the treatment duration through a Risk Sharing Arrangement.
- The early resolution resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early resolution timing is not acceptable, a standard re-entry pathway is available.

7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.

Addendum to the March 2024 PBAC Public Summary Document:

7.02 OSILODROSTAT,

Tablet 1 mg,

Tablet 5 mg,

Isturisa[®],

Recordati Rare Diseases Australia Pty. Ltd.

8 Background

- 8.1 The early resolution resubmission requested a General Schedule Authority Required (Telephone/Online) listing for osilodrostat for the treatment of endogenous Cushing's syndrome (CS). Osilodrostat was considered by the PBAC and not recommended for PBS listing at the March 2024 meeting. At that meeting, the PBAC accepted that osilodrostat represented an effective therapy for a disease where high clinical need exists. However, the PBAC considered that the economic model was not informative for decision-making as it did not capture the important long-term quality of life benefits associated with osilodrostat, resulting in an unreliable and very high and uncertain cost effectiveness ratio. The PBAC noted that the pre-PBAC response provided an alternative economic analysis using an incremental cost per responder. The PBAC noted that responders to osilodrostat would likely continue on therapy long-term, although it is likely that clinicians will continue to look for surgical options and osilodrostat treatment may be ceased for this, or other reasons related to morbidities of CS. As such, it was unclear how long patients will remain on treatment with osilodrostat. The PBAC considered that, as osilodrostat may be used as a chronic therapy, the incremental cost per responder should be closer to those previously accepted for longer term treatments. It was also considered the overall benefits of a response to osilodrostat had been inadequately supported in the resubmission. The PBAC advised that additional justification of the cost per responder approach was required and a resubmission would need to provide a stronger interpretation of the quality-of-life benefit of cortisol control in the short-term (up to one year), medium-term (2–3 years) and long-term (beyond 3 years).
- 8.2 The PBAC considered that the outstanding issues could be addressed using the early resolution pathway if the matters were addressed as outlined in Table 20. A summary of the resubmission's approach to these matters is also provided in Table 20.

Table 20: Issues to be addressed (March 2024 PBAC minutes)

Matter of Concern	Resubmission
Matters Raised by PBAC (minutes, para 7.16)	
<p>1 Provide expected duration of therapy (in years) entailing whether this would be a lifelong treatment or time-limited treatment considering ongoing attempts to identify the source for surgical removal. This may be drawn from available evidence such as literature, clinical expert opinion or case studies</p>	<p>The resubmission stated that no new data has become available that would provide a better estimate of the duration of treatment with osilodrostat than the estimated 4.62 years in the March 2024 submission.</p> <p>The resubmission stated factors that may impact the duration of osilodrostat treatment include:</p> <ul style="list-style-type: none"> • whether eCS is caused by a malignant tumour • subsequent surgery • prior radiotherapy • impact of osilodrostat on comorbidities and survival
<p>2 Justify the value proposition of treatment over time, i.e., provide additional context on QoL improvements regarding cost per responder for at least partial response for expected duration of therapy (this may be short-term, medium-term, and/or long-term depending on what the expected duration of therapy is deemed to be). If the majority of use is expected to be long-term, the cost per responder should be provided in the context of precedents for longer-term treatments for comparison</p>	<p>The resubmission presented clinical evidence to demonstrate the following:</p> <ul style="list-style-type: none"> • The wide range of comorbidities experienced by patients with eCS. • Normalising cortisol improves key clinical parameters that are well established surrogates for final outcomes of eCS associated comorbidities in the short- and long term. • The improvements in the key clinical parameters (e.g., HbA1c, blood pressure, BMI, BMD) are maintained whilst the patient remains on treatment, irrespective of the eCS subtype. • Longer term treatment with osilodrostat will avoid clinical events (e.g., stroke, myocardial infarction, kidney failure, fractures, sepsis) which allows patients to maintain or improve QoL for longer compared with those with uncontrolled cortisol. This is in addition to patients with controlled cortisol experiencing improved survival.
<p>3 Provide revised financial estimates incorporating the estimated duration of therapy. The PBAC noted that it may be possible to address the uncertainty associated with the treatment duration through a Risk Sharing Arrangement.</p>	<p>The resubmission stated that, except for some minor updates to pharmacy fees and copayments, the financial estimates remain largely unchanged from those presented in the March 2024 submission.</p> <p>The resubmission stated that while the PBAC noted that the uncertainty associated with the treatment duration could be addressed with a risk sharing arrangement, the sponsor does not believe that such an arrangement would be required.</p>

BMD = bone mineral density; BMI = body mass index; eCS = endogenous Cushing's syndrome

8.3 The resubmission proposed the same ex-manufacturer price (EMP) as proposed in the March 2024 submission (EMP for 1 mg tablets= \$| and for 5 mg tablets = \$|).

9 Requested listing

9.1 The early resolution resubmission accepted the Secretariat revisions to the proposed restrictions as outlined in section 3 above.

10 Consideration of the evidence

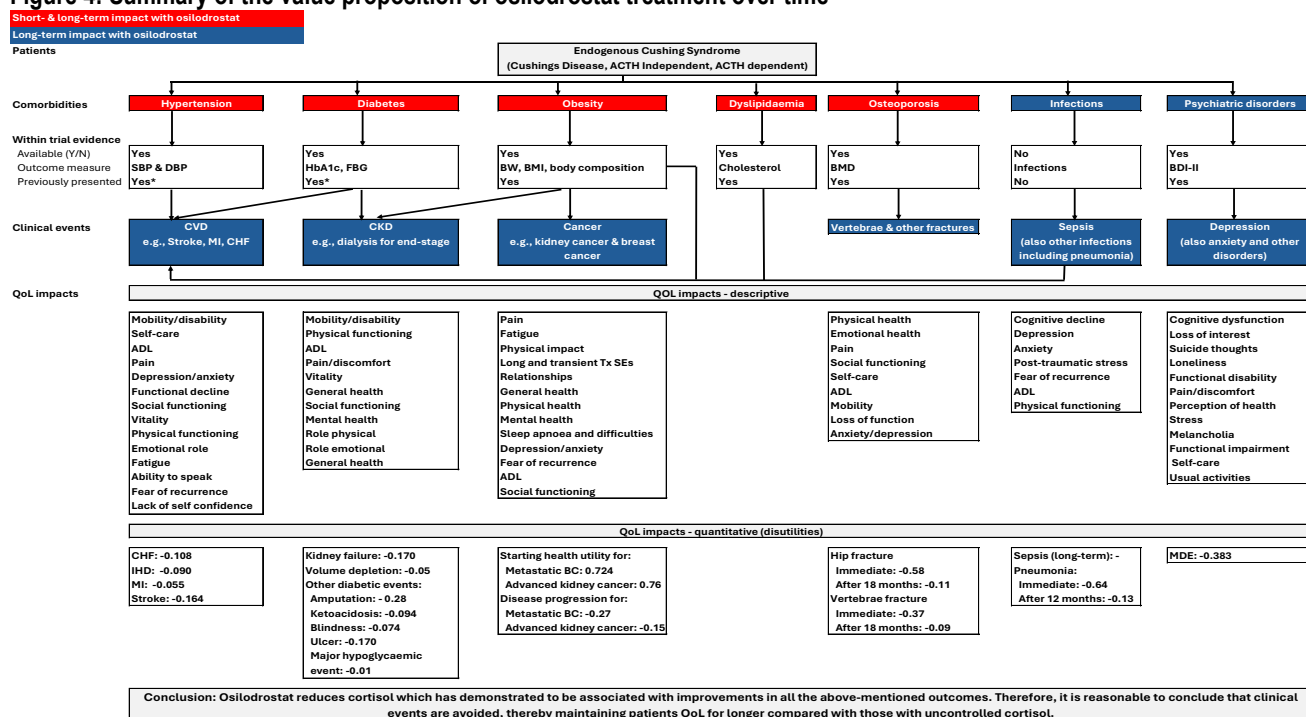
Economic analysis

10.1 The early resolution resubmission presented a summary of the value proposition of osilodrostat treatment over time, depicted in Figure 1 below.

10.2 The resubmission stated that (page 30):

“Although osilodrostat only acts on reducing cortisol, the clinical evidence showed that the impact of reducing cortisol in patients with eCS extends well beyond the short-term QoL improvements. Indeed, reducing cortisol in patients with eCS also has a meaningful impact on key clinical parameters of a range of common comorbidities (e.g., hypertension, diabetes, obesity, dyslipidaemia, osteoporosis). For most key clinical parameters (e.g., systolic and diastolic blood pressure, HbA1c, body weight, BMI, cholesterol, bone mineral density, etc.) of the common comorbidities experienced by patients with eCS, the PBAC has previously accepted that improvements are associated with reductions in clinically significant events (e.g., CVD, CKD, cancer, fractures, sepsis, depression), extension of overall survival and improvements in quality of life.”

Figure 4: Summary of the value proposition of osilodrostat treatment over time



Adapted from Mondin et al (2023), Gadelha et al (2022), Fleseriu et al (2022), Chihaoui et al. (2023), Castinetti et al (2014), Abimanyi-Ochom et al. (2015), Cho et al. (2019), Cuthbertson et al. (2013), Hakeem Ismael and Omer Rashid (2020), Juenger et al. (2002), Luijks et al. (2024), Madureira et al. (2012), Nayak et al. (2017), Nguyen et al. (2018), Pocock et al. (2021), Rizzo et al. (2022), Shankar-Hari and Rubinfeld (2016), Shirali et al. (2020), UKPDS (1999), Clarke et al. (2002), Bagust and Beale (2005), McEwan et al. (2022), Mangan et al. (2017), Luijks et al. (2024), Lloyd et al. (2006), Mason et al. (2023), tirzepatide PBAC PSD (July 2023), esketamine PBAC PSD (July 2021), abemaciclib PBAC PSD (March 2022), Arnold et al (2024), Dormoy et al (2023)

* Additional evidence also provided in this submission

Abbreviations: ACTH = Adrenocorticotropic hormone; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HbA1c = Glycated haemoglobin; FBG = Fasting blood glucose; BW = Bodyweight; BMI = Body mass index; BMD = Bone mineral density; BDI = Beck Depression Inventory; CVD = Cardiovascular disease; CKD = Chronic kidney disease; MI = Myocardial infarction; CHF = Congestive heart failure; ADL = Activities of daily living; Tx = Treatment; SE = Side-effect; BC = Breast cancer; MDE = Major depressive episode

10.3 The early resolution resubmission argued that, in contrast to the precedents listed in Table 10 above, the impact of osilodrostat on reducing cortisol is multifaceted. The early resolution resubmission suggested that the PBAC had not previously considered listing of a new medicine on an incremental cost per responder basis with similar characteristics to osilodrostat, whereby the reduction in one clinical parameter has significant flow-on impacts to multiple other clinical parameters that are associated with clinical events. As such it was reasoned there was no suitable frame of reference and therefore the PBAC was requested to consider the result of the incremental cost per responder analysis for osilodrostat on its own merits.

10.4 The early resolution resubmission did not provide a revised price offer, instead requesting the PBAC accept the previously presented incremental cost of \$1 per responder over 26 weeks (see Table 9). It was argued this was justified given the multifaceted clinical impacts of osilodrostat, the high clinical need for new therapies due to the significant morbidity of CS and the absence of any PBS listed medicines. It was noted the estimated mean duration of treatment was 4.62 years (unchanged from

March 2024), with an estimated cost of \$¹ for responders in the first year and \$¹ in the years thereafter.

Estimated PBS usage and financial implications

- 10.5 As noted in Table 20, the PBAC had requested further information regarding expected duration of therapy and that this be incorporated into revised financial estimates. The early resolution resubmission stated factors that may impact the duration of osilodrostat treatment include: whether eCS is caused by a malignant tumour; subsequent surgery; prior radiotherapy; and the impact of osilodrostat on comorbidities and survival.
- 10.6 The early resolution resubmission concluded that most patients with eCS would receive lifelong treatment with osilodrostat in the absence of any initial and continuing response assessment criteria. However, the PBS restriction requires patients to demonstrate at least a partial response to osilodrostat after 26 weeks of treatment and maintain a response as assessed every six months thereafter to continue PBS subsidised treatment.
- 10.7 The early resolution resubmission stated there are no data from other countries that can be used to provide a real-world estimate of the duration of treatment with osilodrostat. The duration of treatment therefore continues to be informed by the estimated duration of response from the LINC 4 trial, extrapolated using a lognormal distribution resulting in a mean duration of treatment of 4.62 years.
- 10.8 The revised estimated financial implications of listing osilodrostat are presented in Table 21. The early resolution resubmission stated the first year of listing was revised to reflect the calendar year 2025 and pharmacy fees and patient copayments were updated.

Table 21: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Financial implications						
Net R/PBS cost (\$)	■ ¹	²	²	²	²	²
MBS cost (\$)	■ ¹	¹	¹	¹	¹	¹
Net cost health budget (\$)	■ ¹	²	²	²	²	²
Net cost health budget, March 2024 (\$)	■ ¹	²	²	²	²	²

Source: Table 4-1 of resubmission; Isturisa (osilodrostat) – endogenous CS – Early resolution – UCM.xls; Table 18, osilodrostat minutes, March 2024 PBAC meeting

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

² \$10 million to < \$20 million

- 10.9 The total cost to the PBS/RPBS of listing osilodrostat was estimated to be \$0 to < \$10 million in Year 1 and increases to \$10 million to < \$20 million in Year 6, and a total of \$60 million to < \$70 million in the first 6 years of listing. Including the MBS costs for monitoring patients, the net cost to the health budget is \$0 to < \$10 million

in Year 1 increasing to \$10 million to < \$20 million in Year 6, and the total cost of \$60 million to < \$70 million in the first 6 years of listing (previous total cost was \$60 million to < \$70 million in March 2024 — see paragraph 6.81).

11 PBAC Outcome

- 11.1 The PBAC recommended the General Schedule Authority Required (Telephone/Online) listing of osilodrostat for the treatment of endogenous Cushing’s syndrome (CS) in adults. The PBAC was satisfied that osilodrostat provides, for some patients, a significant improvement in efficacy over placebo. In making this recommendation, the PBAC acknowledged the high unmet clinical need for effective treatments for CS, and the Committee recalled it had previously considered that osilodrostat was superior to placebo in normalising cortisol in the majority of treated patients. The PBAC noted the information presented in the early resolution resubmission to support the value of at least a partial cortisol response over the short-, medium-, and long-term and the estimated duration of therapy. The PBAC agreed with the early resolution resubmission that the value proposition for osilodrostat over time reflects multiple factors beyond cortisol response and this represented a point of difference to the precedents for other chronic therapies that had been recommended on the basis of an incremental cost per responder analyses. Overall, the PBAC accepted osilodrostat would be cost-effective based on the incremental cost per responder as presented in this resubmission. The PBAC noted no additional information was available to support the estimated duration of therapy or the proportion of patients who may discontinue but that use is expected to be lifelong in patients who respond to treatment. The PBAC considered that, as the expected mean duration of use remained uncertain and therefore the financial estimates also uncertain, a risk sharing arrangement was required to manage the estimated cost and uncertainty to Government.
- 11.2 The early resolution resubmission described how cortisol control may translate into improvements in important clinical parameters, such as blood glucose, blood pressure, body mass index (BMI), and bone mineral density (BMD) leading to multifaceted long-term quality of life benefits for patients from avoiding events such as stroke, myocardial infarction, kidney failure, fractures, and sepsis. The PBAC noted the wide range of short-, medium- and long-term impacts of cortisol control on clinical outcomes and quality of life.
- 11.3 The PBAC noted that the March 2024 incremental cost-utility analysis did not adequately quantify and translate these long-term benefits into QALY gains. The PBAC accepted that such an analysis would be complex and involve multiple and variable data sources beyond the trial evidence and, as such, would likely result in a highly uncertain ICER. The PBAC reaffirmed that an incremental cost per responder analysis provides a reasonable alternative assessment of cost-effectiveness in this instance. The PBAC noted the incremental cost per responder proposed in this resubmission was considerably higher than the precedents previously noted for other chronic

therapies. The PBAC agreed with the early resolution resubmission that the multifaceted benefits of cortisol control should be taken into consideration when determining the acceptable ICER. The PBAC considered that, combined with the high unmet need for effective therapy, that the cost-effectiveness of osilodrostat based on the incremental cost of \$| per responder over a period of 26 weeks was adequately supported by the descriptive analyses of the longer-term impacts of cortisol normalisation.

- 11.4 The PBAC recalled it had requested more information on the expected duration of treatment and whether it would be expected to be lifelong or time limited. The PBAC noted the early resolution resubmission explored the circumstances under which treatment may need to be time-limited, but that there was no reliable data or real-world evidence on such use and that treatment is expected to be lifelong in patients who respond to treatment. The PBAC noted the early resolution resubmission assumed no change in the previously estimated duration of treatment which was 4.62 years. The PBAC noted the uncertainty in the extrapolated duration of treatment, as discussed in paragraphs 6.50 and 6.51. As such, the PBAC considered that the residual uncertainty of time on treatment and subsequently overall cost to Government should be managed with a risk sharing arrangement. The PBAC accepted that 4.62 years duration of treatment was the best available estimate, however in context of uncertain cost-effectiveness for longer-term use, a rebate of at least |% for expenditure above the estimated financial estimates would be required.
- 11.5 The PBAC affirmed the Secretariat revised restrictions in section 3 were appropriate. The PBAC recommended a Telephone/Online Authority is appropriate. The PBAC recommended the grandfather restriction is appropriate. The PBAC recommended a maximum quantity of 1 pack, with 6 repeats for initial and grandfathered treatment, to allow up to 28 weeks (approximately 7 months) to assess response; with 5 repeats for continuing treatment.
- 11.6 The PBAC recommended that osilodrostat should not be treated as interchangeable with any other drugs.
- 11.7 The PBAC advised that osilodrostat is not suitable for prescribing by nurse practitioners.
- 11.8 The PBAC recommended that the Early Supply Rule should not apply.
- 11.9 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically the PBAC found that in the circumstances of its recommendation for osilodrostat:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over placebo by normalising cortisol in the majority of treated patients with endogenous Cushing’s syndrome;
 - b) The treatment is expected to address a high and urgent unmet clinical need as

there are currently no approved safe and effective medical alternatives;

- c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

11.10 The PBAC advised that this submission would not meet the criteria for an Independent Review as received a positive PBAC recommendation.

Outcome:

Recommended

12 Recommended listing

12.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OSILODROSTAT					
Osilodrostat 1 mg tablet, 60	NEW	1	60	6	Isturisa, Recordati Rare Diseases Australia Pty Ltd.
Osilodrostat 5 mg tablet, 60	NEW	1	60	6	Isturisa, Recordati Rare Diseases Australia Pty Ltd.
Restriction Summary [new1] / Treatment of Concept: [new2]					
Concept ID (for internal Dept. use)	Category / Program: Section 85 – General Schedule				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction Type – <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)					
	Caution: The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period: <ul style="list-style-type: none"> • QTc prolongation via an electrocardiogram • Hypocortisolism • Corticotroph tumour growth 				
	Administrative advice: Cortisol levels should be monitored at regular intervals, since hypocortisolism-related events can occur at any time during treatment.				
	Administrative advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Episodicity: Chronic				
	Severity: NA				
	Condition: Endogenous Cushing's Syndrome				
	Indication: Endogenous Cushing's syndrome				
	Treatment Phase: Initial treatment				
	Clinical criteria:				
	The condition must be, at least one of:				

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	(i) persistent hypercortisolism after surgery, (ii) recurrent hypercortisolism after surgery, (iii) inappropriate for surgery.
	AND
	Clinical criteria:
	Patient must have active endogenous Cushing's Syndrome determined by a mean urinary free cortisol (UFC) level greater than 1.3 times the upper limit of normal (ULN). OR
	Patient must have undergone treatment for this condition with conventional therapies to control cortisol production resulting in an improved UFC level prior to applying for the initial authority application of this drug.
	AND
	Treatment criteria:
	Must be treated by an endocrinologist.
	Population criteria:
	Patient must be at least 18 years of age.
	Prescribing Instructions: For the purposes of administering this restriction, the mean UFC is the average of at least two values being 1.3 times greater than the ULN.
	Prescribing Instructions: Patient must undergo a dose titration period whereby responses must be assessed every 1-2 weeks until the mean UFC levels are within the normal range.
	Prescribing Instructions: At the time of authority application, medical practitioners must request the appropriate number of packs to provide sufficient drug, based on the prescribed dose of the patient, for 4 weeks of treatment. A separate authority prescription form must be completed for each strength requested. The dose must not exceed 30 mg twice daily. Up to a maximum of 6 repeats will be authorised
	Prescribing Instructions: Where there is a current, approved PBS prescription with valid repeat prescriptions specified (i.e., where the dose is changing), mark the prescription that is intended for no further supply as 'Cancelled'.
	Prescribing Instructions: The condition is inappropriate for surgery if the patient: <ul style="list-style-type: none"> • has a medical contraindication for surgery • has inoperable tumours • has been determined that surgery is unlikely to reduce hypercortisolism • refuses surgery • can't access surgical treatment
	Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Restriction Summary [new3] / Treatment of Concept: [new4]	
	Indication: Endogenous Cushing's syndrome
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment – 'grandfather' arrangements
	Clinical criteria:
	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]

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	AND
	Clinical criteria:
	The condition must have been, at least one of: (i) persistent hypercortisolism after surgery, (ii) recurrent hypercortisolism after surgery, (iii) inappropriate for surgery, prior to commencing non-PBS subsidised treatment with this drug
	AND
	Clinical criteria:
	Patient must have had active endogenous Cushing's Syndrome determined by a mean urinary free cortisol (UFC) level greater than 1.3 times the upper limit of normal (ULN) prior to commencing non-PBS subsidised treatment with this drug.
	AND
	Clinical criteria:
	Patient must have demonstrated a complete response if they have received at least 26 weeks of initial non-PBS subsidised therapy OR
	Patient must have demonstrated a partial response if they have received at least 26 weeks of initial non-PBS subsidised therapy.
	Treatment criteria:
	Must be treated by an endocrinologist
	Population criteria:
	Patients must be at least 18 years of age.
	Prescribing Instructions: For the purposes of administering this restriction, a complete response is defined as a mean urinary free cortisol (UFC) level of less than or equal to the upper limit of normal (ULN). A partial response is defined as mean UFC level of greater than ULN but with at least 50% reduction from the baseline value. The mean UFC should be the average of at least two urine samples.
	Prescribing Instructions: Patient must undergo a dose titration period whereby responses must be assessed every 1-2 weeks until the mean UFC levels are within the normal range.
	Prescribing Instructions: At the time of authority application, medical practitioners must request the appropriate number of packs to provide sufficient drug, based on the prescribed dose of the patient, for 4 weeks of treatment. A separate authority prescription form must be completed for each strength requested. The dose must not exceed 30 mg twice daily. Up to a maximum of 5 repeats will be authorised.
	Prescribing Instructions: Where there is a current, approved PBS prescription with valid repeat prescriptions specified (i.e., where the dose is changing), mark the prescription that is intended for no further supply as 'Cancelled'.
	Prescribing Instructions: The condition is inappropriate for surgery if the patient: <ul style="list-style-type: none"> • has a medical contraindication for surgery • has inoperable tumours • has been determined that surgery is unlikely to reduce hypercortisolism • refuses surgery • can't access surgical treatment
	Prescribing Instructions: An application for the continuing treatment must be accompanied with the assessment of response conducted after 26 weeks from the first dose of osilodrostat and no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for patients who meet the continuing restriction for PBS-subsidised treatment.

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	Prescribing Instructions: A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the continuing treatment criteria.
	Administrative Advice: This Grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria
	Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OSILODROSTAT					
Osilodrostat, 1 mg oral tablet	New	1	60	5	ISTURISA
Osilodrostat, 5 mg oral tablet	New	1	60	5	ISTURISA

Restriction Summary [new5] / Treatment of Concept: [new6]

Concept ID (for internal Dept. use)	Category / Program: Section 85 – General Schedule
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Type – <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)
	Caution: The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period: <ul style="list-style-type: none"> • QTc prolongation via an electrocardiogram • Hypocortisolism • Corticotroph tumour growth
	Administrative advice: Cortisol levels should be monitored at regular intervals, since hypocortisolism-related events can occur at any time during treatment.
	Administrative advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Episodicity: Chronic
	Severity: NA
	Condition: Endogenous Cushing's Syndrome
	Indication: Endogenous Cushing's syndrome
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have demonstrated a complete response after at least 26 weeks of treatment with this drug OR
	Patient must have demonstrated a partial response after at least 26 weeks of treatment with this drug
	Treatment criteria:

	Must be treated by an endocrinologist.
	Population criteria:
	Patients must be at least 18 years of age.
	Prescribing Instructions: For the purposes of administering this restriction, a complete response is defined as a mean urinary free cortisol (UFC) level of less than or equal to the upper limit of normal (ULN). A partial response is defined as mean UFC level of greater than ULN but with at least 50% reduction from the baseline value. The mean UFC should be the average of at least two urine samples.
	Prescribing Instructions: At the time of authority application, medical practitioners must request the appropriate number of packs to provide sufficient drug, based on the prescribed dose of the patient, for 4 weeks of treatment. A separate authority prescription form must be completed for each strength requested. The dose must not exceed 30 mg twice daily. Up to a maximum of 5 repeats will be authorised.
	Prescribing Instructions: Where there is a current, approved PBS prescription with valid repeat prescriptions specified (i.e., where the dose is changing), mark the prescription that is intended for no further supply as 'Cancelled'.
	Prescribing Instructions: An application for the continuing treatment must be accompanied with the assessment of response conducted after 26 weeks from the first dose of osilodrostat and no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for patients who meet the continuing restriction for PBS-subsidised treatment.
	Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicessaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

13 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Recordati Rare Diseases welcomes the PBAC's decision to recommend the inclusion of Isturisa (osilodrostat) for the treatment of endogenous Cushing's syndrome on the PBS.