

## 5.02 OSILODROSTAT,

Tablet 1 mg,

Tablet 5 mg,

Tablet 10 mg,

Isturisa<sup>®</sup>,

Recordati Rare Diseases Australia Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 1 submission requested Authority Required (telephone/online) listing for 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.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis (trial-based evaluation) versus three comparators – placebo, metyrapone and ketoconazole.

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

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 1 – 2 mg bid with dose titration permitted up to 30 mg bid. Usual maintenance dose in clinical studies varied between 2 and 7 mg bid.
Comparator	Placebo; metyrapone 500 – 3,000 mg/day; ketoconazole 400 – 2400 mg/day.
Outcomes	Complete response rate, defined as the proportion of patients achieving normalisation of mean urinary free cortisol.
Clinical claim	Osilodrostat is superior to placebo with respect to efficacy and non-inferior with respect to safety; osilodrostat is superior to metyrapone with respect to efficacy and safety; osilodrostat is superior to ketoconazole with respect to efficacy and safety.

Source: Table 1.1-1, p6 of the submission.

bid = twice daily

### 2 Background

#### Registration status

- 2.1 TGA status at time of PBAC consideration: osilodrostat was registered by the TGA on 12 May 2022 for the treatment of endogenous Cushing's syndrome in adults.
- 2.2 Market authorisation had also been granted by the FDA (6 March 2020), the EMA (9 January 2020), in Japan (23 March 2021) and in Switzerland (12 October 2020).

### 3 Requested listing

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

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MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
OSILODROSTAT					
osilodrostat 1 mg tablet, 60 - initial	\$2,561.28 published price \$█ effective price	1	60	2	Isturisa
osilodrostat 5 mg tablet, 60 - initial	\$9,821.28 published price \$█ effective price	1	60	2	Isturisa
osilodrostat 10 mg tablet, 60 - initial	\$10,261.28 published price \$█ effective price	1	60	2	Isturisa
osilodrostat 1 mg tablet, 60 - continuing	\$2,561.28 published price \$█ effective price	1	60	5	Isturisa
osilodrostat 5 mg tablet, 60 - continuing	\$9,821.28 published price \$█ effective price	1	60	5	Isturisa
osilodrostat 10 mg tablet, 60 - continuing	\$10,261.28 published price \$█ effective price	1	60	5	Isturisa

**Proposed listing of medicine – Initial Treatment**

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№. of Rpts	Available brands
OSILODROSTAT					
Osilodrostat, 1 mg oral tablet	New	1	60	2	ISTURISA
Osilodrostat, 5 mg oral tablet	New	1	60	2	ISTURISA
Osilodrostat, 10 mg oral tablet	New	1	60	2	ISTURISA

**Restriction Summary [new1] / Treatment of Concept: [new2]**

Concept ID  (for internal Dept. use)	<b>Category / Program:</b> Section 85 – General Schedule
	<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	<b>Restriction Type – assessment time by Services Australia – Method of obtaining authority approval (if Authority Required)</b> <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Services Australia; retrospective audit of patient records possible) <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues) <input type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as 'FULL' for full assessment by Services Australia)
	The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period: <ul style="list-style-type: none"> <li>• QTc prolongation via an electrocardiogram</li> <li>• Hypocortisolism</li> </ul>
	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.
	<b>Episodicity:</b> Chronic

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<b>Severity:</b> NA
<b>Condition:</b> Endogenous Cushing's Syndrome
<b>Indication:</b> <del>Patients with Chronic</del> Endogenous Cushing's syndrome
<b>Treatment Phase:</b> Initial treatment
<b>Clinical criteria:</b>
<del>Patients must have failed surgery for the removal of the primary tumour</del> Patients must have The condition must be, at least one of: (i) persistent or recurrent hypercortisolism after surgery OR (ii) recurrent hypercortisolism after surgery, OR (iii) inappropriate for surgery.
<b>OR</b>
<del>Patients must not be considered candidates for surgery</del>
<b>AND</b>
Patients 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).
<b>Treatment criteria:</b>
<del>Patients Must be treated and supervised by a physicians experienced in endocrinology or internal medicine by an endocrinologist or a general medicine physician specialising in general medicine</del>
Treatment criteria:
The treatment must not exceed 12 weeks of treatment under this restriction
<b>Population criteria:</b>
Patients must be aged 18 years or older at least 18 years of age.
<b>Prescribing Instructions:</b> <del>To assess patients eligible for initial treatment, The mean UFC should be is the average of at least three urine samples collected preferably on three consecutive days, with at least 2 values being 1.3 times greater than the ULN.</del>  <del>Patients 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. Only patients who demonstrate a complete response between month 2 and 3 are eligible for continuing treatment.</del>  <del>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 daily dose must not exceed 30 mg twice daily. Up to a maximum of 2 repeats will be authorised. Patients must not exceed more than 3 months of treatment under this restriction. The daily dose must not exceed 60mg. Patients must not exceed more than 3months of treatment under this restriction.</del>  <del>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.</del> <del>Patients who failed surgery are defined as those with recurrent or persistent hypercortisolism (UFC &gt; 1.3x ULN).</del>  <del>Patients who are not candidates for surgery are defined as:</del> <ul style="list-style-type: none"> <li><del>• those with a medical contraindication for surgery</del></li> <li><del>• those with inoperable tumours</del></li> <li><del>• surgery unlikely to reduce hypercortisolism</del></li> <li><del>• those who refuse surgery</del></li> </ul> <del>surgical treatment being unavailable to the patient</del>
<b>Prescribing Instructions:</b> 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.
<b>Prescribing Instructions:</b>

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	At the time of authority application, medical practitioners must <del>should</del> request the appropriate number of packs of appropriate strength(s) to provide sufficient drug for 4 weeks as per the product information <del>based on the prescribed dose of the patient, one month of treatment</del> . A separate authority prescription form must be completed for each strength requested. The daily dose must not exceed 30 mg twice daily. Up to a maximum of 2 repeats will be authorised. <del>Patients must not exceed more than 3 months of treatment under this restriction.</del>
	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'.
	<b>Prescribing Instructions:</b> <del>Patients who failed surgery are defined as those with recurrent or persistent hypercortisolism (UFC &gt; 1.3x ULN).</del>  <del>Patients who are not candidates for surgery are defined as:</del> The condition is inappropriate for surgery if the patient: <ul style="list-style-type: none"> <li>• <del>those with</del> has a medical contraindication for surgery</li> <li>• <del>those with</del> has inoperable tumours</li> <li>• has been determined that surgery is unlikely to reduce hypercortisolism</li> <li>• <del>those who</del> refuses surgery</li> <li>• <del>cannot access surgical treatment being unavailable to the patient</del></li> </ul>
	<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
	<b>Notes:</b> <del>Patients who failed surgery are defined as those with recurrent or persistent hypercortisolism (UFC &gt; 1.3x ULN).</del>  <del>Patients who are not candidates for surgery are defined as:</del> <ul style="list-style-type: none"> <li>• <del>those with a medical contraindication for surgery</del></li> <li>• <del>those with inoperable tumours</del></li> <li>• <del>surgery unlikely to reduce hypercortisolism</del></li> <li>• <del>those who refuse surgery</del></li> <li>• <del>surgical treatment being unavailable to the patient</del></li> </ul>
	<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Caution:</b> The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period: <ul style="list-style-type: none"> <li>• <del>QTc prolongation via an electrocardiogram</del></li> <li>• <del>Hypocortisolism</del></li> </ul> <del>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</del>

The requested restriction for continuing treatment is presented below.

**Proposed listing of medicine – Continuing Treatment**

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
Osilodrostat, 10 mg oral tablet	New	1	60	5	ISTURISA

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Restriction Summary [new3] / Treatment of Concept: [new4]	
Concept ID  (for internal Dept. use)	<b>Category / Program:</b> Section 85 – General Schedule
	<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	<b>Restriction Type – assessment time by Services Australia – Method of obtaining authority approval (if Authority Required)</b> <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Services Australia; retrospective audit of patient records possible) <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues) <input type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as 'FULL' for full assessment by Services Australia)
	The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period: <ul style="list-style-type: none"> <li>• QTc prolongation via an electrocardiogram</li> <li>• Hypocortisolism</li> </ul>
	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.
	<b>Episodicity:</b> Chronic
	<b>Severity:</b> NA
	<b>Condition:</b> Endogenous Cushing's Syndrome
	<b>Indication:</b> <del>Patients with Chronic</del> Endogenous Cushing's syndrome
	<b>Treatment Phase:</b> Continuing treatment
	<b>Clinical criteria:</b>
	Patient must have received PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	Clinical criteria:
	Patient must have demonstrated a complete response to this drug.
	<b>Treatment criteria:</b>
	<del>Patients must be treated and supervised by a physicians experienced in endocrinology or internal medicine</del> by an endocrinologist or a <del>general medicine</del> physician specialises in general medicine.
	<b>Population criteria:</b>
	Patients must be at least aged 18 years of age <del>or older</del>
	<b>Prescribing Instructions:</b> A complete response is defined as a mean urinary free cortisol (UFC) less than or equal to the upper limit of normal (ULN). The mean UFC should be the average of at least three urine samples collected within seven days.
	<b>Prescribing Instructions:</b>

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	At the time of authority application, medical practitioners must request the appropriate number of packs of appropriate strength(s) to provide sufficient drug for 4 weeks as per the product information. A separate authority prescription form must be completed for each strength requested. The daily dose must not exceed 30 mg twice daily. Up to a maximum of 5 repeats will be authorised
	<b>Prescribing Instructions:</b> 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'.
	<b>Administrative advice:</b> 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.
	<b>Prescribing Instructions:</b> <del>For the first authority application for continuing treatment, a patient must have demonstrated a complete response to osilodrostat between month 1 and 3 after commencing initial treatment.</del>  <del>For subsequent authority applications for continuing treatment, a patient must have demonstrated a complete response prior to applying for further continuing treatment.</del>  <del>A complete response is defined as a mean urinary free cortisol (UFC) less than or equal to the upper limit of normal (ULN). The mean UFC should be the average of at least three urine samples collected within seven days.</del>  <del>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</del>
	<del><b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.</del>
	<del><b>Administrative Advice:</b> Special Pricing Arrangements apply.</del>
	<b>Caution:</b> The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period: <ul style="list-style-type: none"> <li>• <del>QTc prolongation via an electrocardiogram</del></li> <li>• <del>Hypocortisolism</del></li> </ul> <del>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.</del>

**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	2	ISTURISA
Osilodrostat, 5 mg oral tablet	New	1	60	2	ISTURISA
Osilodrostat, 10 mg oral tablet	New	1	60	2	ISTURISA

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

<b>Concept ID</b>  (for internal Dept. use)	<b>Category / Program:</b> Section 85 – General Schedule
	<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	<b>Restriction Type – assessment time by Services Australia – Method of obtaining authority approval (if Authority Required)</b> <input type="checkbox"/> Unrestricted benefit

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	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Services Australia; retrospective audit of patient records possible) <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues) <input type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as ‘FULL’ for full assessment by Services Australia)
	<p>The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period:</p> <ul style="list-style-type: none"> <li>• QTc prolongation via an electrocardiogram</li> <li>• Hypocortisolism</li> </ul> <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>
	<b>Episodicity:</b> Chronic
	<b>Severity:</b> NA
	<b>Condition:</b> Endogenous Cushing’s Syndrome
	<b>Indication:</b> <del>Patients with</del> Endogenous Cushing’s syndrome
	<b>Treatment Phase:</b> Grandfather treatment
	<b>Clinical criteria:</b>
	Patient must have previously received non-PBS subsidised drug for this condition prior to [list date]
	<b>AND</b>
	<p><del>Patients must have failed surgery for the removal of the primary tumour</del> <del>Patients with persistent or recurrent hypercortisolism after surgery</del></p> <p>The condition must have been, at least one of:</p> <p>(i) persistent hypercortisolism after surgery OR</p> <p>(ii) recurrent hypercortisolism after surgery, OR</p> <p>(iii) inappropriate for surgery, at the time non-PBS subsidised treatment was commenced with this drug</p>
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have demonstrated a complete response to this drug if received at least 3 months of initial non-PBS subsidised therapy.
	<b>OR</b>
	<del>Patients must not be considered candidates for surgery</del>
	<b>Treatment criteria:</b>
	<p><del>Patients must be treated and supervised by a physicians experienced in endocrinology or internal medicine by an endocrinologist or a general medicine physician</del> Must be treated by an endocrinologist or a physician specialises in general medicine</p>
	<b>Population criteria:</b>
	Patients must be at least 18 years of age. <del>aged 18 years or older</del>
	<p>Prescribing Instructions: Only patients who demonstrate a complete response between months 2 and 3 of initial therapy are eligible for continuing treatment.</p>
	<b>Prescribing Instructions:</b>

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	A complete response is defined as a mean urinary free cortisol (UFC) less than or equal to the upper limit of normal (ULN). The mean UFC should be the average of at least three urine samples collected within seven days.
	<b>Prescribing Instructions:</b> At the time of authority application, medical practitioners must request the appropriate number of packs of appropriate strength(s) to provide sufficient drug for 4 weeks as per the product information <del>based on the prescribed dose of the patient, one month of treatment.</del> A separate authority prescription form must be completed for each strength requested. The daily dose must not exceed 30 mg twice daily. Up to a maximum of 5 repeats will be authorised. <del>Patients must not exceed more than 3 months of treatment under this restriction.</del>
	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'.
	<b>Prescribing Instructions:</b> 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.
	<b>Prescribing Instructions:</b> <del>Patients who failed surgery are defined as those with recurrent or persistent hypercortisolism (UFC &gt; 1.3x ULN).</del>  <del>Patients who are not candidates for surgery are defined as:</del> The condition is inappropriate for surgery if the patient: <ul style="list-style-type: none"> <li>• <del>those with</del> has a medical contraindication for surgery</li> <li>• <del>those with</del> has inoperable tumours</li> <li>• has been determined that surgery is unlikely to reduce hypercortisolism</li> <li>• <del>those who</del> refuses surgery</li> <li>• cannot access surgical treatment <del>being unavailable to the patient</del></li> </ul>
	<b>Prescribing Instructions:</b> <del>Only patients who demonstrate a complete response between month 2 and 3 are eligible for continuing treatment.</del>  <del>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 2 repeats will be authorised. Patients must not exceed more than 3 months of treatment under this restriction. The daily dose must not exceed 60mg. Patients must not exceed more than 3 months of treatment under this restriction.</del>  <del>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.</del>
	<b>Notes:</b> <del>Patients who failed surgery are defined as those with recurrent or persistent hypercortisolism (UFC &gt; 1.3x ULN).</del>  <del>Patients who are not candidates for surgery are defined as:</del> <ul style="list-style-type: none"> <li>• <del>those with</del> a medical contraindication for surgery</li> <li>• <del>those with</del> inoperable tumours</li> <li>• <del>surgery unlikely to reduce</del> hypercortisolism</li> <li>• <del>those who</del> refuse surgery</li> <li>• surgical treatment being unavailable to the patient</li> </ul>
	<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.

	<b>Administrative Advice:</b> 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 <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
	<p><b>Caution:</b>  <del>The following should be assessed prior to receiving treatment and closely monitored throughout the treatment period:</del></p> <ul style="list-style-type: none"> <li><del>• QTc prolongation via an electrocardiogram</del></li> <li><del>• Hypocortisolism</del></li> </ul> <p><del>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.</del></p>

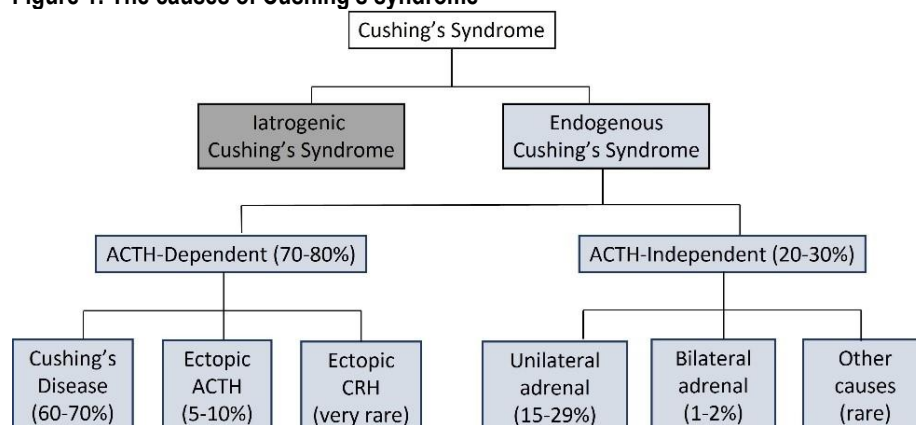
3.2 The requested restriction is narrower than the TGA indication, as the requested restriction specifies that patients must have failed surgery or not be considered candidates for surgery, while the TGA only specifies that patients must have endogenous CS. The osilodrostat clinical trials used in this submission specified that newly diagnosed Cushing’s Disease (CD) patients must not be candidates for surgery, and for patients that had prior pituitary surgery, in LINC 4 it must have been 3 months prior and in LINC 3 at least 30 days prior.

3.3 A grandfathering restriction was requested with the submission, consistent with the initial treatment restriction. The Secretariat noted that the addition of the following clinical criterion to the grandfathering restriction would be important for consistency with the initial treatment restriction: “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”.

## 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, p10 of the submission.

- 4.2 The most common cause of adrenocorticotrophic hormone (ACTH) dependent CS is a pituitary adenoma (approximately 70%), also known as Cushing's disease. 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 submission 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 Cushing's disease are due to excess cortisol secretion and are indistinguishable from other causes of Cushing's syndrome (ectopic ACTH production and adrenal tumours). The ACTH-secreting pituitary adenomas are small, and do not alter the secretion of other pituitary hormones or compress adjacent structures. The diagnostic process therefore begins with establishing that there is excess cortisol secretion, and then proceeds to distinguish the various specific causes. However, as the list of clinical features implies, Cushing's disease is a remote diagnostic possibility in many common clinical presentations. The pre-test probability is usually low, no single test has high sensitivity and specificity, and some common conditions whose clinical features may lead to a suspicion of Cushing's disease are associated with physiological increase in cortisol levels (severe obesity, major depressive disorder, alcohol abuse, etc). Establishing that there is excess cortisol secretion may, therefore, be difficult. Once the presence of excess cortisol secretion is established, ACTH measurement distinguishes ACTH-dependent (Cushing's disease 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 Cushing's disease 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, and neuropsychiatric symptoms improve but are often not cured. Osteoporosis improves over one to two years, but fractures caused by osteoporosis are a common cause of long-term disability and preventing them is a reason to achieve control of hypercortisolism as soon as possible after diagnosis.

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

## **5 Comparator**

- 5.1 The submission nominated three comparators: placebo, metyrapone and ketoconazole. The submission stated that placebo was nominated as a comparator on the basis that there are no PBS-listed medicines that will be replaced by osilodrostat and the two additional comparators, metyrapone and ketoconazole, were nominated because they are the medicines most likely to be replaced by osilodrostat in clinical practice.
- 5.2 The submission indicated that based on informal discussions with clinicians as well as completed questionnaires, metyrapone and ketoconazole are the most used medicines in the treatment of endogenous CS in Australia. There were three questionnaires provided with the submission, all completed by individual clinicians, although one was identified as representative of the views of the Endocrinology Society of Australia (ESA). The questionnaires from the individual clinicians identified the most common first-line treatment as fluconazole, ketoconazole, cabergoline, and metyrapone and ketoconazole if cabergoline fails. The questionnaire from the ESA named ketoconazole (in 70% of patients) and metyrapone (in 20% of patients) as the most common first-line treatments. The submission noted that metyrapone is used off-label for the treatment of CS, and the oral form of ketoconazole was deregistered by the TGA in 2013 and requires importation from overseas.
- 5.3 The submission did not indicate if patients accessed metyrapone and ketoconazole privately or through the Special Access Scheme (SAS), although SAS data indicates that between 2017 and 2021, approximately (a maximum of) 184 people were prescribed with ketoconazole, 33 with metyrapone, and three with osilodrostat.

- 5.4 Other relevant comparators include combined metyrapone and ketoconazole, which was included as a treatment option on the clinician questionnaires, and levoketoconazole, for which there is published evidence indicating benefit over 6 months and longer term (Fleseriu 2019<sup>1</sup>; Fleseriu 2021<sup>2</sup>; Fleseriu 2022<sup>3</sup>).
- 5.5 The ESC considered that placebo was an appropriate comparator to assess comparative effectiveness given other therapies are not approved for use in CS. Metyrapone and ketoconazole are relevant supplementary comparators given they are being used in current clinical practice.

*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 highlighted the significant and severe morbidities associated with CS, and the high clinical need for a long-term therapy. The clinician reiterated the limited therapeutic options for CS and highlighted that the benefits associated with treatment of CS were often gradual to accrue, for example, with radiation therapy, there was usually a delayed onset of response, with symptom improvement occurring after 12 months. The clinician further added that in clinical practice, partial response to treatment could also lead to important clinical benefits. The PBAC considered that the hearing was informative as it provided a clinical perspective on the unmet clinical need for an effective PBS therapy for treating this uncommon disease.

### Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (2), health professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with osilodrostat as well as personal experiences of living with CS, including the limitations of current treatment options and the clinical need, the quality of life benefits associated with osilodrostat, and the need for regular monitoring of side effects. The PBAC noted the patient perspective provided valuable insight particularly given the limitations of the clinical trials.

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<sup>1</sup> Fleseriu M, Pivonello R, Elenkova A, Salvatori R et al. Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label, single-arm trial. *Lancet Diabetes Endocrinol* 2019; 7(11): 855-865.

<sup>2</sup> Fleseriu M, Auchus RJ, Pivonello R, Salvatori R et al. Levoketoconazole: a novel treatment for endogenous Cushing's syndrome. *Expert Rev Endocrinol Metab* 2021; 16:4: 159-174.

<sup>3</sup> Fleseriu M, Auchus RJ, Greenman Y, Zacharieva S et al. Levoketoconazole treatment in endogenous Cushing's syndrome: extended evaluation of clinical, biochemical and radiologic outcomes. *Eur J Endocrinol* 2022; 187: 859-871.

## Clinical trials and studies

6.3 The submission was based on 3 osilodrostat trials, one metyrapone study and 2 ketoconazole studies.

6.4 Details of the trials and studies presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
Osilodrostat trials		
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.
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.	September 2020; July 2021  J Clin Endocrinol Metab 2022; 107(7): e2882-e2895.
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 11 $\beta$ -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.
Metyrapone study		
PROMPT NCT02297945	Prospective, single arm, open-label, multicenter, international study to assess the effects of metyrapone in patients with endogenous Cushing's syndrome during a 12-week treatment period followed by an extension period of 24 weeks. Conference abstract: Nieman LK, Boscaro M, Scaroni CM, Deutschbein T et al. Metyrapone treatment in endogenous Cushing's syndrome: Results at week 12 From PROMPT, a prospective international multicenter, open-label, phase III/IV study. Nieman L, Boscaro M, Carla S, Deutschbein T et al. Metyrapone treatment in endogenous Cushing's syndrome. Long term efficacy and safety results of the extension of the phase III/IV study PROMPT. Presented at Society for Endocrinology ECE2021. Poster presentation: Nieman LK, Akinci B, Beckers A, Bolanowski M et al. PROMPT: a prospective study to assess efficacy and safety of metyrapone in endogenous Cushing's syndrome.	August 2021  J Endocr Soc 2021; 5:A515-A515.  Endocrine Abstracts 2021; 73 OC3.3.  20 <sup>th</sup> European Congress of Endocrinology, Barcelona Spain 2018; poster P859.
Ketoconazole studies		
Castinetti 2008	Castinetti F, Morange I, Jaquet P, Conte-Devolx B, Brue T. Ketoconazole revisited: A preoperative or postoperative treatment in Cushing's disease.	Eur J Endocrinol 2008; 158: 91-99.
Castinetti 2014	Castinetti F, Guignat L, Giraud P, Muller M et al. Ketoconazole in Cushing's disease: Is it worth a try?	J Clin Endocrinol Metab 2014; 99:1623-1630.

Source: Table 2.2-7, p82-84; Table 2.8-9, p212-213 of the submission

6.5 The key features of the trials and studies presented by the submission are summarised in Table 3. The same osilodrostat trials (LINC 3, LINC 4, C1201) were used across the three comparisons (placebo, metyrapone, ketoconazole), with one metyrapone study (PROMPT) and two ketoconazole studies used (Castinetti 2008; Castinetti 2014), although Castinetti 2014 was not included in the indirect comparison.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in trial-based evaluation
<b>Osilodrostat vs. placebo</b>						
LINC 3 and LINC 4 osilodrostat vs. placebo; C1201 included in pooled comparison in trial-based economic evaluation						
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	Complete, partial, overall response <sup>a</sup> ; time to escape; QoL; safety	Sensitivity analysis only (complete responders)
LINC 4	73	R, DB 12 wks then OL osi wk 12 to 48	Low	As for LINC 3 except: mUFC >1.3 × ULN with ≥2 of UFC values being > 1.3 × ULN		Complete responders
C1201	9	OL single arm 48 wks	High	Adult Japanese patients with endogenous CS other than CD	Response rate; QoL	Sensitivity analysis only (complete responders)
<b>Osilodrostat vs. metyrapone</b>						
LINC 3, LINC 4, C1201 for osilodrostat; PROMPT for metyrapone						
PROMPT	49	OL metyrapone to 12 weeks then optional extension phase to Week 36	High	Adults with persistent or recurrent CD after surgery or who are newly diagnosed but unsuitable for surgery; ectopic ACTH syndrome; CS from adrenal causes who are unsuitable or wish to defer surgery mUFC ≥1.5 × ULN on 3 samples	Complete response; QoL; safety	Sensitivity analysis only (complete responders)
<b>Osilodrostat vs. ketoconazole</b>						
LINC 3, LINC 4, C1201 for osilodrostat; Castinetti 2008 and Castinetti 2014 for ketoconazole						
Castinetti 2008	33	Retrospective, observational, single centre	High	Active CD treated with ketoconazole between 1995 and 2005; for most, surgery not curative or not a candidate for surgery	Complete response	Sensitivity analysis only (complete responders)
Castinetti 2014	200	Retrospective, observational, multicentre	High	Active CD treated with ketoconazole between 1995 and 2012; for most, surgery not curative or not a candidate for surgery	Complete response; safety	Not used

Source: Table 2.4-1, p100; Table 2.4-9, p119; Table 2.8-14, p222-223; Table 2.8-23, p233 of the submission.

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

<sup>a</sup> 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.

- 6.6 Given that LINC 3 started with an open label period (N=137) of 26 weeks and only patients responding to osilodrostat treatment were randomised at that point (N=71), this trial must be considered at high risk of bias given only responding patients were randomised. The selection bias in LINC 3 means that any estimate of effect size was likely to be overestimated. LINC 4 had a low risk of bias for efficacy and safety outcomes although patient-reported outcomes would have a higher risk of performance bias. The remaining studies (PROMPT; Castinetti 2008; Castinetti 2014) were non-randomised, single-arm studies and all were at an overall high risk of bias, even with some efficacy outcomes objectively measured.

## Comparative effectiveness

### Osilodrostat vs. placebo

- 6.7 The comparison of osilodrostat and placebo for complete response rate is provided in Table 4.

**Table 4: Osilodrostat vs. placebo: complete response rate**

Trial/ outcome	Osilodrostat	Placebo
<b>LINC 3 – Week 34 (randomisation of responders at 26 weeks)</b>		
N	N=36	N=34
Complete response, n (%)	31 (86.1%)	10 (29.4%)
OR (95% CI)	<b>13.7 (3.7, 53.4)</b>	
<b>LINC 4 – Week 12</b>		
N	N=48	N=25
Complete response, n (%)	37 (77.1%)	2 (8.0%)
OR (95% CI)	<b>43.4 (7.06, 343.19)</b>	
Partial response, n (%)	2 (4.2%)	2 (8.0%)
OR, RD, RR (95% CI)	OR = 0.50 (0.07, 3.78); RD = -0.04 (-0.16, 0.08); RR = 0.52 (0.08, 3.48)	
Overall response, n (%)	39 (81.3%)	4 (16.0%)
OR, RD, RR (95% CI)	OR = <b>22.75 (6.25, 82.79)</b> ; RD = <b>0.65 (0.47, 0.83)</b> ; RR = <b>5.08 (2.05, 12.60)</b>	

Source: Table 2.5-1, p124; Table 2.5-12, p138; Table 2.5-13, p138 of the submission.

Complete response: mUFC  $\leq$  ULN; partial response: mUFC > ULN but  $\geq$ 50% reduction from baseline; overall response: either a complete or partial response.

CI = confidence interval; OR = odds ratio; RD = risk difference; RR = relative risk; **bold** = statistically significant

- 6.8 The proportion of patients with complete response was used by the submission as the basis of the economic evaluation. Although the outcome was statistically significant in favour of osilodrostat, the 95% confidence intervals were very wide, particularly in LINC 4 (7.06 to 343.19). Acknowledging the reasonably small sample size of LINC 4 (N=73), the wide confidence interval suggests low precision and values with low credibility, and therefore uncertainty in the estimate of benefit.
- 6.9 Comparisons of osilodrostat and placebo at Week 12 for cardiovascular and metabolic parameters and physical features showed mixed results. There was a statistically significant greater improvement for osilodrostat-treated patients compared to placebo for HbA1c, cholesterol, LDL, cholesterol, and supine blood pressure. There was also a statistically significant greater reduction in HDL cholesterol for osilodrostat-treated patients, although as acknowledged by the submission, a reduction in HDL cholesterol may be undesirable. There were no differences between osilodrostat and

placebo for fasting glucose, triglycerides, standing blood pressure, body weight, waist circumference and improvements in physical features.

- 6.10 The submission provided longer-term response data for the LINC 4 trial, with complete, partial and overall response at Week 36 and Week 48. In LINC 4, from Week 12 to 48 all patients received osilodrostat, and then responding patients could enter the extension phase of the trial. As can be seen in Table 5, response decreased over time, in both osilodrostat, and placebo + osilodrostat-treated patients.

**Table 5: Complete response in LINC 4 – Week 48 to Week 96**

	Complete response n/N (%)	
	Osilodrostat	Placebo + osilodrostat
Week 48	34/48 (70.8%)	16/25 (64.0%)
Week 60	25/44 (56.8%)	16/24 (66.7%)
Week 72	25/41 (61.0%)	15/24 (62.5%)
Week 84	18/38 (47.4%)	13/23 (56.5%)
Week 96	4/19 (21.1%)	6/13 (46.2%)

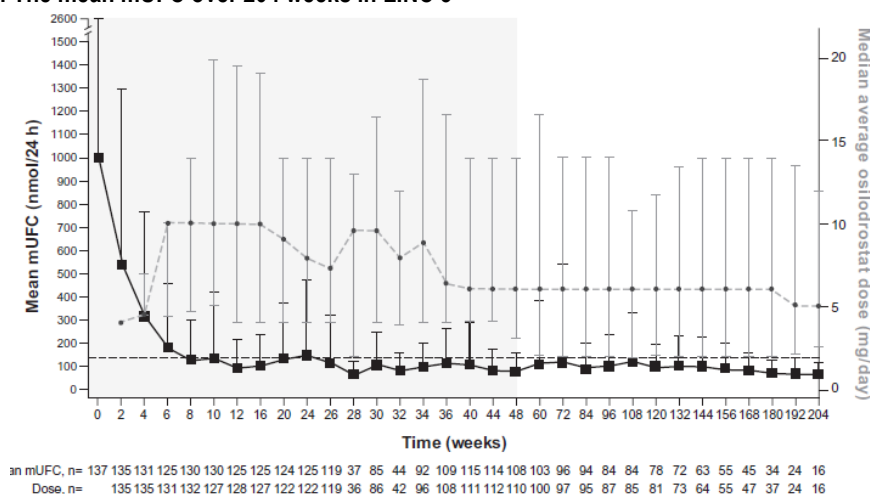
Source: Table 14.2-3.1, p109-114 of the LINC 4 CSR.

- 6.11 There were no statistical comparisons provided of the Week 48, or longer-term extension phase data, but the proportions of complete responders show a decrease for osilodrostat (21.1% at Week 96), and placebo + osilodrostat-treated patients (46.2% at Week 96). This calls into question the durability of response with osilodrostat. While the submission provides a trial-based evaluation based on Week 12 data for its economic evaluation (see below), the available LINC 4 evidence indicates response was not maintained. The Pre-Sub-Committee Response (PSCR) stated that the apparent differences in response rates were an artifact of missing data due to discontinuation of the treatment or due to the COVID-19 pandemic, and non-responder imputation during the optional extension phase. The PSCR indicated that the lower response rates in the osilodrostat group reflected greater missing data than in the placebo group. The PSCR goes on further to argue that rather than the analysis by time point in the extension phase of LINC 4, the End of Treatment (EOT) analysis provides a more meaningful estimate of the response rate. The EOT analysis considers the response of patients at their last available response assessment. In the EOT analysis, 73.7% (28/38) patients in the osilodrostat group and 70.0% (14/20) of patients in the placebo group had a complete response, noting that all patients were treated with osilodrostat at this time (LINC 4 Final Clinical Study Report [CSR], Table 11-1, p47-48). The proportions of complete responders showed a decrease for osilodrostat (21.1% at Week 96), and placebo + osilodrostat-treated patients (46.2% at Week 96), which showed that the response was not maintained. The PSCR stated that the low response rate was a result of non-responder imputation and missing data due to the COVID-19 pandemic or discontinuation of treatment during the optional extension phase rather than loss of response. The PSCR added that the End of Treatment (EOT) analysis which considered the response at the last available response assessment provided a more meaningful estimate of the response rate. In the EOT analysis, 73.7% (28/38) patients in the osilodrostat group and 70.0% (14/20) of

patients in the placebo group had a complete response, noting that all patients were treated with osilodrostat at this time.

6.12 The pre-PBAC response considered that the durability of response was better reflected in LINC 3, which showed complete response rate of 66.4% (91/137) at Week 48 and 81.1% (86/106) at Week 60 and Week 72. The pre-PBAC response also included the figure below to illustrate the durability of response with osilodrostat, based on 204 weeks of follow up from LINC 3.

Figure 2: The mean mUFC over 204 weeks in LINC 3



Shaded area indicates the core phase of LINC 3. The horizontal reference line indicates the upper limit of normal mean 24-h urinary free cortisol. Black lines indicate mean UFC. The dashed lines indicate the median average osilodrostat dose. Source: Fleseriu et al. (2022) Figure 2B p 535; Pre-PBAC response, p1.

6.13 The results of the single arm C1201 osilodrostat trial for complete response at Week 12 were included as part of the pooled osilodrostat data used in sensitivity analyses of the trial-based economic evaluation. The proportion of patients with complete, partial and overall response in C1201 are provided in Table 6.

Table 6: Complete, partial and overall response rate in C1201

	C1201		
	Week 12 (N=9)	Week 24 (N=3)	Week 48 (N=2)
Complete response, n (%)	6 (66.7%)	2 (66.7%)	1 (50.0%)
Partial response, n (%)	1 (11.1%)	1 (33.3%)	1 (50.0%)
Overall response, n (%)	7 (77.8%)	3 (100%)	2 (100%)

Source: Table 2.5-31, p157 of the submission.

6.14 Results for quality of life (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. Table 7 provides a summary of these comparisons.

**Table 7: Change from baseline to Week 12 for QoL data in LINC 4: osilodrostat vs. placebo comparisons**

Scale/ outcome	Osilodrostat		Placebo	
<b>Cushing QoL</b>				
N	N=48		N=25	
Baseline, mean (SD)	49.1 (19.60)		56.9 (18.99)	
Week 12, mean (SD)	55.1 (22.18)		65.6 (17.26)	
Adjusted change from baseline (95% CI)	<b>5.65 (2.18, 9.13)</b>		<b>9.42 (4.59, 14.25)</b>	
Osilodrostat vs. placebo (95% CI)	-3.77 (-9.75, 2.21)			
<b>BDI-II</b>				
N	N=48		N=25	
Baseline, mean (SD)	12.2 (10.22)		8.4 (7.82)	
Week 12, mean (SD)	10.6 (8.38)		4.6 (5.99)	
Adjusted change from baseline (95%CI)	-1.10 (-2.68, 0.49)		<b>-4.74 (-6.94, -2.54)</b>	
Osilodrostat vs. placebo (95% CI)	3.64 (0.92, 6.37)			
<b>EQ-5D-5L</b>	<b>Utility index</b>		<b>VAS</b>	
	<b>Osilodrostat</b>	<b>Placebo</b>	<b>Osilodrostat</b>	<b>Placebo</b>
N	N=48	N=24	N=48	N=23
Baseline, mean (SD)	0.83 (0.15)	0.90 (0.11)	70.3 (17.26)	76.7 (17.88)
Week 12, mean (SD)	0.82 (0.15)	0.92 (0.10)	70.3 (18.81)	76.4 (16.67)
Adjusted change from baseline (95%CI)	-0.01 (-0.05,0.02)	0.04 (0.00, 0.09)	-0.84 (-4.61,2.93)	0.83 (-4.54,6.20)
Osilodrostat vs. placebo (95% CI)	-0.06 (-0.11, 0.00)		-1.67 (-8.26, 4.92)	

Source: Table 2.5-19, p146 of the submission.

CI = confidence interval; BDI-II = Beck Depression Inventory; QoL = quality of life; SD = standard deviation; VAS = visual analogue scale; **bold** indicates statistically significant results

## Unanchored indirect comparisons

6.15 Results for the indirect comparisons for complete response at Week 12 are in Table 8 and Table 9.

**Table 8: Indirect comparison: osilodrostat vs. metyrapone – complete response at Week 12**

Osilodrostat n/N (%)	Metyrapone n/N (%)	RD (95% CI)	RR (95% CI)	OR (95% CI)
<b>LINC 4 vs. PROMPT</b>				
37/48 (77.1%)	23/49 (47%)	<b>0.30 (0.12; 0.48)</b>	<b>1.64 (1.17; 2.30)</b>	<b>3.80 (1.58; 9.13)</b>
<b>Pooled osilodrostat (LINC 3, LINC 4, C1201) vs. PROMPT</b>				
141/194 (72.7%)	23/49 (47%)	<b>0.26 (0.10, 0.41)</b>	<b>1.55 (1.14, 2.11)</b>	<b>3.01 (1.58, 5.73)</b>

Source: Table 2.6-4, p188 of the submission.

CI = confidence interval; OR = odds ratio; RD = risk difference; RR = relative risk; **bold** indicates statistically significant results**Table 9: Indirect comparison: osilodrostat vs. ketoconazole – complete response at Week 12**

Osilodrostat n/N (%)	Ketoconazole n/N (%)	RD (95% CI)	RR (95% CI)	OR (95% CI)
<b>LINC 4 vs. Castinetti 2008</b>				
37/48 (77.1%)	17/38 (44.7%)	<b>0.32 (0.13, 0.52)</b>	<b>1.72 (1.17, 2.53)</b>	<b>4.16 (1.64, 10.51)</b>
37/48 (77.1%)	20/38 <sup>a</sup> (52.6%)	<b>0.24 (0.05, 0.44)</b>	<b>1.46 (1.04, 2.06)</b>	<b>3.03 (1.20, 7.65)</b>
<b>Pooled osilodrostat (LINC 3, LINC 4, C1201) vs. Castinetti 2008</b>				
141/194 (72.7%)	17/38 (44.7%)	<b>0.28 (0.11; 0.45)</b>	<b>1.62 (1.13; 2.34)</b>	<b>3.29 (1.61; 6.71)</b>
141/194 (72.7%)	20/38 <sup>a</sup> (52.6%)	<b>0.20 (0.03; 0.37)</b>	<b>1.38 (1.01; 1.89)</b>	<b>2.39 (1.18; 4.87)</b>

Source: Table 2.8-33, p251 of the submission.

CI = confidence interval; OR = odds ratio; RD = risk difference; RR = relative risk; **bold** indicates statistically significant results.<sup>a</sup> Three patients who were uncontrolled at end of follow-up but who were initially controlled as responders at Week 12 have been included.

6.16 All comparisons showed statistically significant differences for complete response for osilodrostat compared to metyrapone and compared to ketoconazole. The submission

provided discussion of transitivity issues for the indirect comparisons, and noted that the baseline mUFC values were lower in LINC 4, and a greater proportion of patients in LINC 4 had prior surgery (85.4%) compared to those in PROMPT (60%) and Castinetti 2008 (45%). The submission acknowledged that the lower baseline mUFC values in LINC 4 were likely related to the patients having prior surgery, but the submission also claimed, in its discussion of transitivity for the osilodrostat vs. ketoconazole comparison, that previous surgery and baseline mUFC were not considered to impact transitivity. This conclusion was not reasonable, and it is likely that previous surgery and baseline mUFC values will affect the comparisons made.

- 6.17 It should also be noted that the indirect comparisons presented by the submission did not have a common comparator and used single arm, non-randomised studies to provide the comparative data. Overall, the quality of the comparison was low, and this should be considered in interpretation of the statistically significant differences.

### **Comparative harms**

- 6.18 Comparison of osilodrostat and placebo for the occurrence of adverse events (AEs) in the LINC 3 and LINC 4 trials is provided in Table 10.

Table 10: Adverse events: osilodrostat vs. placebo up to Week 12 in LINC 3 and LINC 4

Adverse event	Osilodrostat (N=36)	Placebo (N=35)	RD (95% CI)	RR (95% CI)	OR (95% CI)
<b>LINC 3</b>					
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 <sup>a</sup>	0 <sup>a</sup>	0.00 (-0.05, 0.05)	NE	NE
<b>AEs of special interest</b>					
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 <sup>a</sup>	0 <sup>a</sup>	0.00 (-0.05, 0.05)	NE	NE
Related to QT prolongation	0 <sup>a</sup>	0 <sup>a</sup>	0.00 (-0.05, 0.05)	NE	NE
Arrhythmogenic potential	0 <sup>a</sup>	0 <sup>a</sup>	0.00 (-0.05, 0.05)	NE	NE
<b>LINC 4</b>					
	<b>Osilodrostat (N=48)</b>	<b>Placebo (N=25)</b>	<b>RD (95% CI)</b>	<b>RR (95% CI)</b>	<b>OR (95% CI)</b>
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 <sup>a</sup>	0 <sup>a</sup>	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%)	<b>0.33 (0.10, 0.56)</b>	<b>1.75 (1.10, 2.80)</b>	<b>4.28 (1.52, 12.08)</b>
Death	0 <sup>a</sup>	0 <sup>a</sup>	0.00 (-0.06, 0.06)	NE	NE
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	<b>0.15 (0.03, 0.26)</b>	7.89 (0.47, 132.61)	9.22 (0.50, 168.33)
Pituitary tumour enlargement-related AEs	0 <sup>a</sup>	0 <sup>a</sup>	0.00 (-0.06, 0.06)	NE	NE
Arrhythmogenic potential and QT prolongation	0 <sup>a</sup>	0 <sup>a</sup>	0.00 (-0.06, 0.06)	NE	NE

Source: Table 2.5-54, p169; Table 2.5-55, p170; Table 2.5-59, p175; Table 2.5-60, p176 of the submission.

AE = adverse event; CI = confidence interval; NE = not evaluable; OR = odds ratio; RD = risk difference; RR = relative risk; **bold** indicates statistically significant results.

<sup>a</sup> The submission stated that where no patients reported a safety outcome in either the experimental or control arm, 0.5 was added to both cells. It was not clear exactly which 'cells' the submission was referring to, but for LINC 3 the 95% CIs for the safety outcomes with 0 in each arm had a value of -0.05 or 0.05, and in LINC 4, when safety outcomes were 0 in each arm the 95% CIs had a value of -0.06 and 0.06. With point estimates of 0.00, the reason for presentation of corresponding 95% CI values of 0.05 or 0.06 was not clear.

6.19 In the LINC 3 trial, there were no statistically significant differences in the occurrence of overall AEs and AEs of special interest between osilodrostat and placebo. In the LINC 4 trial, there was statistically significantly greater occurrence of AEs requiring additional therapy for osilodrostat-treated patients. The submission provided no indication of what these AEs were, or what type and extent of additional therapy was required.

6.20 Table 11 provides a summary of AEs in the metyrapone and ketoconazole studies.

**Table 11: Summary of AEs in the metyrapone and ketoconazole studies**

Summary of AEs in PROMPT – metyrapone ITT population (N=50)		
	Week 12	Week 36
Duration of treatment, mean weeks (SD)	NR	30.6 (10.9)
Any AE	42 (84%)	47 (94%)
Mild intensity	35 (70%)	NR
Severe intensity	4 (8%)	NR
Any SAE	10 (20%)	12 (24%)
Adrenal insufficiency	6 (12%)	6 (12%)
Discontinuation due to AE	1 (2%)	4 (8%)
Dose reduction related to AEs	5 (10%)	6 (12%)
Temporary dose interruption related to AE	7 (14%)	9 (18%)
Summary of AEs for ketoconazole		
	Castinetti 2008 (N=38)	Castinetti 2014 (N=190)
Median follow-up, months (range)	12 (0.2 - 72)	NR
Discontinuation due to AE	5 (13.2%)	41 (20.5%) <sup>a</sup>
Severe increase in $\gamma$ -GT (5-fold increase)	1 (2.6%)	NR
Clinical intolerance (nausea and diarrhea)	7 (18.4%)	NR
Biological intolerance (8 x ULN in AST and ALT)	1 (2.6%)	NR
Adrenal insufficiency	0	10 (5.4%)
Liver enzyme increase		
$\leq 5 \times$ ULN	NR	30 (15.8%)
5 to $10 \times$ ULN		4 (2.1%)
$>10 \times$ ULN		1 (0.5%)

Source: Table 2.5-69, p183; Table 2.5-71, p184; Table 2.8-31, p247; Table 2.8-32, p248 of the submission.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NR = not reported; SAE = serious adverse event;  $\gamma$ -GT =  $\gamma$ -glutamyl transpeptidase

<sup>a</sup> Discontinuation due to AEs was reported for the ITT population, N=200.

6.21 The indirect comparison of safety outcomes was based on AEs up to Week 12 for the osilodrostat vs. metyrapone comparison (Table 12), and discontinuation due to AEs for the osilodrostat vs. ketoconazole comparison (Table 13).

**Table 12: Indirect comparison: osilodrostat vs. metyrapone – AEs up to Week 12**

Adverse event	Osilodrostat n/N (%)	Metyrapone n/N (%)	RD (95% CI)	RR (95% CI)	OR (95% CI)
<b>LINC 4 vs. PROMPT</b>					
Any AE	46/48 (95.8%)	42/50 (84%)	<b>0.12 (0.00; 0.23)</b>	1.14 (1.00; 1.31)	4.38 (0.88; 21.81)
Any SAE	2/48 (4.2%)	10/50 (20%)	<b>-0.16 (-0.28; -0.03)</b>	<b>0.21 (0.05; 0.90)</b>	<b>0.17 (0.04; 0.84)</b>
AE leading to discontinuation	1/48 (2.1%)	1/50 (2%)	0.00 (-0.06; 0.06)	1.04 (0.07; 16.19)	1.04 (0.06; 17.15)
AE leading to dose interruption	13/48 (27.1%)	7/50 (14%)	0.13 (-0.03; 0.29)	1.93 (0.84; 4.43)	2.28 (0.82; 6.34)
Adrenal insufficiency	7/48 (14.6%)	6/50 (12%)	0.03 (-0.11; 0.16)	1.22 (0.44; 3.36)	1.25 (0.39; 4.04)

Source: Table 2.6-5, p189 of the submission.

AEs = adverse events; CI = confidence interval; OR = odds ratio; RD = risk difference; RR = relative risk; **bold** indicates statistically significant results.

6.22 There were more osilodrostat-treated patients who reported any AE, and more metyrapone-treated patients who reported SAEs. For the other AE outcomes, there were numerically more osilodrostat-treated patients who had AEs leading to dose interruption. The submission claimed a statistically significant advantage for

osilodrostat, but this was based on an unanchored indirect comparison using a non-randomised single arm study as the comparator and a claim of statistical significance was questionable.

**Table 13: Indirect comparison: osilodrostat vs. ketoconazole – discontinuation due to AEs up to Week 12**

Adverse event	Osilodrostat n/N (%)	Ketoconazole n/N (%)	RD (95% CI)	RR (95% CI)	OR (95% CI)
<b>LINC 4 vs. Castinetti 2008</b>					
Discontinuation due to AEs	1/48 (2.1%)	5/38 (13.2%)	-0.11 (-0.23; 0.00)	0.16 (0.02; 1.30)	0.14 (0.02; 1.26)
<b>Pooled osilodrostat (LINC 3, LINC 4, C1201) vs. Castinetti 2008</b>					
Discontinuation due to AEs	7/194 (3.6%)	5/38 (13.2%)	-0.10 (-0.21; 0.02)	<b>0.27 (0.09; 0.82)</b>	<b>0.25 (0.07; 0.83)</b>

Source: Table 2.8-34, p252 of the submission.

AEs = adverse events; CI = confidence interval; OR = odds ratio; RD = risk difference; RR = relative risk; **bold** indicates statistically significant results.

6.23 The outcome of discontinuation due to AEs showed no statistically significant difference between osilodrostat and ketoconazole, although the rate was lower for osilodrostat (2.1%) compared to ketoconazole (13.2%).

## Benefits/harms

6.24 A summary of the comparative benefits and harms for osilodrostat versus placebo is presented in Table 14. Benefits and harms for the indirect comparisons versus metyrapone and ketoconazole are not provided.

**Table 14: Summary of comparative benefits and harms for osilodrostat and placebo**

Trial	Osilodrostat	Placebo	OR (95% CI)	Event rate/100 patients		RD <sup>a</sup> (95% CI)
				Osilodrostat	Placebo	
<b>Benefits</b>						
<b>Complete response<sup>b</sup></b>						
LINC 4	37/48	2/25	<b>43.4 (7.06, 343.19)</b>	77.1	8.0	0.69 (0.47, 0.80) <sup>a</sup>
<b>Harms</b>						
	Osilodrostat	Placebo	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Osilodrostat	Placebo	
<b>AEs requiring additional therapy</b>						
LINC 4	37/48	11/25	<b>1.75 (1.10, 2.80)</b>	77.1	44.0	<b>0.33 (0.10, 0.56)</b>
<b>Hypocortisolism-related AEs</b>						
LINC 4	7/48	0	7.89 (0.47, 132.61)	14.6	-	<b>0.15 (0.03, 0.26)</b>

Source: Table 2.5-1, p124; Table 2.5-55, p170 of the submission

OR = odds ratio; RD = risk difference; RR = risk ratio; **bold** indicates statistically significant results.

<sup>a</sup> For the comparison of osilodrostat and placebo for complete response the submission provided results based on odds ratio only. The risk difference result was calculated during the evaluation.

<sup>b</sup> Complete response is defined as the normalisation of mean urinary free cortisol.

6.25 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 69 additional patients would have complete response.

- Approximately 33 additional patients would experience AEs requiring additional therapy.
- Approximately 15 additional patients would experience hypocortisolism-related AEs.

## Clinical claim

6.26 The submission described osilodrostat as superior to placebo with regard to efficacy and non-inferior in regard to safety. While there were statistically significant advantages for osilodrostat compared to placebo for complete response and other outcomes, the results should be interpreted with caution:

- The comparison of osilodrostat and placebo for complete response in LINC 4 had very wide 95% CI (OR = 43.4; 95% CI: 7.06, 343.19) which highlighted the limited nature of the data. While there was evidence that osilodrostat was effective, the magnitude of the benefit was considered highly unreliable given the wide CI.
- The durability of response was questionable, as the proportions of complete responders showed a decrease for osilodrostat (21.1% at Week 96) and placebo + osilodrostat-treated patients (46.2% at Week 96).
- There were statistically significant advantages for osilodrostat for changes in some cardiovascular and metabolic parameters, but not for others. There were no statistically significant differences between osilodrostat and placebo for improvement in physical features. The PSCR highlighted that LINC 4 was not powered to detect statistically significant differences in these secondary outcomes, and that it was unlikely that there would be significant improvements in cardiovascular and metabolic parameters and physical features during a short period of 12 weeks. The PSCR also noted that most cardiovascular and metabolic parameters and physical features improved by Week 48 for osilodrostat-treated patients compared to baseline.
- While there were no statistically significant differences between osilodrostat and placebo in Cushing QoL, there was a numerically greater improvement for placebo-treated patients, and placebo-treated patients also had greater improvement on the BDI-II. The PSCR stated LINC 4 was not powered to detect a statistically significant difference in these outcomes, nor was it expected that there would be significant improvements in quality of life over such a short period of 12 weeks. It was further claimed that it may be more appropriate to assess a patient's quality of life over a longer period of exposure to osilodrostat up to Week 48, the end of the core phase of LINC 4. The mean change of 12.0 points in Cushing QoL from baseline to Week 48 exceeded the minimal clinically important difference (MCID) of a 10.1-point change from baseline (LINC 4). The mean change of -30.0% in Beck Depression Inventory (BDI-II) from baseline to Week 48 exceeded the MCID of -17.5% (LINC 4). Similar changes were observed from baseline to Week 48 in LINC 3 for Cushing QoL (mean change: 13.0 points) and BDI-II (mean change: -31.8%).

Together, these results demonstrated that treatment with osilodrostat resulted in clinically meaningful improvements in patients' QoL. However, the ESC considered that given there was no clear evidence of improvement in patient-relevant outcomes after 12 weeks of treatment, this was critical to the relevance of the trial-based economic evaluation (see below).

- 6.27 There were AEs which occurred in a statistically significantly greater proportion of osilodrostat-treated patients, specifically AEs requiring additional therapy and hypocortisolism-related AEs. There was numerically greater occurrence of adrenal hormone precursor accumulation, although the difference was not statistically significant. The ESC acknowledged that there were no Grade  $\geq 3$  hypocortisolism-related AEs in both treatment arms up to Week 12 and a similar proportion of patients experienced Grade  $\geq 3$  AEs requiring additional therapy up to Week 12. However, the ESC considered this may not reflect the adverse-events of longer-term use of osilodrostat, particularly after dose titration, and it was noted that close monitoring for hypocortisolism and QTc prolongation was required throughout treatment. The pre-PBAC response argued that hypocortisolism occurred more frequently during dose titration compared with during long-term treatment and the incidence of QTc prolongation was low throughout the treatment period. The pre-PBAC response also added that the comparative safety of osilodrostat versus placebo during the first 12 weeks of LINC 3 was likely an overestimate of the long-term safety of osilodrostat and therefore argued the clinical claim of non-inferior safety was appropriate.
- 6.28 For the comparison with metyrapone, the submission claimed that osilodrostat was superior in efficacy and safety. This claim was statistically supported for efficacy but was based on an unanchored indirect comparison. The claim for safety was based on a single arm comparison with greater proportion of metyrapone-treated patients with any SAE, but there was also a numerically greater proportion of osilodrostat-treated patients with adrenal insufficiency and AEs leading to dose interruption, as well as a higher proportion of osilodrostat-treated patients with any AEs.
- 6.29 The submission described osilodrostat as superior to ketoconazole with regard to efficacy and safety. As for the metyrapone comparison, the efficacy claim versus ketoconazole was statistically supported, but was based on an unanchored indirect comparison. The safety claim was not strongly supported, as it was based on a single outcome of discontinuation due to AE. The PSCR stated that liver toxicity from oral ketoconazole was well acknowledged, with ketoconazole being deregistered by the TGA and a black box warning assigned by the FDA. The ESC acknowledged the safety concerns with ketoconazole treatment; however, it was difficult to make an overall conclusion due to the limited data.
- 6.30 The PBAC considered that the claim of superior comparative effectiveness to placebo, and to ketoconazole and metyrapone was reasonable.

6.31 The PBAC considered that the claim of non-inferior safety to placebo and superior safety to metyrapone and ketoconazole was reasonable, noting regular monitoring of side effects of hypocortisolism was required.

### Economic analysis

6.32 The submission presented a trial-based economic evaluation, based on direct randomised trials for the comparison versus placebo (LINC 4), and based on indirect comparisons for the comparisons versus metyrapone (PROMPT) and ketoconazole (Castinetti 2008). The type of economic evaluation presented was a cost-effectiveness analysis based on the incremental cost per extra responder.

**Table 15: Key components of the economic evaluation**

Component	Description
Type of analysis	Cost-effectiveness analysis
Outcomes	Proportion of patients achieving complete response (UFC $\leq 1 \times$ ULN)
Time horizon	12 weeks
Methods used to generate results	Decision tree
Health states	- Response (UFC $\leq 1 \times$ ULN) and non-response (UFC $> 1 \times$ ULN)
Cycle length	No cycles, just 12 week response timepoint
Transition probabilities	Response rate: Osilodrostat: 77.1% (37/48; LINC 4) Placebo: 8.0% (2/25; LINC 4) Metyrapone: 47.0% (23/49; PROMPT) Ketoconazole: 44.7% (17/38; Castinetti 2008)
Costs	Drug cost

Source: Table 3.1-1, p279 of the submission.

UFC = urinary free cortisol; ULN = upper limit of normal

6.33 The submission indicated that the intent was to develop a Markov model with multiple health states to evaluate the cost effectiveness of osilodrostat versus placebo, metyrapone and ketoconazole. Since duration of complete response for osilodrostat and placebo could not be estimated given the LINC 4 data, a model was not developed.

6.34 Given there was trial evidence available for 81.1 weeks for LINC 4, with an extension period to 96 weeks, and close to 2 years of follow-up data for ketoconazole, the evaluation stated it could be considered feasible to consider data extrapolation. The PSCR disagreed, stating that to extrapolate time to event data such as time to escape, the observed data must necessarily include events. However, no patients randomised to osilodrostat experienced an escape event during the core or extension phase up to around Week 64. Further, only 2 out of 25 patients randomised to placebo experienced an escape event in LINC 4 and these events occurred after the 12-week placebo-controlled period (i.e., these patients received open-label treatment with osilodrostat). The PSCR further stated that there were no data on the time to loss of response for both ketoconazole and metyrapone thereby preventing the extrapolation of the observed data.

6.35 Results of the trial-based evaluation are in Table 16.

**Table 16: Results of the economic evaluation – 12 week trial-based evaluation**

Component	Osilodrostat	Comparator	Increment
<b>Osilodrostat vs. placebo</b>			
Costs	\$█	\$0	\$█
Complete response	77.1%	8.0%	69.1%
<b>Incremental cost/extra responder (base case)</b>			\$█ <sup>1</sup>
<b>Osilodrostat vs. metyrapone</b>			
Costs	\$█	\$0	\$█
Complete response	77.1%	46.9%	30.1%
<b>Incremental cost/extra responder (base case)</b>			\$█ <sup>2</sup>
<b>Osilodrostat vs. ketoconazole</b>			
Costs	\$█	\$0	\$█
Complete response	77.1%	44.7%	32.4%
<b>Incremental cost/extra responder (base case)</b>			\$█ <sup>3</sup>

Source: Table 3.6-2, p289 of the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

<sup>2</sup> \$55,000 to < \$75,000

<sup>3</sup> \$45,000 to < \$55,000

- 6.36 The incremental cost per extra responder for osilodrostat vs. placebo was \$25,000 to < \$35,000. It was likely that osilodrostat will be used for longer than 12 weeks, with mean treatment duration in the LINC trials ranging from 81.1 to 119 weeks. Cost-effectiveness over a longer time duration was unknown, and it was not reasonable to assume the ICER seen at 12 weeks would be maintained. Published evidence for levoketoconazole in the SONICS trial (Fleseriu 2019) showed that the benefit shown at the end of dose titration (62/94 or 81% with response) was not maintained at 6 months (29/94 or 31%). Longer-term evidence from the LINC 4 trial showed response was not maintained (e.g. at 84 weeks only 18 of 38 patients (47.4%) had complete response).
- 6.37 The cost per extra responder for osilodrostat vs. metyrapone (\$55,000 to < \$75,000) and for osilodrostat vs. ketoconazole (\$45,000 to < \$55,000) had the same problems with respect to duration as the comparison with placebo. These metyrapone and ketoconazole analyses were also impacted by the assumption of no cost for metyrapone and ketoconazole applied in the submission’s base case.

Table 17: Results of sensitivity analyses

Analyses	Incremental cost (\$)	Incremental response rate	ICER	% change ICER
Base case vs. placebo		69.1%	<sup>1</sup>	-
Base case vs. metyrapone		30.1%	<sup>2</sup>	-
Base case vs. ketoconazole		32.4%	<sup>3</sup>	-
Pooled osilodrostat response rate from LINC 3, LINC 4 and C1201 (base case: sourced from LINC 4)				
vs. placebo		65.8%	<sup>1</sup>	+5.0%
vs. metyrapone		26.9%	<sup>2</sup>	+12.1%
vs. ketoconazole		29.1%	<sup>2</sup>	+11.2%
Approximate cost of metyrapone and ketoconazole (base case: \$0)				
vs. placebo		69.1%	<sup>1</sup>	
vs. metyrapone (\$2,575.00)		30.1%	<sup>3</sup>	-14.6%
vs. ketoconazole (\$2,575.00)		32.4%	<sup>3</sup>	-14.6%

Source: Table 3.8-1, p291 of the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

<sup>2</sup> \$55,000 to < \$75,000

<sup>3</sup> \$45,000 to < \$55,000

- 6.38 Sensitivity analysis using pooled osilodrostat data provided limited information. The selection bias in the LINC 3 trial meant that any estimate of effect size was likely to be overestimated, as patients were not randomised unless they were responders, and C1201 was a very small (N = 9) open-label single arm trial that was also at high risk of bias.
- 6.39 The sensitivity analysis applying a cost of \$2,575.38 to both metyrapone and ketoconazole had limited reliability. The drug cost used was sourced from a single clinician questionnaire, and it was highly unlikely the cost for metyrapone and ketoconazole would be identical. A search of ketoconazole costs in pharmacies in the US found costs ranging from \$USD23.57 to \$USD38.52 for 30 tablets of 200 mg, which would provide a month's treatment for an adult. These prices would result in a 12 week cost of \$USD70.71 to \$USD115.56. Using the higher ketoconazole cost of \$USD115.56, converted to AUD\$172.01, would result in an ICER of AUD\$45,000 to < \$55,000, which differed from the submission's result of AUD\$45,000 to < \$55,000. The PSCR highlighted that whilst ketoconazole was not FDA approved for the treatment of CS, it was EMA approved for the treatment of CS, with the regulated pharmacy purchase (ex-manufacturer) prices for 60 x 200 mg tablets ranging between €556 (AUD\$907) and €627 (AUD\$1023) in France, Germany, and Italy and £515 (AUD\$958) in the UK.
- 6.40 The ESC considered that interpretation of the results was hindered by the lack of evidence of patient-relevant health benefits over time and the signal of a potential loss of response with longer term use. The ESC advised that the model should have tested incorporating a decline in response over a longer period and should at a minimum have aligned with the duration of treatment assumed for the financial implications (in this submission the mean duration of treatment was assumed to be 169.5 weeks based on a logarithmic trendline of the time to escape data from LINC 3; this assumption had not been evaluated for the purposes of this economic evaluation).

If transformation of complete response into final outcomes or QALYS was not feasible, then further qualitative description was required to support the value of the response outcome being modelled and whether longer term comorbidities described in section 4 above could be expected to be improved and, if so, sustained long-term if remission was not durable and treatment discontinued.

- 6.41 The pre-PBAC response provided a revised cost per responder analysis considering a longer time horizon of 48 weeks and assuming a weekly probability of loss of response of 1.05% for both osilodrostat and placebo. The probability of loss of response was estimated based on the 68.5% of patients who achieved a complete response to osilodrostat at week 12 and maintained this response at week 48. The weekly cost of osilodrostat was applied to the proportion of patients that continued to be responders and the cost of placebo remained nil. Based on these assumptions, an alternative estimate of the incremental cost per responder at week 48 was \$95,000 to < \$115,000. The pre-PBAC response further argued that the evidence of durability of response from LINC 3 at Week 48 coupled with improvement in QoL and physical features from LINC 4 translated to responders experiencing at least 0.04 QALYs, 12-point improvement in Cushing’s QoL, 30% improvement in BDI-II as well as improvements in physical features (i.e., facial rubor, hirsutism, striae, supraclavicular fat pad, dorsal fat pad, muscle atrophy, central obesity and ecchymoses) and bone mineral density.

**Drug cost/patient/year: \$ [REDACTED]**

**Table 18: Drug cost per patient for proposed drug**

	LINC 4 dose and duration	Trial-based evaluation	Financial estimates	Comparators: placebo; metyrapone; ketoconazole
Mean dose	8.79 mg/day	8.79 mg/day	8.79 mg/day	The submission assumed no cost for the comparators in the trial-based evaluation, and metyrapone and ketoconazole were not included in the financial estimates.
Mean duration	81.1 weeks	1 year	1 year	
Cost/patient/year	NR	\$ <sup>a</sup>	\$ <sup>a</sup> (N = 68 continuing patients only)	

Source: Table 2.4-6, p109 of the submission; Excel workbook 'Isturisa (osilodrostat) – CEA' and Excel workbook 'Isturisa (osilodrostat) – UCM'.

NR = not reported

<sup>a</sup> Based on the average annual cost for each dose used and the proportion using each dose in LINC 4 for all patients.

- 6.42 The LINC 4 CSR reported that the mean dose for patients in the osilodrostat arm of LINC 4 was higher, at 9.2 mg/day, than the dose of 8.79 mg/day calculated for all patients. This may suggest that the inclusion of placebo-treated patients in the calculation of mean osilodrostat dose underestimated the osilodrostat dose used.

**Estimated PBS usage & financial implications**

- 6.43 This submission was considered by DUSC. The submission used an epidemiological approach to calculate the financial estimates, outlined in Table 19.

Table 19: Key inputs for financial estimates

Component	Data source	DUSC Comment	
<b>Epidemiology</b>			
Incidence and prevalence: eligible patients	<p><u>ABS data</u>: The submission used estimates of the total Australian population, aged 18 years and older which were sourced from the ABS data included in the Department of Health and Aged Care's Section 4 Excel workbook.</p> <p><u>Prevalence and incidence</u>: The submission 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;). Detail on the studies is available in Section 4.1.2 of the submission. The submission indicated the prevalence and incidence rates ranged from 57 and 79 per million persons and 1.5 and 3.2 per million persons, respectively. Given this variance in estimates, the submission used an average of the rates in the studies. Estimation of eligible patients for Year 1 was based on prevalent patients only.</p> <p><u>Commentary</u>: This was appropriate as it avoided double-counting for incident patients in Year 1.</p> <p>Prevalence: 67 per million Incidence: 2.2 per million</p> <p><u>Endogenous CS</u> 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.</p> <p><u>Surgery eligibility and success rates</u> 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). See Table 4.2.2 of the commentary on the submission for the rates.</p>	<p><u>Prevalent Population</u></p> <ul style="list-style-type: none"> <li>• DUSC considered the prevalence and incidence used in the submission as reasonable, however there might be an underestimation of the incident population.</li> <li>• The Bolland study prevalence period of 45 years is possibly too long for a prevalence estimate.                             <ul style="list-style-type: none"> <li>○ DUSC noted that the submission has used a higher end average.</li> </ul> </li> </ul> <p>DUSC commented that the distribution of CS sub-populations (Cushing's disease (CD) 70%, other ACTH dependent 10%, and ACTH independent 20%) was reasonable, noting that the figures were obtained through a clinician survey. The PSCR stated that as endogenous CS is a rare disease with limited published data that using clinician estimates provided the best available evidence. 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.</p> <p>DUSC agreed with the commentary (5.02.COM.93-96) that the CS sub-population variable estimates need testing in a sensitivity analysis. Noting that:</p> <ul style="list-style-type: none"> <li>• One of three responses was an</li> </ul>	

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Component	Data source						DUSC Comment																																										
	10%						<p>outlier, the Endocrine Society of Australia (ESA) collated survey responses took priority.</p> <ul style="list-style-type: none"> <li>The rates correlate with National Organization for Rare Disorders (NORD) estimates.</li> </ul> <p>DUSC commented that the estimate for the proportion of patients in whom first and second surgery is successful might be reasonable but dependent on the surgical setting. DUSC considered surgical eligibility and success might be informed by reports in the literature<sup>4</sup>, with many estimates of surgical success substantially higher than those utilised by the submission, which would lead to substantial underestimation. It was however noted that that lower surgical success rates, particularly outside of specialised centres, can be a substantive source of uncertainty in the utilisation and financial estimates, the magnitude of which are unlikely to be accurately captured by either the literature or by the KOL questionnaire.</p> <p>DUSC noted that the Bolland study had 11% of patients who were not biomedically cured at follow-up (6 years average follow up), whereas the submission estimate was 30%.</p> <p>DUSC noted the possibility of leakage to patients before and during radiotherapy and surgery might result in the estimates from the submission being underestimated.</p>																																										
	Ineligible for surgery (50%) = eligible	71	2	2	2	2																																											
	Unsuccessful 1 <sup>st</sup> surgery (17%) = eligible	12	0	0	0	0																																											
	Eligible	82	3	3	3	3																																											
	<b>ACTH-independent</b>																																																
	ACTH-independent: 20%	283	9	10	10	10																																											
	Ineligible for surgery (5%) = eligible	14	0	0	0	0																																											
	Unsuccessful 1 <sup>st</sup> surgery (5%) = eligible	13	0	0	0	0																																											
	Eligible <sup>a</sup>	28	0	0	0	0																																											
	<b>Total eligible</b>	<b>440<sup>b</sup></b>	<b>14</b>	<b>14</b>	<b>15</b>	<b>15</b>																																											
	<table border="1"> <thead> <tr> <th>Eligible patients</th> <th>Year 1</th> <th>Year 2</th> <th>Year 3</th> <th>Year 4</th> <th>Year 5</th> <th>Year 6</th> </tr> </thead> <tbody> <tr> <td>Endogenous CS</td> <td>1,413</td> <td>47</td> <td>48</td> <td>49</td> <td>49</td> <td>50</td> </tr> <tr> <td>Cushing's disease</td> <td>330</td> <td>11</td> <td>11</td> <td>11</td> <td>12</td> <td>12</td> </tr> <tr> <td>ACTH-dependent</td> <td>82</td> <td>3</td> <td>3</td> <td>3</td> <td>3</td> <td>3</td> </tr> <tr> <td>ACTH-independent<sup>a</sup></td> <td>28</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td><b>Total eligible</b></td> <td><b>440<sup>b</sup></b></td> <td><b>14</b></td> <td><b>14</b></td> <td><b>15</b></td> <td><b>15</b></td> <td><b>15</b></td> </tr> </tbody> </table>							Eligible patients	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Endogenous CS	1,413	47	48	49	49	50	Cushing's disease	330	11	11	11	12	12	ACTH-dependent	82	3	3	3	3	3	ACTH-independent <sup>a</sup>	28	0	0	0	0	0	<b>Total eligible</b>	<b>440<sup>b</sup></b>	<b>14</b>	<b>14</b>	<b>15</b>	<b>15</b>	<b>15</b>
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	<p>Source: 5.02.COM.90.</p> <p><sup>a</sup> In the submission's Section 4 Excel workbook, the values for Years 2 to 6 ranged from 0.45 to 0.47 but the submission rounded these up to 1. The values have been returned to 0.</p> <p><sup>b</sup> The submission presented the total number eligible in Year 1 as 420 in Table 4.2-1 and Table 4.2-2, however 330 + 82 + 28 = 440, which corresponds to the values in the Section 4 workbook.</p>																																																
<b>Utilisation</b>																																																	
Uptake and treatment	<p>Uptake: Prevalent population: █████% in Year 1, █████% in Year 2 and █████% in Year 3. Incident population: █████% in Years 2 to 6.</p> <p>Continuing treatment based on complete response rate from LINC 4 at 12 weeks (77.1%). The estimated number of treated patients is in Table 20 of the commentary on the submission, presented for each year separately, with continuing patients not included across years. Given the</p>						<p>DUSC considered that:</p> <ul style="list-style-type: none"> <li>█████% uptake in Year 1 is low and probably an underestimate, noting that complications are common with the disease without treatment. DUSC noted that the</li> </ul>																																										

<sup>4</sup> <https://doi.org/10.3171/2008.8.jns08339> and <https://doi.org/10.1056/nejm198301133080216>

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Component	Data source	DUSC Comment
	<p>number of prevalent patients in Year 1, the assumed uptake rates and treatment duration (see below), it would be expected that patient and script numbers will decrease from Year 4 (5.02.COM.20).</p> <p><u>Grandfathered patients:</u> From the sponsor's managed access program, the submission estimated 5 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> <p>Commentary:</p> <ul style="list-style-type: none"> <li>This was consistent with Section 7.2.4 (p25) of the user manual for the Utilisation and Cost Model Workbook for PBAC Submissions and the PBAC Guidelines (Section 4.2.1) (5.02.COM.20).</li> <li>The estimated net cost to the PBS/RPBS for osilodrostat was highly variable, and particularly given the low estimated uptake in Year 1 by the submission (1%), the estimates were not likely to be accurate. It is likely a risk-share arrangement will be required (5.02.COM.1).</li> </ul>	<p>commentary changed the Year 1 uptake rate to █%, however DUSC commented that since this is a small population in specialist care with symptomatic complications, that uptake is likely to be high. DUSC recommended that an initial uptake rate of █% would be more appropriate. It should be noted that these estimates would primarily affect the distribution of uptake over time rather than overall utilisation, leading to a skew to earlier years in the estimates period, as demonstrated by the sensitivity analysis in the commentary.</p> <ul style="list-style-type: none"> <li>The proportion of patients who achieved a complete response at Week 12 may be underestimated. This may be higher in practice with low-grade leakage within the indication.</li> </ul>
Number of scripts	<p><u>Dosage:</u> The dosage used in the financial estimates was based on the dosage used in LINC 4. The average dose was 8.79 mg/day.</p> <p><u>Treatment duration:</u> Treatment duration was based on the time to escape data from LINC 3 (refer to Table 2.5-7 of the main submission pp. 129-130). The submission indicated that the inverse of the combined observed and extrapolated (logarithmic trendline) time to escape data, the mean duration of treatment was 169.5 weeks, with 12.0 weeks for initial treatment and 157.5 weeks for continuing treatment.</p> <p>Commentary:</p> <ul style="list-style-type: none"> <li>There is potential for inaccuracy, as LINC 3 only included responding patients in the randomised withdrawal phase and follow-up. It is possible that this enriched sample may overestimate treatment duration, or at may not accurately represent treatment duration, in what is likely to be a highly variable population.</li> <li>The incremental cost per extra responder for osilodrostat vs. placebo was \$25,000 to &lt; \$35,000. It is likely that osilodrostat will be used for longer than 12 weeks, with mean treatment duration in the LINC trials ranging from 81.1 to 119 weeks (COM.17)</li> <li>The cost per extra responder for osilodrostat vs. metyrapone (\$55,000 to &lt; \$75,000) and for osilodrostat vs. ketoconazole (\$45,000 to &lt; \$55,000) have the same problems with respect to duration as the comparison with placebo. These</li> </ul>	<p>DUSC considered that the eventual dosage was reasonable, with data from LINC 4 correlating with that from other published cohorts, and that overtreatment being unlikely given the small upwards titration. DUSC noted that moving to a high dose too quickly was a primary cause of adverse events (AEs) including hypocortisolism.</p> <p>DUSC considered treatment duration was under-estimated in the prevalent population with some people potentially needing longer or lifetime treatment, as noted in the LINC 2 and LINC 3 extension cohorts<sup>5</sup>.</p> <p>The submission limited treatment duration to three years which results in a substantial fall in usage estimates from year 4 onwards. DUSC considered the usage estimates in the latter years to be under-estimated.</p>

<sup>5</sup> <https://doi.org/10.1007%2Fs11102-022-01280-6> and <https://ej-e-bioscientific-com.eu1.proxy.openathens.net/view/journals/eje/187/4/EJE-22-0317.xml>

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Component	Data source		DUSC Comment
	<p>metyrapone and ketoconazole analyses are also impacted by the assumption of no cost for metyrapone and ketoconazole applied in the submission's base case.</p> <p><u>Scripts:</u> Given the distribution of doses from LINC 4 and assumed treatment duration, over one year a fully compliant patient requires 12.18 prescriptions. Estimated script numbers are in Table 20 of the commentary on the submission.</p>		<p>DUSC noted that wastage was possible, especially with uptitration using tablets of varying strengths.</p> <p>DUSC considered that the average script count was under-estimated noting that:</p> <ul style="list-style-type: none"> <li>• Using the suggested dose titration, successful treatment could take up to 6 months to reach the highest dose at 1/2mg per week which has not been accounted for in the estimate of scripts</li> <li>• It takes 3 initiation scripts and more than 6 months to get to stable for 40mg and 60mg patients. DUSC noted that this was longer than the trials.</li> <li>• Wastage due to missed or lost tablets has not been factored into the number of scripts.</li> </ul>
<p><b>Cost of medicines</b></p>	<p>Osilodrostat</p>	<p>1 mg tablet, 60: \$2,561.28 published price \$ [REDACTED]                      effective price                      5 mg tablet, 60: \$9,821.28 published price \$ [REDACTED]                      effective price                      10 mg tablet, 60: \$10,261.28 published price \$ [REDACTED]                      effective price</p>	<p>DUSC considered that monitoring costs have not been included. Noting that:</p> <ul style="list-style-type: none"> <li>• It is recommended that cortisol levels (e.g. 24-hour urinary free cortisol, serum/plasma cortisol) be monitored every 1-2 weeks until adequate clinical response is maintained and that on each occasion multiple readings may be required.</li> <li>• 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.</li> </ul> <p>The above requirements would result in patients needing approximately 15-20 UFC tests at a cost of around \$30.50 per test and possibly additional endocrinologist consultations.</p>
	<p>Metyrapone and ketoconazole</p>	<p>Not included.</p>	
	<p>Patient copayment</p>	<p>Copayment was based on use of octreotide for the treatment of acromegaly in the 2021 calendar year. General copayment of \$30.00 was used, as well as \$6.80 for concessional and RPBS. Calculated copayment was \$16.06 for PBS and \$5.84 for RPBS.</p>	

Source: Table 4.1-4, p301; Table 4.1-6, p302; Table 4.2-1, p305; Table 4.2-2, p306; Table 4.2-3, p306; Table 4.2-5, p307 of the submission. ACTH = adrenocorticotrophic hormone; CD = Cushing's disease; CS = Cushing's syndrome

6.44 The estimated patient numbers, prescription numbers and costs for the PBS/RPBS listing of osilodrostat are provided below.

Table 20: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use<sup>a</sup></b>						
Initiating patients	█ 1	█ 1	█ 1	█ 1	█ 1	█ 1
Continuing patients (77.1% <sup>b</sup> )	█ 1	█ 1	█ 1	█ 1	█ 1	█ 1
Number of scripts dispensed <sup>c</sup>	█ 2	█ 2	█ 2	█ 2	█ 2	█ 2
<b>Estimated financial implications of osilodrostat</b>						
<b>Cost to PBS/RPBS less copayments<sup>d</sup></b>	█ 3	█ 4	█ 5	█ 4	█ 4	█ 3

Source: Table 4.2-2, p306; Table 4.3-1, p309 of the submission.

<sup>a</sup> The submission's presentation of initiating and continuing patients was based on the number of estimated patients for each year separately, continuing patients were not included across years. The number of scripts dispensed provides a representation of estimated usage over time, e.g. see script numbers in Year 4.

<sup>b</sup> Complete response rate from LINC 4.

<sup>c</sup> Assuming 12.18 scripts per year for a fully compliant patient as estimated by the submission. Based on distribution of doses from LINC 4 and assumed treatment duration from LINC 3.

<sup>d</sup> General copayment of \$30.00 was used, as well as \$6.80 for concessional and RPBS. Calculated copayment based on use of octreotide for the treatment of acromegaly in the 2021 calendar year was \$16.06 for PBS and \$5.84 for RPBS.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5000

<sup>3</sup> \$0 to < \$10 million

<sup>4</sup> \$10 million to < \$20 million

<sup>5</sup> \$20 million to < \$30 million

6.45 The estimated total cost to the PBS/RPBS varied across the first 6 years of listing, from \$0 to < \$10 million in Year 1 to \$20 million to < \$30 million in Year 3 to \$0 to < \$10 million in Year 6, with a total of \$80 to < \$90 million in the first 6 years of listing.

6.46 The estimated total cost to the PBS/RPBS for osilodrostat varied highly in the sensitivity analyses below (Table 21). The sensitivity analyses showed that

- Changes in prevalence rate altered net cost by approximately 15%. As prevalent patients made up the bulk of the treated population, variation in these estimates would be expected to have a significant impact.
- As patients with CD made up the majority of the patient population (70%), variation in the proportion eligible for surgery changed the financial estimates by -17% to +28%.
- Change to the surgery success rate had considerable impact on the financial estimates. If surgery is successful, patients would not require osilodrostat, so decreases in surgery success resulted in increased net cost, and vice versa. The changes ranged from -62% to +35%.
- Altering uptake had essentially no impact on estimated cost over the 6 years of listing, but had considerable impact on individual years. This has particular relevance given the submission has assumed uptake in prevalent patients of only █% in Year 1, which appears quite low. If uptake in Year 1 is increased to █%, the Year 1 costs increase 150%. The remaining years show a decrease, or little or no change.

Table 21: Sensitivity analyses – estimated financial implications of PBS/RPBS listing of osilodrostat for treatment of endogenous CS

Analysis	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	% change
<b>Base case (\$)</b>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	-
<b>Prevalence rate (base case: 67 per million)</b>							
57 per million (\$)	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	-13%
79 per million (\$)	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>2</sup>	█ <sup>1</sup>	+16%
<b>Proportion eligible for surgery (base case: CD 98% 1<sup>st</sup>, 50% 2<sup>nd</sup>; ACTH-dependent 50%; ACTH-independent 95%)</b>							
CD 1 <sup>st</sup> : 80% (\$)	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>2</sup>	█ <sup>1</sup>	+28%
CD 2 <sup>nd</sup> : 98% (\$)	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	-17%
<b>Surgery success rate (base case: CD 60% 1<sup>st</sup>, 40% 2<sup>nd</sup>; ACTH-dependent 83%; ACTH-independent 95%)</b>							
CD 1 <sup>st</sup> : 80% (\$)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	-35%
CD 1 <sup>st</sup> : 40% (\$)	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>4</sup>	█ <sup>3</sup>	█ <sup>2</sup>	█ <sup>1</sup>	+35%
ACTH-independent: 60% (\$)	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>2</sup>	█ <sup>1</sup>	+21%
ACTH-independent: 40% (\$)	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>4</sup>	█ <sup>3</sup>	█ <sup>2</sup>	█ <sup>1</sup>	+34%
<b>Uptake (base case: prevalent population █% Year 1, █% Year 2, █% Year 3; incident population █% Years 2–6)</b>							
50% Year 1 prevalent (\$)	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	-0.0002%
% change per year	+150%	-4%	0%	-30%	-17%	0%	
50% Year 1 + 70% Year 2 prevalent (\$)	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	0%
% change per year	+150%	+35%	-2%	-30%	-48%	-30%	
50% Year 2 prevalent+90% Year 2 – 6 incident (\$)	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	+1%
% change per year	+150%	-3%	+1%	-29%	-14%	+7%	
<b>Surgery eligibility and surgery success rate (base case: CD: 98% and 60% first-line; 50% and 40% second-line)</b>							
85% eligible 1 <sup>st</sup> line: CD (\$)	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>2</sup>	█ <sup>1</sup>	+20%
50% success 1 <sup>st</sup> line: CD (\$)	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>2</sup>	█ <sup>1</sup>	+18%
95% success 1 <sup>st</sup> line: CD (\$)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	-62%

Source: Table 4.5-1, p311 of the submission; Excel workbook 'Isturisa (osilodrostat) – UCM'.

ACTH = adrenocorticotrophic hormone; CD = Cushing's disease; CS = Cushing's syndrome

The redacted values correspond to the following ranges:

<sup>1</sup> \$0 to < \$10 million

<sup>2</sup> \$10 million to < \$20 million

<sup>3</sup> \$20 million to < \$30 million

<sup>4</sup> \$30 million to < \$40 million

6.47 DUSC noted that MBS costs for the UFC tests required for monitoring were not accounted for in the utilisation and cost model.

6.48 DUSC advised that the eligible population who were unable to achieve a surgical cure and the prevalent uptake rate of █% in Year 1 were underestimated. The DUSC recommended an initial uptake of █% in Year 1, █% in Year 2 and █% for all subsequent years. The DUSC further considered that the usage estimates in later years to be underestimated and the utilisation and cost model should be revised by flowing half the prevalent population through the entire 6 year of estimates. The pre-PBAC

response agreed with the DUSC advice and provided a revised financial estimate, using the DUSC approach as below (Table 22; Revised UCM DUSC).

**Table 22 Net financial implications to the R/PBS**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
DUSC Advice (\$)	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>
Revised UCM DUSC (incl. 50% prev. pat. cont. 6 years) (\$)	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>2</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>
Revised UCM <sup>^</sup> (\$)	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>2</sup>	■ <sup>1</sup>	■ <sup>3</sup>	■ <sup>3</sup>

Source: Isturisa (osilodrostat) – UCM – Pre PBAC.xlsx (Attachment 3)

Abbreviations: incl. = include; prev. = prevalent; cont. = continuing; UCM = utilisation and cost model.

<sup>^</sup> revised UCM applies the methods used in the submission but increases the uptake of the prevalent population to 60% in Year 1 and 70% in Year 2.

The redacted values correspond to the following ranges:

<sup>1</sup> \$10 million to < \$20 million

<sup>2</sup> \$20 million to < \$30 million

<sup>3</sup> \$0 to < \$10 million

### Quality Use of Medicines

6.49 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. DUSC noted that these risks could be mitigated by keeping the listing as a speciality endocrinology prescriber base.

### Financial Management – Risk Sharing Arrangements

6.50 The submission did not propose an RSA.

*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 considered that although there was evidence that osilodrostat was effective in the short term and response would likely be maintained for longer periods, the magnitude of the benefit of this therapy and its cost-effectiveness was uncertain. The PBAC considered that the economic analysis of incremental cost per extra responder as presented was not informative as it did not capture the costs and value of the long-term use and improvement in quality of life that may result from treatment with osilodrostat.
- 7.2 The PBAC acknowledged that there was a high clinical need for new therapies for CS, given the high mortality and morbidity associated with the disease, and that there was no PBS listed medicine for this condition.
- 7.3 The PBAC noted the consumer comments were supportive of making osilodrostat available on PBS as a treatment option and noted the clinician hearing highlighted the difficulty with access to off label metyrapone and ketoconazole.
- 7.4 The PBAC noted the requested PBS restriction limited access to patients with endogenous CS who had failed surgery or were not considered candidates for surgery, and that the continuation criteria required demonstration of complete response by week 12, defined as urinary free cortisol (UFC) level less than or equal to the upper limit of normal. There was also a grandfathering restriction proposed for patients currently accessing treatment on a compassionate access program. The PBAC considered that there are other treatment settings in which osilodrostat may be considered for use in clinical practice, such as pre-operative medical therapy, or in combination with other therapy if UFC was only partially controlled. However, there was no clinical evidence presented in these additional places in therapy and patients would not be eligible for PBS access if currently treated under these conditions in the compassionate access program.
- 7.5 The PBAC considered 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.
- 7.6 The PBAC noted the comparison of osilodrostat and placebo was based on 2 randomised placebo-controlled trials (LINC 3; LINC 4) and one open-label phase II study (C1202). 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.
- 7.7 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)). The PBAC noted the issues raised during evaluation and ESC regarding the durability of response. The PBAC also noted the PSCR and pre-PBAC response which indicated how different approaches to the open-label data of both LINC trials revealed better reflections of a durable response (see paragraphs 6.11 and 6.12). Overall, 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. 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.

- 7.8 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.
- 7.9 The PBAC considered the pre-PBAC response explanation that hypocortisolism occurred more frequently during dose titration and there was low level of QTc prolongation throughout the treatment period, was acceptable. 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. The PBAC considered that adverse events relating to pituitary tumour enlargement should be monitored and required further investigation to better understand the impact of this phenomenon.
- 7.10 The PBAC considered that the claims of superior efficacy and safety to metyrapone and ketoconazole were reasonable, noting the significant toxicity associated with ketoconazole and metyrapone.
- 7.11 The PBAC agreed with the ESC that the 12-week trial-based incremental cost per responder analyses did not allow for assessment of cost-effectiveness of long-term use of osilodrostat in this chronic condition (see paragraph 6.40). However, as noted in paragraph 7.7 the PBAC considered a durable response was biologically plausible. The PBAC noted the pre-PBAC response included an incremental cost per responder analysis over a 48-week time horizon. The PBAC noted the increase in the cost-effectiveness ratio due to the accumulation of costs over a longer period with response measured at a single point in time, although considered the issues regarding interpretation remained. 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).

- 7.12 The PBAC noted that the financial estimates in the submission limited treatment duration to 3 years which resulted in a substantial fall in usage from year 4 onwards. The PBAC agreed with the DUSC that the usage estimates in the latter years was under-estimated as it would be unlikely for patients to cease treatment after 3 years from initiation if the treatment was effective. As a result, the total number of prevalent patients receiving ongoing therapy and the overall financial estimates were underestimated. The PBAC 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, as implied in paragraph 6.47, was not reasonable. The PBAC also agreed with the DUSC revised uptake rates of  $\frac{1}{2}$ % in Year 1,  $\frac{1}{2}$ % in Year 2 and  $\frac{1}{2}$ % for all subsequent years.
- 7.13 The PBAC recommended a resubmission, which may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway. The PBAC advised that the resubmission should address the following issues:
- provide a cost effectiveness or cost utility analysis which incorporates longer duration of therapy (>12 weeks), and longer-term benefits of response, including quality of life data
  - provide revised financial estimates that align better with the expected duration of therapy for responders and uptake rates.
- 7.14 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.