NHS ENGLAND SPECIALISED SERVICES

CLINICAL PANEL REPORT

Date: 17 April 2024

Intervention: osilodrostat phosphate

Indication: endogenous Cushing's syndrome (adults)

URN: 2331

Gateway: 2, Round 1

Programme: Internal Medicine

CRG: Specialised Endocrinology

Information provided to the Panel

Policy Proposition

Evidence Reviews 2331a and 2331b - completed by Solutions for Public Health

Clinical Priorities Advisory Group (CPAG) Summary Report

Evidence to Decision (EtD) Summary

Equalities and Health Inequalities (EHIA) Assessment

Patient Impact Assessment

Blueteq® Forms – Adult and Medicines for Children initiation and continuation

Policy Working Group (PWG) Appendix

This Policy Proposition recommends the use of osilodrostat phosphate in adults with endogenous Cushing's syndrome. Osilodrostat phosphate is licensed for this indication.

Endogenous Cushing's syndrome occurs due to the body excessively producing cortisol. Approximately 70% of endogenous Cushing's syndrome cases are caused by an adrenocorticotrophic hormone (ACTH)-secreting adenoma of the pituitary, a condition known as Cushing's disease. Other causes of Cushing's syndrome include benign or malignant tumours or hyperplasia of the adrenal gland. Cushing's syndrome leads to a broad spectrum of clinical signs and symptoms, including central obesity, muscle wasting, high blood pressure and type 2 diabetes. First-line treatment for most patients is surgery to the source of their Cushing's. However, pre-surgery, patients often require treatment to reduce their cortisol level in order to reduce surgical risks. Some patients may not be suitable for surgery or will have a recurrence of Cushing's despite surgery. Current available medical treatments include metyrapone and ketoconazole, which are considered by the PWG as limited by their effectiveness and side-effect profile.

Two evidence reviews were completed, one for this treatment in people with endogenous Cushing's syndrome (excluding people with Cushing's disease), the other for people with Cushing's disease.

The first evidence review consisted of four studies – a cohort study and prospective and retrospective case series. The studies provided very low certainty evidence. Comparative evidence was available from one study for clinical effectiveness and safety. Limitations included risk of bias across all four studies with very small patient numbers.

The second evidence review consisted of four studies reported in seven papers. The studies provided moderate to very low certainty evidence. The limitations were highlighted as a risk of bias which could affect confidence in the outcomes reported and lack of statistical analysis for some outcomes.

No cost effectiveness studies were included.

Outcomes that were considered critical and important to decision making were presented to Panel members. Clinical Panel members debated the evidence at length. Whilst the evidence returned demonstrated some improvements such as in clinical disease response and biochemical disease, Panel members considered the two evidence reviews and agreed that the stronger evidence appears to relate to Cushing's disease contained in the review 2331b. Panel members were surprised at the small numbers of patients included in the studies as this condition covers are much larger population.

The proposition and the supporting documentation were considered by Clinical Panel members. Several questions raised for clarification and amendments requested.

A question was raised regarding the constitution of the multidisciplinary team. This is detailed in the service specification, which is referenced in the Governance section.

EHIA – two amendments requested.
PIA – no amendments requested.

Recommendation

Clinical Panel recommends that this proposition returns to a future meeting for further consideration.

Why the panel made these recommendations

Panel members agreed that further consideration is needed by the PWG regarding the focus of the proposition, amongst other listed amendments required.

Documentation amendments required

Policy Proposition:

- The evidence base appears to be strongest in the population with Cushing's disease yet the proposition covers the whole spectrum of Cushing's syndrome. PWG to consider as Panel members were uncertain why the proposition is not more focused on Cushing's disease.
- Current treatment section - page 4 – second to last sentence in first paragraph 'For those with Cushing's disease…', the end of the sentence is missing words currently. Words to be added are '*treatment option'*.
- Implementation – page 4 – amendment needed. 'NHS England will routinely commission osilodrostat phosphate in accordance with the patient pathway for patients meeting any

of the following inclusion criteria, and none of the exclusion criteria. Please note that the use of osilodrostat phosphate as outlined in this policy proposition is within the product's marketing authorisation'.

- Inclusion criteria – suitability for radiotherapy and place in the treatment pathway is not mentioned. PWG to consider including this.
- Monitoring – page 6, 3rd paragraph - 'Treatment response is defined as mean 24-hour urinary free cortisol (mUFC) levels over a treatment …' should this define what the response is? Is it mUFC of less than or equal to ULN?
- The multidisciplinary team (MDT) - this is detailed in the service specification, which is referenced in the Governance section. Strengthen wording that the MDT is described in the specification.
- What is a specialised centre for this?
- Patient Pathway – refers to combination treatments which are not referred to in the proposition. PWG to check. The diagram is quite complex and would benefit from the PWG reviewing to see if it can be simplified.

EHIA

- Race and Ethnicity section – the reference to Asians being affected. This is a very broad term and consider revising to be more focused.
- Looked after children section – reference to involvement of paediatricians. PWG to check the accuracy of this reference as this is an adult focused proposition.

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- The Medicines for Children form – criteria relating to pregnancy and counselling need to be included.

Declarations of Interest of Panel Members: None received.

Panel Chair: Anthony Kessel, Deputy Medical Director, Specialised Services

Post Panel Amendments

Policy Proposition		
Panel Comment	**Amendment**	**Page number (if applicable)**
The evidence base appears to be strongest in the population with Cushing's disease yet the proposition covers the whole spectrum of Cushing's syndrome. PWG to consider as Panel members were uncertain why the proposition is not more focused on Cushing's disease.	Cushing's syndrome is a rare disorder (1.8–3.2 cases per million population per year). 70% of Cushing's syndrome cases are caused by Cushing's disease (a pituitary secreting adenoma). Other causes of Cushing's syndrome include malignancy and adrenal hyperplasia. As these causes are less common within an already rare disorder, the PWG expected for there to be a smaller evidence base. All causes of endogenous Cushing's were included in this policy proposition for several reasons: • Osilodrostat phosphate blocks the enzyme 11β-hydroxylase, the enzyme involved in	N/A

	the last step of the production of cortisol in the adrenal glands. Osilodrostat phosphate does not t arget a specific cause of high cortisol. Therefore, the PWG felt there was no pathophysiological reason to separate out causes of endogenous Cushing's syndrome. • Patients with the rarest forms of Cushing's syndrome are often more acutely unwell with their hypercortisolaemia than those with Cushing's disease due to more severe and rapid-onset cortisol excess. This is seen in the evidence review. A case series (Dormoy et al, 2023) reports 30/33 patients with Cushing's syndrome caused by a paraneoplastic syndrome or ectopic adrenocorticotropic secretion were receiving inpatient treatment for the complications of their Cushing's syndrome. The availability of osilodrostat phosphate may prevent them from developing life-threatening complications such as sepsis, thromboembolic events, and hypertensive crises. • Therefore, to exclude these patients would create an inequity of access and would not be in line with the drugs marketing authorisation (which includes all causes of endogenous Cushing's syndrome).	
Current treatment section - page 4 – second to last sentence in first paragraph 'For those with Cushing's disease…', the end of the sentence is missing words currently. Words to be added are '*treatment option'*.	This sentence has been amended.	P4
Implementation – page 4 – amendment needed. 'NHS England will routinely commission osilodrostat phosphat e in accordance with the patient pathway for patients meeting any of the following inclusion criteria, and none of the exclusion criteria. Please note that the use of osilodrostat phosphate as outlined in this policy proposition is	This sentence has been amended.	P4

within the product's marketing authorisation'.		
Inclusion criteria – suitability for radiotherapy and place in the treatment pathway is not mentioned. PWG to consider including this.	Radiotherapy is used to treat persistent or relapsing Cushing's disease only. Radiotherapy takes some time to reduce the cortisol and patients often face waiting lists to get access to this treatment. Additionally, it is considered after surgery and medications have failed, as outlined in the patient pathway on P7. Therefore, suitability for radiotherapy would not be considered in osilodrostat phosphate inclusion criteria.	N/A
Monitoring – page 6, 3rd paragraph - 'Treatment response is defined as mean 24-hour urinary free cortisol (mUFC) levels over a treatment …' should this define what the response is? Is it mUFC of less than or equal to ULN?	This sentence has been amended and now defines what the response is: treatment response is defined as mean 24-hour urinary free cortisol (mUFC) levels in relation to the upper limit of normal over a treatment period with osilodrostat phosphate of up to 3 months at the maximum tolerated dose and following SmPC recommended titration. The definitions of complete, partial and absent treatment response have now been included in the text.	P6
The multidisciplinary team (MDT) - this is detailed in the service specification, which is referenced in the Governance section. Strengthen wording that the MDT is described in the specification.	A sentence has now been added to strengthen the wording 'The composition of these MDTs are described in the Specialised Endocrinology Service Specification A03/S/a, Appendix 1.'	P5
What is a specialised centre for this?	A sentence has now been added in the starting criteria to include the definition to a specialised centre 'as described in the Specialised Endocrinology Service Specification A03/S/a.	P5
Patient Pathway – refers to combination treatments which are not referred to in the proposition. PWG to check. The diagram is quite complex and would benefit from the PWG reviewing to see if it can be simplified.	The patient pathway has been amended and combination treatment has been removed. In order to comprehensively demonstrate the patient pathway, the PWG did not feel the diagram could be simplified further.	P7
EHIA		
Race and Ethnicity section – the reference to Asians being affected. This is a very broad term and consider revising to be more focused.	This phrasing is taken directly from the SmPC, which states: 'the recommended starting dose is 2mg osilodrostat twice daily. For patients of Asian ancestry, a reduced starting dose of 1 mg twice daily is recommended'. This is mirrored in the British National Formulary, which states: 'adult (patients of Asian origin) 1mg twice	N/A

	daily, increased, if tolerated, in steps of 1–2 mg initially'. The evidence review did not return evidence specific to dosing and ethnicity. Therefore, the dosing recommendations have been kept in line with the marketing authorisation as described above.	
Looked after children section – reference to involvement of paediatricians. PWG to check the accuracy of this reference as this is an adult focused proposition.	Although this is an adult only policy proposition, post-pubescent children will have access to osilodrostat phosphate through the NHS England Medicines for Children policy. As part of the Medicines for Children policy, children need to be discussed at an MDT which includes paediatricians.	N/A
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The Medicines for Children form – criteria relating to pregnancy and counselling need to be included.	The phrasing relating to pregnancy and counselling has now been included (in line with the adult Blueteq).	P1