Clinical commissioning policy:

Pasireotide: an injectable medical therapy for the treatment of Cushing's disease

Summary

Pasireotide is recommended to be available as a routine commissioning treatment option for Cushing's disease within the criteria set out in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources. This policy document outlines the arrangements for funding of this treatment for the population in England.

The policy is restricted to adults (≥18 years) as there is insufficient evidence to confirm safety and/or it is not recommended through the licence authorisation process to be used in those age groups not included in the policy.

What we have decided

NHS England has carefully reviewed the evidence to treat patients with Cushing's disease with pasireotide, including pasireotide diaspartate and pasireotide pamoate. We have concluded that there is enough evidence to consider making the treatment available at this time.

Links and updates to other policies

This document updates the clinical commissioning policy: Pasireotide diaspartate: an injectable medical therapy for the treatment of Cushings' Disease. Reference: NHS England: 16052/P.

This document has been informed by: 2013/14 Specialised Commissioning Service Specification for Specialised Endocrinology Services (Adult) [A03/S/A].

Plain language summary

About Cushing's disease

Cushing's disease is caused by a tumour of the 'pituitary gland'.

- This means that the pituitary gland makes too much of a hormone called 'adrenocorticotropic hormone' (ACTH).
- ACTH then causes the 'adrenal gland' to make too much of another hormone called 'cortisol'.

- Cortisol is known as the ‘stress hormone’ and is involved in lots of processes in the body, including control of blood sugar and immune responses.

Cushing’s disease is rare - affecting only one or two people in every million, per year. However, it can lead to a number of medical problems and shorten life expectancy. Without treatment, around half of people with Cushing’s disease would not live for longer than 5 years. The main causes of death are heart disease and stroke.

About the current treatment

The first treatment for Cushing’s disease is usually an operation to remove the tumour. However, in around 20% to 40% of people, this does not cure the illness. In these people, other treatments will be needed. This may include:

- another operation on the pituitary gland
- radiotherapy
- an operation on the adrenal gland

Medicines, including metyrapone and ketoconazole, are often used as part of treatment to help control the illness. However, these treatments are not a cure and cannot be used for a long time as they may cause side effects. Medicines that might be used include:

- those that stop cortisol being made
- those that stop the adrenal gland from releasing cortisol
- those that stop cortisol working in the same way in the body
- those that stop the pituitary gland from releasing ACTH

About the new treatment

Pasireotide is a medicine that stops the pituitary gland from releasing ACTH. It is put forward as an alternative treatment that might benefit patients if:

- they are not able to tolerate the usual medicines
- their symptoms are not well controlled by the usual medicines.

Pasireotide may be administered as pasireotide diaspartate, by subcutaneous injection given twice daily, or as pasireotide pamoate, by deep intramuscular injection given every four weeks. The choice of preparation should be guided by individual patient need and through discussion with the treating clinician.

Epidemiology and needs assessment

Cushing's disease is a rare condition with an incidence of 1-2 per million population per year. For some patients (20-40%) primary pituitary surgery is not curative and further treatment is required. Medical therapy is used in order to manage the condition whilst waiting for curative treatment to become possible or effective. Expert clinical opinion is that an estimated 25 patients per year in England require medical therapy at any stage in the pathway and that 5-10 may require treatment with pasireotide when metyrapone and ketoconazole have not been tolerated or are not clinically effective.

Cushing's disease is a heterogeneous disorder requiring a multi-disciplinary and individualised approach to patient management. Generally, the treatment of choice for Cushing's disease is curative surgery with selective pituitary resection. Second- line treatments include more radical surgery, pituitary radiation therapy, medical therapy, and bilateral adrenalectomy.

Because of the significant morbidity of Cushing's disease, early diagnosis and prompt therapy is important.

Implementation

Inclusion criteria

Adult patients (aged 18 years and above) should be considered for treatment with pasireotide if they meet **ALL** of the following criteria:

- Diagnosis of Cushing's disease

  AND

- Requiring medical therapy

  AND

- The decision to use pasireotide is endorsed by the patient's multidisciplinary team[1] (MDT) (with experience in the management of Cushing's disease) with support from other services

  AND

- Definitive curative therapy is planned (further surgery, radiotherapy, or bilateral adrenalectomy)

  AND EITHER

  - Have not achieved control

  OR

  - Unable to tolerate metyrapone and ketoconazole

Pasireotide should only be used for a defined period (for example, while waiting for radiotherapy treatment to become effective or to stabilise prior to surgery). In all cases initial therapy will be for a defined period of 2 months. Pasireotide therapy may continue if tolerated by the patient and if measures of cortisol production show a 50% fall compared to levels measured before commencing treatment.

Exclusion criteria

Patients are excluded if they meet **ANY** of the following criteria:

- Patients who require medical therapy but have not trialled, and are not contraindicated to, metyrapone and ketoconazole.

[1] The following specialities should be represented at the MDT: pituitary surgery, pituitary endocrinology, laparoscopic adrenal surgery and pituitary radiotherapy.

- Patients who are contraindicated to pasireotide as per the Summary of Product Characteristics.

Starting criteria

As a number of treatment modalities are available, patients will have their condition managed by a full multi-disciplinary team with access to a dedicated pituitary surgeon, pituitary endocrinologist, laparoscopic adrenal surgeon and pituitary radiotherapist. The decision to use pasireotide must be endorsed by the patient's multi-disciplinary team (with experience in the management of Cushing's disease) with support from other relevant service areas.

Stopping criteria

Treatment will be stopped in patients who meet **ANY** of the following criteria:

- Treatment is not tolerated by the patient
- Measures of cortisol production do not show an improvement at 2 months and a 50% fall from baseline at 4 months
- Definitive therapy becomes effective (this may require a trial period off pasireotide therapy to demonstrate normal or low cortisol production (pasireotide may need to be reinstated if unsuccessful))

Dosing

The use of pasireotide as outlined in this policy is in line with its licensed indications.

Pasireotide diaspartate

The recommended initial dose for the treatment of Cushing’s disease with pasireotide diaspartate is 0.6 mg twice daily for 2 months by subcutaneous injection. The dose may be increased if necessary to a maximum of 0.9 mg based on response and tolerability.

Management of suspected adverse reactions at any time during the treatment may require temporary dose reduction. Dose reduction by decrements of 0.3 mg twice a day is suggested. If a dose of pasireotide diaspartate is missed, the next injection should be administered at the scheduled time. Doses should not be doubled to make up for a missed dose.

Pasireotide pamoate

The recommended initial dose for the treatment of Cushing’s disease with pasireotide pamoate is 10 mg every 4 weeks by deep intramuscular injection. The patient should be evaluated for clinical benefit after the first month of treatment and periodically thereafter. The dose may be titrated every 2 to 4 months based on response and tolerability up to a maximum of 40 mg every 4 weeks.

Dose reduction and/or dose interruption may be required based on individual safety and/or tolerability. If no clinical benefit is observed, the patient should be considered for discontinuation. This should be determined by the treating clinician.

Management of suspected adverse reactions or over-response to treatment (cortisol levels < lower limit of normal) may require dose reduction, interruption or discontinuation of pasireotide pamoate.

Monitoring

Cortisol production must be monitored every 2 months with a trial of withdrawal as cortisol production returns to the normal range.

Patient pathway

Patients with recurrent/persistent Cushing's will have their condition managed by a full multi-disciplinary team with access to a dedicated pituitary surgeon, pituitary endocrinologist, laparoscopic adrenal surgeon and pituitary radiotherapist. The structure of the service will be developed locally; however, will usually involve joint care between local hospitals and specialised centres.

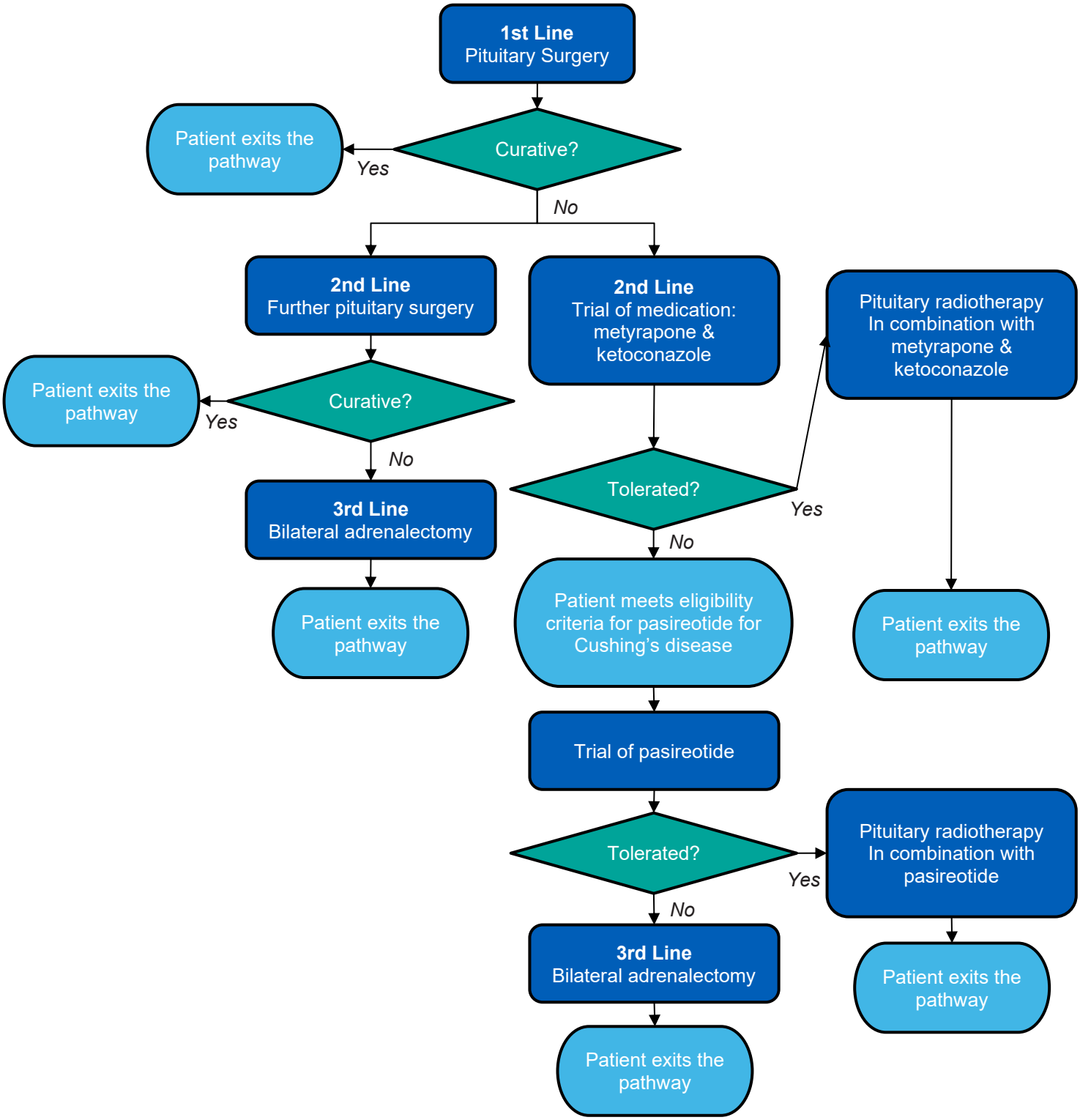
Primary treatment for Cushing's disease is pituitary surgery. For some patients (30- 40%) this is not curative and radiotherapy to the tumour remnant can result in cure over the following months or years. Medical therapy is most commonly used at this stage in order to manage the condition whilst waiting for radiotherapy to become effective. In all cases where medical therapy is prescribed, pasireotide diaspartate or pasireotide pamoate is commissioned as a second line treatment where metyrapone and ketoconazole have not been tolerated or are not clinically effective. Pasireotide should only be used for a defined period for patients who are on a curative pathway - for example patients who are waiting for radiotherapy treatment to become effective or require additional condition management prior to surgery. In particular, the license for pasireotide diaspartate states: after two months, the patient’s response to treatment should be evaluated, and the dose adjusted as appropriate or treatment stopped if no benefit is seen. In some circumstances it may be clinically appropriate to commence treatment with the short acting subcutaneous formulation of pasireotide (pasireotide diaspartate) and then switch to the monthly intramuscular (long-acting) preparation of pasireotide (pasireotide pamoate) when treatment has stabilised. There is no clinical data available on switching from the subcutaneous to the intramuscular pasireotide formulation. If such a switch should be required, the recommended initial dose for the treatment of Cushing's disease is 10 mg of pasireotide pamoate by deep intramuscular injection every 4 weeks. The patient should be monitored for response and tolerability, and further dose adjustments may be needed.

For some patients who are unable to tolerate medical therapy, adrenalectomy may be considered as a more radical approach to reduce treatment time.

In summary, the treatment pathway for an individual patient can be complex and medical therapy may be used at a number of stages to stabilise the condition however it will not in itself result in a long-term cure. Patients who do not receive or respond to curative therapy would likely require lifelong palliative support.

A flow diagram of the most common patient pathway is outlined below.

Figure 1: Patient pathway for pasireotide for Cushing's disease



Governance arrangements

The service specification for Specialised Endocrinology describes the care pathways and key aspects being commissioned and should be referred to in conjunction with this policy. Accurate assessment of disease activity is essential to determine both the eligibility for pasireotide and assessing efficacy of treatment. This will require a multidisciplinary assessment of disease by clinicians experienced in assessing and treating Cushing's disease.

Mechanism for funding

Pasireotide will be funded through local Specialised Commissioning teams.

Audit requirements

Clinicians will be required to record both short term and long-term outcomes of individuals with Cushing's disease who receive pasireotide, including consistent monitoring of the patients' cortisol levels.

Provider organisations must register all individuals receiving pasireotide using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined. This information is collected to inform future policy revisions.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

Cushing’s disease	Sub-type of Cushing’s syndrome caused by pituitary adenoma releasing high levels of adrenocorticotropic hormone (ACTH)
Pasireotide	A novel cyclohexapeptide, injectable somatostain analogue. Like the natural peptide hormones somatostatin-14 and somatostatin-28 (also known as somatotropin release inhibiting factor (SRIF)) and other somastostatin analogues, pasireotide diaspartate exerts its pharmacological activity via binding to somatostatin receptors.
Pasireotide diaspartate	An injectable formulation of pasireotide. Administered by subcutaneous injection twice daily.
Pasireotide pamoate	A long-acting injectable formulation of pasireotide. Administered by deep intramuscular injection every four weeks.

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