

Clinical Commissioning Policy: Pasireotide diaspartate: an injectable medical therapy for the treatment of Cushings' Disease

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Clinical Commissioning Policy: Pasireotide diaspartate: an injective medical therapy for the treatment of Cushing's disease

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Policy Statement

NHS England will commission pasireotide diaspertate as an injectable medical therapy for the treatment of Cushing's disease in accordance with the criteria outlined 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.

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

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 'adrenocorticotrophic 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.

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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
- radio-therapy
- an operation on the adrenal gland.

Medicines 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 diaspertate 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.

What we have decided

NHS England has carefully reviewed the evidence to treat patients with Cushing's disease with pasireotide diaspertate. We have concluded that there is enough evidence to consider making the treatment available.

1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a policy to routinely commission pasireotide diaspartate in the treatment of Cushing's disease.

Cushing's disease is caused by a tumour of the pituitary gland that secretes high levels of adrenocorticotrophic hormone (ACTH) that in turn drives the adrenal gland to secrete high levels of the hormone cortisol. It is a rare condition with an incidence of 1-2 per million population per year, with a 50% 5-year mortality in the untreated condition.

With modern diagnosis and management, the prognosis is greatly improved although the condition is still associated with considerable morbidity including: cardiovascular disease, infection, hypertension, osteoporosis, depression, and psychosis. Despite treatment, mortality is still significantly higher than control populations, with cardiovascular disease the greatest risk. This is due, in part, to delays in diagnosis and also the availability of effective therapy. Medical treatment for Cushing's disease is commonly used as second line treatment following pituitary surgery when further curative treatment is planned. The most effective agents currently used are metyrapone and ketoconazole and whilst these medications are effective for the majority of individuals, their usefulness is limited by toxicity in some people. Pasireotide diaspartate has been determined as a beneficial, alternative medical therapy used within its licence for those patients who are intolerant to, or whose symptoms are not appropriately managed by, the conventional therapies.

2 Definitions

Cushing's disease is a sub-type of Cushing's syndrome caused by pituitary adenoma releasing high levels of adrenocorticotrophic hormone (ACTH).

Pasireotide diaspartate is a novel cyclohexapeptide, injectable somatostatin analogue. Like the natural peptide hormones somatostatin-14 and somatostatin-28 (also known as somatotropin release inhibiting factor (SRIF)) and other

somastostatin analogues, pasireotide diaspertate exerts its pharmacological activity via binding to somatostatin receptors.

3 Aims and Objectives

This policy aims to describe NHS England's commissioning approach for pasireotide diaspertate in the treatment of Cushing's disease.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for individuals with Cushing's disease.

4 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 diaspertate when metyrapone and ketoconazole have not been tolerated or are not clinically effective (see section 8).

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.

5 Evidence base

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of pasireotide diaspartate in the treatment for patients with Cushing's disease requiring medical therapy who have not achieved control, or who are unable to tolerate metyrapone and ketoconazole.

The evidence for clinical effectiveness of pasireotide diaspartate in Cushing's disease (CD) comes from a single drug-company sponsored, relatively large, randomised study (Colao et al, 2012). This Phase III trial of pasireotide diaspartate in CD was a multicentre study that included 162 patients with persistent or recurrent disease or who were ineligible for surgery. 128 patients had a history of pituitary surgery for the treatment of their Cushing's disease, 78 were on medication and 7 had a past history of pituitary irradiation. Patients were randomized to receive pasireotide diaspartate 600 µg (n = 82) or 900 µg (n = 80) subcutaneously twice daily for 12 months. There were high and similar levels of drop outs in both treatment arms. The rate of drop out remained broadly steady throughout the trial period (29 by month 3, another 26 by month 6 and 29 more by month 12). In total 26 were for adverse events, 37 for lack of efficacy and another 21 either withdrew consent or breached the protocol.

Only the higher initial dose regime arm met the primary outcome measure (normalised urinary free cortisol) – which was a cohort of 53 at month 6. The authors conclude that it would have been unethical to have a non-treatment control group, but also state there was no comparator arm as there is “no approved medical therapy”. There are several concerns within the methodology including the lack of a comparator treatment arm and the shifting nature of patients between randomised and open-label participants.

An additional limitation of the Phase III study is the imbalance in baseline UFC levels between the two treatment groups (higher in the 600 µg group), which may have had an effect on outcomes. The mean daily dose of pasireotide diaspartate in both treatment groups also increased over the 12 months study period (1353 µg/day in 600 µg group vs 1813 µg /day at month 12) suggesting the actual effective dose may be much higher than the 600 µg and 900 µg dosage used in the study. The lack of

blinding also increases the possibility of bias in the study - after month 3 only patients who met the primary endpoint continued in a double blind fashion through to month 6 and the rest entered into an open label phase. All patients were entered into an open label phase after 6 months of study. It is likely that this unblinding could have introduced some bias, particularly in relation to patient reported outcome measures. As the primary outcome measure was based on urine estimation of UFC, it is recognised that unblinding is unlikely to have influenced the primary outcome measure.

There are two further publications based on data from this trial providing an analysis of the impact of pasireotide diaspertate on secondary outcome measures (Pivonello et al, 2014) and quality of life (Webb et al, 2014). Decreases in urinary free cortisol from baseline to months 6 and 12 were statistically significant in both treatment groups ($P < 0.001$). Normalisation of urinary free cortisol was more likely to be achieved in patients with lower baseline levels than in patients with higher baseline levels. Most patients (approximately 90%) whose hypercortisolism was uncontrolled ($UFC > ULN$ but with $\leq 50\%$ reduction from baseline) at months 1 and 2 continued to have uncontrolled hypercortisolism at months 6 and 12 indicating patients unlikely to have a response to pasireotide diaspertate can be identified within the first few months of treatment. Improvements in other secondary outcomes measures were seen including systolic blood pressure ($P = 0.03$), diastolic blood pressure ($P = 0.03$), low-density lipoprotein (LDL) cholesterol ($P < 0.001$) and weight ($P < 0.001$).

The impact of pasireotide diaspertate on quality of life was studied using Cushing QoL. Cushing QoL increased as mUFC levels declined but a statistically significant correlation of -0.40 ($p < 0.01$) was observed from baseline to 12 months and not at 6 months. This relation was maintained even after adjusting for number of variables through regression analysis. There was moderately large (0.53) effect sizes for Cushing QoL improvements from baseline to 6 months and 12 months. A strong correlation ($r = -0.70$) was observed between Cushing QoL and Becks Depression Index-II indicating lower QoL was associated with greater depression severity.

Long term effects of pasireotide diaspertate (up to 4 years) have been reported in two studies (MacKenzie et al, 2014 and Simeoli et al, 2015). Both involved the study of a small number of phase 3 trial patients entering into an extension phase of

treatment. Simeoli et al demonstrated that after 24 months of treatment of 8 patients with microadenoma with pasireotide diaspertate, a >25% reduction in tumour volume was found in 62.5% and in 100% of patients after 6 and 12 months, respectively. The study by MacKenzie et al, 2014 involved 4 patients in an extension phase, of these two patients had sustained biochemical and clinical response after 9 months of treatment. All 4 patients developed glucose intolerance and complications included second degree atrioventricular block type 1 without QT prolongation in one patient with pre-existing sinus bradycardia, and symptomatic cholelithiasis requiring cholecystectomy.

There are no published studies evaluating cost effectiveness of pasireotide diaspertate. Similarly there are no published studies comparing pasireotide diaspertate with other drugs used in management of Cushing's disease or studies evaluating pasireotide diaspertate in combination with other drugs used in CD.

The evidence of effectiveness on a number of other drugs used in CD comes from limited number of small retrospective case series with varying definition of primary end point and therefore difficult to compare effectiveness against each other.

6 Criteria for Commissioning

Pasireotide diaspertate should be used, according to its licensed dose, for patients with Cushing's disease requiring medical therapy who have not achieved control, or who are unable to tolerate, metyrapone and ketoconazole.

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 diaspertate 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.

Pasireotide diaspertate may only be used where a definitive curative therapy is planned (further surgery, radiotherapy or bilateral adrenalectomy) and 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 diaspertate 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. Cortisol production must be monitored every 2 months with a trial of withdrawal as cortisol production returns to the normal range.

Exclusions: Patients who require medical therapy but have not trialled, and are not contraindicated to, metyrapone and ketoconazole. Patients who are contraindicated to pasireotide diaspertate as per the licence.

Starting Criteria: Pasireotide diaspertate may be used as defined above.

Stopping Criteria: Pasireotide diaspertate will be stopped if treatment is not tolerated by the patient. Pasireotide diaspertate will be stopped if measures of cortisol production do not show an improvement at 2 months and a 50% fall from baseline at 4 months. Pasireotide diaspertate will be withdrawn when definitive therapy becomes effective. This may require a trial period off pasireotide diaspertate therapy to demonstrate normal or low cortisol production (pasireotide diaspertate may need to be reinstated if unsuccessful).

7 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 diaspertate is commissioned as a second line treatment where metyrapone and ketoconazole have not been tolerated or are not clinically effective. Pasireotide diaspertate should only

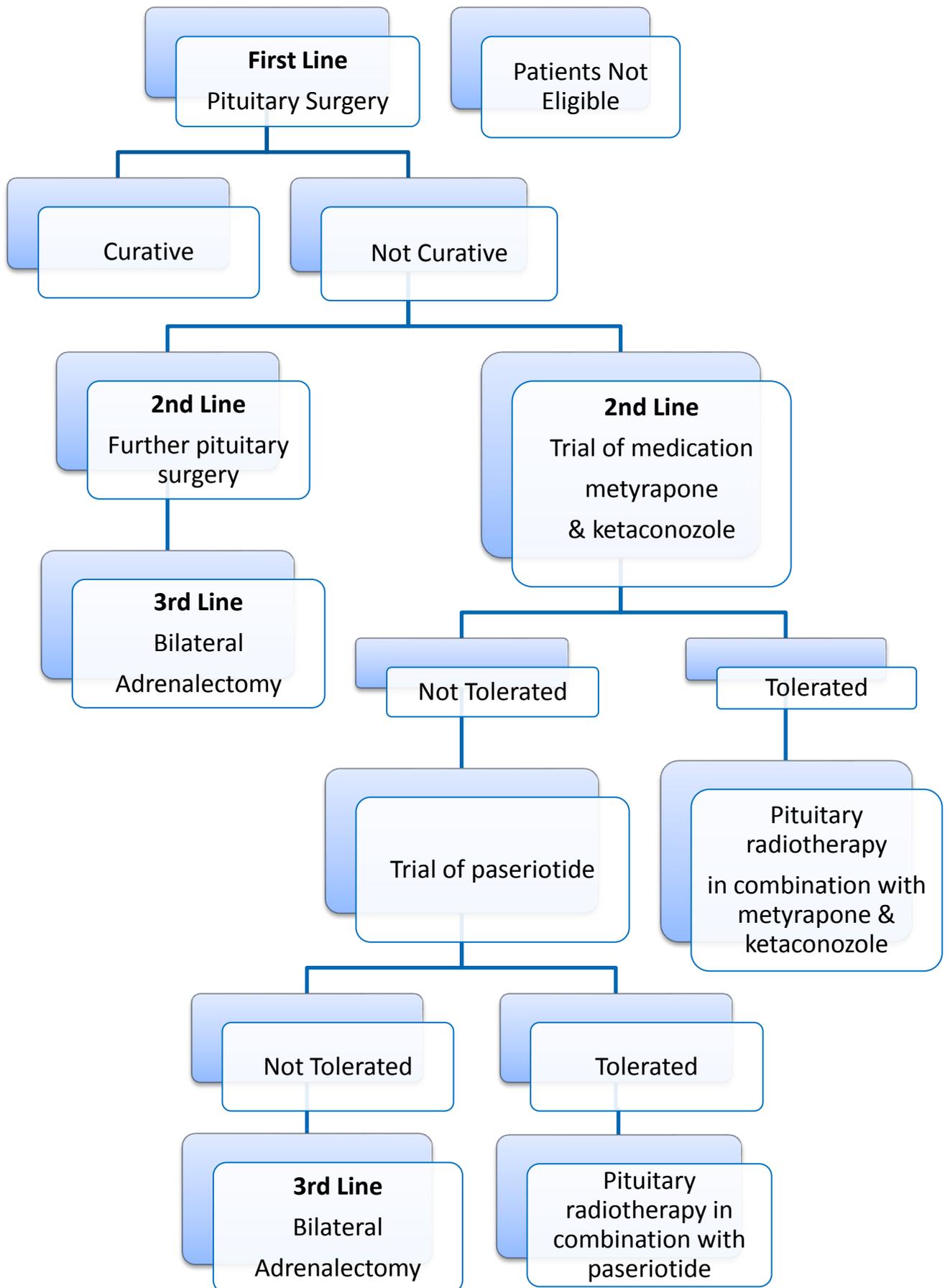
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be used for a defined period for patients who are on a curative pathway - for example patients who are waiting for radiotherapy treatment to become effective or require additional condition management prior to surgery. The license states: after two months, the patient's response to treatment should be evaluated, and the dose adjusted as appropriate or treatment stopped if no benefit is seen.

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.



8 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 diaspartate and assessing efficacy of treatment. This will require a multidisciplinary assessment of disease by clinicians experienced in assessing and treating Cushing's disease.

9 Mechanism for Funding

Pasireotide diaspartate will be funded through local Specialised Commissioning teams.

10 Audit Requirements

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

11 Documents which have informed this Policy

2013/14 Specialised Commissioning Service Specification for Specialised Endocrinology Services (Adult) [A03/S/A].

12 Date of Review

This policy document will be reviewed after 5 years.

References

Colao, Annamaria; Petersenn, Stephan; Newell-Price, John; Findling, James W.; Gu, Feng; Maldonado, Mario; Schoenherr, Ulrike; Mills, David; Salgado, Luiz Roberto; Biller, Beverly M. K.; Pasireotide B2305 Study Group. A 12-month phase 3 study of pasireotide in Cushing's disease. *N. Engl. J. Med.*. 2012

MacKenzie Feder, Jessica; Bourdeau, Isabelle; Vallette, Sophie; Beauregard, Hugues; Ste-Marie, Louis-Georges; Lacroix, André. Pasireotide monotherapy in Cushing's disease: a single-centre experience with 5-year extension of phase III Trial. *Pituitary*. 2014

Pivonello, Rosario; Petersenn, Stephan; Newell-Price, John; Findling, James W.; Gu, Feng; Maldonado, Mario; Trovato, Andrew; Hughes, Gareth; Salgado, Luiz R.; Lacroix, André; Schopohl, Jochen; Biller, Beverly M. K.; Pasireotide B2305 Study Group. Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing's disease: results from a Phase III study. *Clin. Endocrinol. (Oxf)*. 2014

Simeoli, Chiara; Auriemma, Renata Simona; Tortora, Fabio; De Leo, Monica; IacuanIELLO, Davide; Cozzolino, Alessia; De Martino, Maria Cristina; Pivonello, Claudia; Mainolfi, Ciro Gabriele; Rossi, Riccardo; Cirillo, Sossio; Colao, Annamaria; Pivonello, Rosario. The treatment with pasireotide in Cushing's disease: effects of long-term treatment on tumor mass in the experience of a single center. *Endocrine*. 2015