



# **Clinical Commissioning Policy Proposition: Pasireotide for acromegaly as third-line treatment (adults)**

**Reference: NHS England A03X11/01**

## DRAFT FOR PUBLIC CONSULTATION

*Information Reader Box (IRB) to be inserted on inside front cover for documents of 6 pages and over, with Publications Gateway reference number assigned after it has been cleared by the Publications Gateway Team. [Publications Gateway guidance and the IRB](#) can be found on the Intranet.*

# **Clinical Commissioning Policy Proposition: Pasireotide for acromegaly as third-line treatment (adults)**

First published: February 2016

Prepared by NHS England Specialised Services Clinical Reference Group for  
**Specialised Endocrinology CRG**

Published by NHS England, in electronic format only.

## Contents

Equality Statement .....	4
Plain Language Summary .....	4
1. Introduction .....	5
2. The proposed intervention and clinical indication .....	5
3. Definitions .....	5
4. Aim and objectives .....	6
5. Epidemiology and needs assessment .....	6
6. Evidence base .....	7
7. Documents which have informed this policy proposition .....	9
8. Date of review .....	9

## Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

## Plain Language Summary

The policy proposition aims to confirm NHS England's commissioning approach to pasireotide for adult patients with acromegaly.

The pituitary gland sits at the base of the brain and is important in controlling growth and development of the human body. Acromegaly is a condition which leads to too much production of growth hormone from this gland. This leads to excess growth of body tissues over time, causing disfiguring physical changes and other physical symptoms. It may also cause heart disease, diabetes and hypertension among other complications.

Most patients will have surgery to manage the disease. If they require further treatment, they may receive radiation therapy and/or medical therapies such as growth hormone inhibitors (drugs which stop growth hormone from causing body tissues to grow excessively).

Pasireotide is a growth hormone inhibitor, and works slightly differently to existing growth hormone inhibitors. As a result, it may help to control acromegaly in patients who did not respond to other growth hormone inhibitors. It is licensed in the UK to treat adult patients with acromegaly when they require further treatment after surgery and other medical therapies do not adequately control their disease.

NHS England has concluded that, on balance of risks and benefits, it does not support a proposal for the routine commissioning of pasireotide for adult patients with acromegaly. It is proposed to review this decision when further published and peer-reviewed evidence becomes available and more experience from UK clinical practice is gained.

## 1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission pasireotide for acromegaly.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether pasireotide for acromegaly will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

## 2. The proposed intervention and clinical indication

Acromegaly is a rare, seriously debilitating condition that usually develops over many years, characterised by excessive secretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). In the vast majority of patients (>99%), it is caused by a GH-secreting pituitary adenoma. Acromegaly is associated with a two to three fold increase in mortality. Factors contributing to increased mortality include higher prevalence of hypertension, hyperglycaemia or diabetes, cardiovascular disease, cardiomyopathy and sleep apnoea.

The clinical manifestations of acromegaly are due to the peripheral actions of the GH excess and elevated IGF-1 concentrations and/or local tumour mass effect. The symptoms and signs of acromegaly can be divided into physical (changes due to excessive amounts of GH and IGF-1), metabolic (effects of excessive amounts of GH) and local (effects of the pituitary tumour).

The therapeutic goals are to reduce mortality to the expected age- and sex-adjusted rates by using treatments that either remove the tumour mass or control its growth and restore GH secretion and action to normal. The biochemical goals are to reduce the circulating IGF-1 levels to normal for age and sex and to reduce serum GH concentrations to < 1 µg/L. The epidemiological data available suggest that reduction of GH to this level or normalisation of IGF-1 improves the standardised mortality rate of acromegalic patients to close to that of the general population. However, despite all the different therapeutic approaches available, several real world studies suggest that a substantial number of patients do not achieve optimal biochemical control.

Pasireotide is a long-acting release somatostatin analogue, licensed in the UK for use in the treatment of adult patients when surgery has failed (or is not an option) and who are inadequately controlled with another somatostatin analogue (SSA) (octreotide/lanreotide).

## 3. Definitions

**Acromegaly:** a condition in which the body produces too much growth hormone (GH) and insulin-like growth factor 1 (IGF-1), leading to the excess growth of body tissues over time.

**Somatostatin:** a protein made naturally in the body which controls hormone production.

## DRAFT FOR PUBLIC CONSULTATION

Somatostatin analogues: drugs that replicate the function of somatostatin, including pasireotide, lanreotide and octreotide.

Pasireotide: a long-acting release somatostatin analogue licensed for use in acromegaly patients who are inadequately controlled with another SSA.

### 4. Aim and objectives

This policy proposition aims to define NHS England's commissioning position on pasireotide as part of the treatment pathway for adult patients with acromegaly .

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with acromegaly.

### 5. Epidemiology and needs assessment

Acromegaly is a rare condition with an estimated incidence of 3-4 cases per million population per year (McKeage K, 2015). Prevalence has been estimated at around 4 to 13 in every 100,000 people, which equates to a prevalence of between 2,500 and 8,300 people in the UK with the condition (NHS Choices).

Acromegaly can affect people of any age, but it is typically diagnosed between the ages of 40-50, affecting males and females equally. The diagnosis is often delayed and can take over a decade from onset, as the symptoms develop gradually over time so patients and their families and GPs may not notice the changes or only notice small changes at first.

Over time patients can experience a range of symptoms that can have a severe impact on their quality of life (QoL). They may suffer from a range of physical changes to their bodies (with corresponding psychological impact), a range of physical symptoms (such as obstructive sleep apnoea, joint pain, carpal tunnel syndrome and debilitating fatigue), and metabolic diseases including hypertension, cardiovascular disease, diabetes mellitus and impaired glucose tolerance. Therefore, acromegaly is associated with considerable morbidity and increased mortality (the rate of mortality among acromegaly patients with elevated GH and IGF-1 is between 2.6 and 3.5 times greater than in the general population [Samson S, 2015]).

The number of adult patients with uncontrolled acromegaly after first-, and second-line treatment in the UK is approximately 350 (Howlett et al, 2013, Orphanet Report, 2014).

## 6. Evidence base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of pasireotide for adult patients with acromegaly. Although it is recognised that there is evidence of effectiveness in some patients, a significant proportion of patients experienced hyperglycaemia adverse events. In particular, more patients experienced hyperglycaemia than reached primary endpoint in Gadelha et al (2014) (PAOLA trial) suggesting that the risk benefit profile is insufficient to propose a routinely commissioned position. It is proposed to review this decision when further published and peer-reviewed evidence becomes available and more experience from UK clinical practice is gained.

All the trials to date were funded by Novartis Pharm AG. Earlier trials adopted a composite endpoint of Growth Hormone (GH)  $<2.5 \mu\text{g/l}$  and normalised Insulin-like Growth Factor (IGF-1); the revised Endocrine Society guidelines have amended the definition of disease control to achieving GH  $<1 \mu\text{g/l}$ .

### **1. Is Pasireotide a clinically effective treatment in adults with acromegaly when surgery has failed (or is not an option) and who remain inadequately controlled with another somatostatin analogue?**

Gadelha et al (2014) (level-1) in the PAOLA phase three trial (n=198) evaluated the clinical effectiveness of Pasireotide LAR at two doses (40mg/monthly (n=65) and 60mg/monthly (n=65)) in patients with acromegaly who were previously inadequately controlled (GH  $>2.5 \mu\text{g/l}$  and IGF-1  $> 1.3$  times the upper limit of normal (ULN)), on either 30mg Octreotide LAR or 120mg Lanreotide monotherapy. 132 of 198 patients had undergone previous surgery. 68 patients continued on their current therapy as an active control group. At 24 weeks 15% of patients in the Pasireotide 40mg group, 26% in the 60mg group and 0% in control group achieved primary endpoint (normalisation of IGF-1 and GH  $<2.5 \mu\text{g/l}$ ). Normalisation of IGF-1 was achieved in 25% of patients in the Pasireotide LAR 40mg group, 26% in the 60mg group and none in the active group. In addition tumour reduction  $>25\%$  was observed in 18.5% of patients in the Pasireotide 40mg group and 10.8% in 60mg group and one patient in the control group. The study concluded that Pasireotide LAR had superior efficacy in patients that were inadequately controlled, compared to Octreotide and Lanreotide. The absolute difference in the control group for 40mg of Pasireotide was 15.4% (p=0.0006) and 20% in the 60mg group p<0.0001.

However, Gadelha et al (2014) also observed the higher incidence of hyperglycaemia adverse events: 33% (n=21) in the 40mg Pasireotide group, 31% (n=19) in 60mg group and 14% (n=3) in the active control group. At baseline assessment, 72% in the 40mg group, 60% in 60mg and 69% in the active control group had diabetes (n=35). An increase in fasting blood glucose levels was observed at all doses (dose of Pasireotide LAR 20, 40 and 60mg), and greatest in the 60mg. Associated reduction in fasting insulin levels and an increase in hbA1c was observed in all patients. 11% of patients in this study experienced a hyperglycaemia related adverse event. The European Medicine Agency has provided clinical guidance and recommended careful monitoring of glycaemic status prior to and during Pasireotide treatment and to manage hyperglycaemia with pharmacotherapy ([www.ema.europa.eu/ema](http://www.ema.europa.eu/ema)).



Petersenn et al (2014) (level 2++) in a randomised multi-centre open label phase I study (n=35) assessed pharmacokinetics, pharmacodynamics and safety of Pasireotide LAR at three doses 20mg, 40mg and 60mg. 34 of the 35 acromegalic patients with a pituitary adenoma had previously received somatostatin analogues but failed to gain biochemical control. Assessment at day 91 following Pasireotide showed GH and IGF-1 levels had decreased in all patients. 51% of patients had a mean GH level  $<2.5 \mu\text{g/l}$ , and 57% a mean IGF-1 level below the upper limit of normal.

Similarly Marina et al (2015) (level 3) reported two patients that failed to achieve biochemical and symptomatic control following surgery and treatment with Octreotide LAR. Following Pasireotide treatment both patients achieved control and symptomatically improved. One patient discontinued treatment after 7 months, as result of hyperglycaemia, with increasing fasting glucose and HbA1c above the reference range.

In summary, the PAOLA trial (level -1), short-term (24 weeks) powered, randomised non-blinded study concluded that Pasireotide can be an effective treatment for adults with acromegaly who remain inadequately controlled with another somatostatin analogue. In this study 67% of patients had undergone previous surgery. Larger multicentre long-term, double blinded randomised trials, with stratification of the patient group would strengthen this evidence base.

### **2. Is Pasireotide more effective than the comparison therapies (listed above) in achieving the critical and important patient outcomes as detailed above?**

Colao et al (2014) (level +1) in a large multicentre double blinded randomised trial (n=358 patients), found Pasireotide LAR at 12 months, to have shown superior efficacy in achieving biochemical control when compared to Octreotide LAR (31.3% vs 19.2% respectively,  $P=0.007$ ), in medically naïve acromegaly patients. Patients were stratified on further analysis as de novo or post-surgical. Normal IGF-1 level, were achieved in 50.7% of post-surgical patients in the Pasireotide group compared to 26.9% in the Octreotide group. Normalisation of IGF-1 levels was achieved in 35% of de novo patients in the Pasireotide group versus 21.2% in Octreotide group. Overall both treatments showed similar reduction in tumour mass from baseline 40% in Pasireotide LAR and 38% in Octreotide LAR ( $P=0.838$ ), and both drugs were similarly effective at improving symptoms and quality of life.

An extension phase of the study (Sheppard et al (2015) (level 1-)) evaluated 120 patients with acromegaly who had  $\text{GH}<2.5\mu\text{g/l}$  and  $\text{IGF-1}\leq 1\times\text{ULN}$  at 12 months and/or experienced clinical benefit. 74 patients in the Pasireotide LAR and 46 patients in the Octreotide LAR group continued with the extension phase. The study found GH and IGF-1 suppression was maintained up to 25 months, 48.6% patients in Pasireotide LAR group and 45.7% (n=21) in Octreotide LAR group achieved primary endpoint.

Colao et al (2014) also found hyperglycaemia related adverse events were more common in the Pasireotide LAR group (57.3% versus 21.7% in the Octreotide group). Sheppard et al (2015) (level 1-) in the extension phase study found the safety profile of Pasireotide LAR to be similar to Octreotide LAR, except the increase in hyperglycaemia related events in the Pasireotide group. The majority of patients experienced one mild/moderate adverse event (86.5% in Pasireotide group versus 77.2% in Octreotide LAR group). Common side effects included diarrhoea and cholelithiasis.

To date, one double blinded randomised study and extension phase of the study shown that Pasireotide can be more effective than comparison therapies.

### **3. Is Pasireotide a cost effective treatment in patients with adults with acromegaly when surgery has failed (or is not an option) and who remain inadequately controlled with another somatostatin analogue?**

No studies have evaluated cost effectiveness of Pasireotide treatment in acromegaly patients when surgery has failed (or is not an option) and who remain inadequately controlled with another somatostatin analogue.

### **4. Is Pasireotide more cost effective than comparison therapies (listed above)?**

No studies have evaluated cost effectiveness of Pasireotide treatment when compared to other therapies.

## **7. Documents which have informed this policy proposition**

Clinical commissioning policy statement: Stereotactic Radiosurgery/Radiotherapy for Ocular Melanoma and Pituitary Adenoma (D05/PS/a)  
NICE guideline CSG10: "Improving outcomes for people with brain and other central nervous system tumours"

## **8. Date of review**

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).