

# **Clinical Commissioning Policy: Cinacalcet for complex primary hyperparathyroidism in adults**

Reference: NHS England: 16034/P



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# **Clinical Commissioning Policy: Cinacalcet for complex primary hyperparathyroidism in adults**

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

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## **Policy Statement**

NHS England will commission cinacalcet for complex primary hyperparathyroidism 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 primary hyperparathyroidism**

Primary hyperparathyroidism (PHPT) is a common illness that affects the parathyroid glands.

In PHPT:

- There may be higher than normal levels of parathyroid hormone (PTH) - compared to the level of calcium in the body.
- This makes blood calcium levels to go up.

Both higher PTH and calcium causes the symptoms of PHPT.

Two of the most important long-term problems with PHPT are:

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- osteoporosis (loss of bone density) with increased risk of fractures
- increased risk of kidney stones.

PHPT has also been linked with many other common illnesses.

### **About the current treatment**

Removing abnormal parathyroid glands by surgery is the accepted treatment for PHPT. This surgery is called parathyroidectomy (PTx). Success rates of parathyroidectomy are high (about 97%). There are differences of opinion over when and if to do PTx - but there are international and UK guidelines.

However, some patients refuse surgery or are not fit for surgery. They may also have some remaining disease or disease that keeps coming back - which is not suitable for further surgery. Some of these patients may be suitable for long-term observation - rather than surgery. However, others need further therapy to manage symptoms of the following:

- high calcium levels ('hyper-calcaemia')
- osteoporosis
- kidney stones.

This policy relates to this group of patients with complex PHPT. Selecting suitable treatment therapy for each of these patients needs tailoring to their individual needs.

### **About the new treatment**

Cinacalcet is a medicine taken by mouth. It can be prescribed for PHPT where surgery is not suitable for a patient - or if surgery could be harmful. It lowers blood calcium levels when they are high. This reduces symptoms that could result in an admission to hospital and improves quality of life. However, it does not directly stop bone loss or kidney problems due to PHPT.

### **What we have decided**

NHS England has carefully reviewed the evidence to treat hyperparathyroidism with cinacalcet in patients who have not had surgery. 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 proposal to routinely commission cinacalcet for adults with complex primary hyperparathyroidism.

Primary hyperparathyroidism (PHPT) is a common condition affecting the parathyroid glands that may cause an inappropriately raised concentration of parathyroid hormone (PTH) relative to the circulating calcium concentration, in turn causing blood calcium concentration to increase and blood phosphate concentration to fall. Both raised PTH and calcium are responsible for the symptoms of PHPT, which include depression, lethargy and bowel disturbance. Two of the most important long-term consequences of PHPT include osteoporosis (loss of bone density) with increased risk of fractures and an increased risk of kidney stones. In severe cases, high calcium concentrations can lead to loss of consciousness and coma. PHPT has also been associated with many other common conditions.

Approximately 30% of patients with PHPT will meet the criteria for surgery (parathyroidectomy). However, of these patients, not all will undergo parathyroidectomy, either due to risk of anaesthesia, patient choice or by having disease pattern not amenable to surgical resection. These patients will currently undertake repeat visits to primary and specialised care centres to monitor calcium concentration and renal function. They are at risk of hypercalcaemic associated complications including a risk of increased bone loss, nephrolithiasis and nephrocalcinosis. These patients may also decompensate at times of concurrent illness, become dehydrated and are admitted acutely with hypercalcaemic crises. This policy considers cinacalcet for this patient group.

Cinacalcet was granted a marketing authorisation in Europe and the USA in 2004, initially for management of secondary hyperparathyroidism in renal failure and for management of hypercalcaemia in parathyroid carcinoma. It was later approved for use in patients with primary hyperparathyroidism, who meet hypercalcaemia criteria for parathyroidectomy but who refuse or cannot undergo surgery.

## 2 Definitions

Primary hyperparathyroidism (PHPT) is when one or more of the parathyroid glands is enlarged or overactive and the abnormality causing it lies within the gland itself. The usual cause of PHPT is a non-cancerous tumour called an adenoma (or more than one adenoma) growing on the parathyroid glands, causing it to become overactive. PHPT may also result from two or more of the glands becoming enlarged (hyperplasia). **In rare cases, PHPT can occur as a result of inherited gene abnormalities and the diagnosis is sometimes made at a younger age. Very rarely, PHPT is caused by cancer of a parathyroid gland (section amended from original – please see explanatory note).**

Parathyroidectomy (PTx) is the surgical procedure of removing one or more parathyroid glands and is effective in 97% of cases. Clinical consensus suggests approximately 30% of patients with PHPT meet the criteria for parathyroidectomy as described in international guidelines:

The criteria for surgery that may be considered include;

- (1) Evidence of end organ disease (e.g. low bone density, renal calculi)
- (2) Symptomatic PHPT (e.g. fatigue, change in cognitive status, nausea, constipation and thirst)
- (3) Asymptomatic patients:
  - with adjusted serum calcium (aCa) greater than 0.25mmol/L above the upper limit of reference range
  - Creatinine clearance less than 60ml/min
  - Low bone mineral density as evidenced by a T score less than -2.5 or previous fragility fractures
  - Patients below 50 years old

Cinacalcet (trade name Mimpara (Europe) or Senispar (North America and Australia)) is an allosteric modulator of the calcium sensing receptor acting to sensitise this receptor to extracellular calcium. It is licensed for the treatment of PHPT where surgery is not clinically appropriate or is contraindicated and it is also



licenced for use in secondary hyperparathyroidism in patients with end-stage renal dialysis (ESRD) on maintenance dialysis therapy.

### 3 Aims and Objectives

This policy aims to define NHS England's commissioning position on cinacalcet as part of the treatment pathway for adult patients with complex primary hyperparathyroidism.

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

### 4 Epidemiology and Needs Assessment

Most cases of hyperparathyroidism occur in people with no family history of the condition. Only about 5% of cases can be linked to an inherited problem. Women are twice as likely as men to develop hyperparathyroidism and the risk increases with age (NHS Choices, 2015).

PHPT is common but parathyroidectomy performed by experienced surgeons is 97% successful at curing the condition (NHS Choices, 2015)

Whilst PHPT is common, its clinical profile has dramatically changed over recent years, shifting from the traditional manifestation described as 'stones, bones, abdominal groans and moans' to a more subtle, asymptomatic form (**section amended from original – please see explanatory note**). In addition, the advancement and variability in biochemical diagnosis of PHPT has resulted in a wide range of quoted prevalence and incidence figures for PHPT. The prevalence range has been quoted as 0.5-34 per 1,000 people and incidence lies between 0.004 and 1.8 per 1,000 person-years (Ning et al., 2009). A recent UK based epidemiological study of PHPT in a UK population notes the prevalence of 6.72 per 1,000 of the population with a cyclical incidence of 0.4 - 1.1 per 1,000 person-years (Ning et al., 2009).

From this epidemiology it is possible to calculate the estimated needs requirement for cinacalcet use in England with an adult (over 18 years of age) population of 42.7 million people (ONS, 2014). With a prevalence of 6.72 per 1,000 population, there are an estimated 286,000 adults with PHPT in England in 2014/2015. Of these patients, clinicians estimate that approximately 30% (85,800) of patients will meet the criteria for parathyroidectomy, however 5% (4,300) of these patients will not undergo surgery due to overall anaesthetic risk, patient choice, or a disease pattern not amenable to resection. Of these, a further 30% (1,290) patients will have a serum calcium above 3.00mmol/L or between 2.85 - 3.00mmol/L and display symptoms and therefore may be suitable for cinacalcet.

In addition, of the 95% of patients fit for surgery, 3% (2,400) will have residual or recurrent disease not amenable to surgery, and of these, an estimated 30% (730) will have calcium levels as described above and therefore may be suitable for cinacalcet.

Therefore, based upon 2014/2015 population estimates, there are an estimated 2,020 patients eligible for treatment with cinacalcet.

## **5 Evidence Base**

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of cinacalcet for the treatment of complex primary hyperparathyroidism.

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder with a prevalence of 6.72 per 1,000 and affects largely women (Ning et al., 2009). In approximately 80% of cases PHPT is a result of a solitary adenoma, 5% multiple adenomas, 15% hyperplasia and rarely (<1%) due to carcinoma of the parathyroid gland (Duntas et al., 2011).

Parathyroidectomy is the definitive treatment option in patients with symptomatic PHPT without surgical contraindication. Surgery should also be considered in

asymptomatic patients with PHPT if serum calcium  $> 0.25\text{mmol/L}$  ( $1.0\text{mg/dl}$ ) above upper limits of normal, creatinine clearance  $<60\text{ml/min}$ , bone mineral density (BMD) T score  $<-2.5$  at site and/or previous fracture fragility and if  $<50$  years of age (Bilezikian et al., 2014).

However, there is a cohort of patients who are not suitable for surgery and/or refuse surgery. Prior to calcimimetics these patients were treated in conjunction with dietary modifications, vitamin supplements, bisphosphonates and hormone replacement therapy. Cinacalcet is the first available calcimimetic that regulates calcium homeostasis, by increasing the sensitivity of the calcium receptor to circulating serum calcium, thus reducing serum calcium and PTH concentrations.

In 2008, cinacalcet was approved by the European Medicines Agency (EMA) for patients with PHPT indicated for parathyroidectomy on the basis of serum calcium levels, but for whom surgery was contraindicated or clinically inappropriate.

Saponaro et al. (2013) found, according to EMA labelling of cinacalcet only 53% of patients with sporadic PHPT (sPHPT) and 26% with familial PHPT (fPHPT) fulfilled the criteria ( $n=135$ ).

### **Clinical effectiveness**

The evidence of clinical effectiveness of cinacalcet in treating patients with PHPT who either refuse surgery, surgery is contraindicated, deemed inappropriate or have residual disease following previous surgery is limited to one multicentre double blinded randomised control trial (level 1+), two further smaller RCTs (level 1-) and predominately level 2 and 3 evidence. The primary outcome measuring efficacy (in the majority of studies) was evaluating normalisation or reduction of serum calcium (albumin corrected calcium and/or ionised calcium). There is sparse documentation of whether there is resolution of symptoms of PHPT, and further robust studies are required to evaluate skeletal health, particularly of interest in post-menopausal women with PHPT.

Khan et al. (2015) (level 1+) in a double-blinded RCT comparing cinacalcet with placebo showed 75.8% ( $n=25/33$ ) of patients receiving cinacalcet achieved

normocalcaemia (from 2.94mmol/L to  $\leq$ 2.56mmol/L,  $p<0.001$ ) during the efficacy phase. They also observed a decrease in PTH from baseline of 23.8% in the treatment group. They found no significant changes in health related quality of life, data on long term outcomes and skeletal health was not assessed. Filopanti et al. (2012) (level 1-) evaluated the use of cinacalcet in patients with PHPT ( $n=15$ ) secondary to multiple endocrine neoplasia-1 (MEN-1). This cohort of patients often have multiple gland hyperplasia and ectopic lesions, resulting in a lower rate of success with parathyroid surgery. In this crossover trial the majority of patients had one or more surgical procedures and the remaining refused because of personal reasons or surgery was contraindicated. The study found patients with MEN-1 PHPT achieved normocalcaemia within one month of initiating cinacalcet therapy (from 2.86mmol/L to 2.38mmol/L  $p<0.001$ ). Peacock et al. (2011) pooled data from three studies, one double blinded randomised control trial and two open label studies ( $n=81$ ) to assess the efficacy of cinacalcet in a spectrum of PHPT patients (level 3 evidence). Patients were divided into three categories, first those that had a history of failed parathyroidectomy ( $n=29$ ), secondly those who met the criteria for surgery but did not undergo surgery ( $n=37$ ), and thirdly patients with mild asymptomatic PHPT ( $n=15$ ). The mean baseline calcium in the first two groups was 2.95mmol/L and 2.75mmol/L respectively, and in patients with mild PHPT calcium was 2.63mmol/L. All patients achieved normocalcaemia by six months and were stable up to four years, with mean decrease in calcium from baseline in group 1-3 being 17.1%, 11.2% and 12.4% respectively ( $p<0.0001$ ). Studies have shown a significant reduction in PTH from baseline with cinacalcet therapy, although rarely achieving levels within normal range (level 1, 2 and 3 studies).

Peacock et al. (2009) in an open label study ( $n=45$ ) found during the 5 year study period no statistically significant changes in Z-aBMD scores at the spine, wrist, femoral neck and total femur, with a non-significant increase of Z-scores at the lumbar spine. These findings are consistent with other studies (level 3). PHPT has an impact upon skeletal health, and additionally post-menopausal women are at an increased risk.

Saponaro et al., 2013 (level 3) ( $n=135$ ) observed over a median follow-up period of 9 months 100 patients with sporadic and 35 patients with familial PHPT. 65% of

patients with sPHPT and 80% with fPHPT achieved normocalcaemia at the study end point with cinacalcet. In the sPHPT group significant decrease of serum calcium from 2.90mmol/L to 2.55mmol/L ( $p<0.0001$ ) and in the fPHPT 2.75mmol/L to 2.47mmol/L. These findings are consistent with the PRIMARA study (Schwarz et al., 2014) (n=303). Patients were predominately female (79.5%), 44% were symptomatic predominately complaining of bone pain or renal stones, with a mean serum calcium level of 2.85mmol/L. 72% of patients completed 12 months of cinacalcet treatment, of which 71% of patients had calcium levels  $\leq 2.56$ mmol/L.

In the current literature there is a lack of data evaluating symptomatic outcome following treatment with cinacalcet. Brardi et al. (2015) (level 1-) evaluated the use of cinacalcet in nephrolithiasis in a randomised pilot study (n=10). At 10 months there was a statistically significant reduction in the number of renal stones in the cinacalcet group from 3 to 2.3 ( $P=0.045$ ), and decrease in diameter of the stones ( $p=0.002$ ).

The majority of studies have started with a dose of 30mg daily or twice daily, and dose titrated in accordance with calcium levels. The dosing patterns are variable with most trials using twice daily and with some increasing to three or four doses/day, possibly mimicking the pulsatile PTH pattern. EMA recommends a starting dose of 30mg twice daily with titration every 2 to 4 weeks with sequential dose increases if required by 30mg with a max dose of 90mg four times daily. In addition the recommendation is to measure serum calcium within one week after initiation of following dose adjustment and to continue monitoring calcium every 2 to 3 months once the dose has been established. The effects of Arg990Glu polymorphism of calcium sensing receptor has not been sufficiently evaluated in terms of dosing and possible increased risk of adverse effects. Further pharmacokinetic studies are required to address these questions.

### **Cinacalcet compared with standard treatment**

There were no comparative studies evaluating the effectiveness of cinacalcet with standard treatment in patients with PHPT.

## **Safety**

Mild to moderate adverse events are very common, Peacock et al. (2011) observed adverse events in up to 99% of patients treated with cinacalcet, nausea and vomiting being commonly reported. Other common adverse events include arthralgia, diarrhoea, myalgia and paraesthesia. There is no mortality data associated directly with cinacalcet therapy in patients with PHPT.

In the majority of studies no serious adverse events were reported, although serious adverse events have occurred as a result of hypocalcaemia, with patients very occasionally requiring hospitalisation for intravenous calcium. Norman et al., 2012 (level 3) reported 4 out of 70 patients required inpatient treatment for hypocalcaemia. EMA has provided further guidance of managing hypocalcaemia associated with cinacalcet usage. Hypocalcaemia has been associated with life threatening events and QT prolongation and ventricular arrhythmia secondary to hypocalcaemia has been identified (EMA report section 4.4).

## **Cost-effectiveness**

No studies have evaluated the cost effectiveness of cinacalcet therapy in this cohort of patients.

## **6 Criteria for Commissioning**

Cinacalcet will be routinely commissioned for patients:

(1) Who have first been discussed with the nominated lead clinician at the specialised endocrinology centre that provides services for patients with calcium and bone diseases;

AND

(2a) Who meet criteria for surgical intervention but who do not undergo surgery because they are unfit from a surgical or anaesthetic perspective or they refuse surgery, despite specialist input and clear counselling on the consequences of their decision;

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OR

(2b) Who, following prior attempted parathyroidectomy, have residual or recurrent PHPT that is inaccessible or not amenable to further surgery **(section amended from original – please see explanatory note)**;

AND

(3a) Are symptomatic (according to Section 3) with a serum calcium concentration between 2.85 - 3.00 mmol/L;

OR

(3b) Have biochemically severe hypercalcaemia (serum calcium >3.0 mmol/L);

AND

(4) Are vitamin D replete (>50nmol/L).

Cinacalcet will be not be routinely commissioned where:

(1) Serum calcium concentration is <2.85 mmol/L.

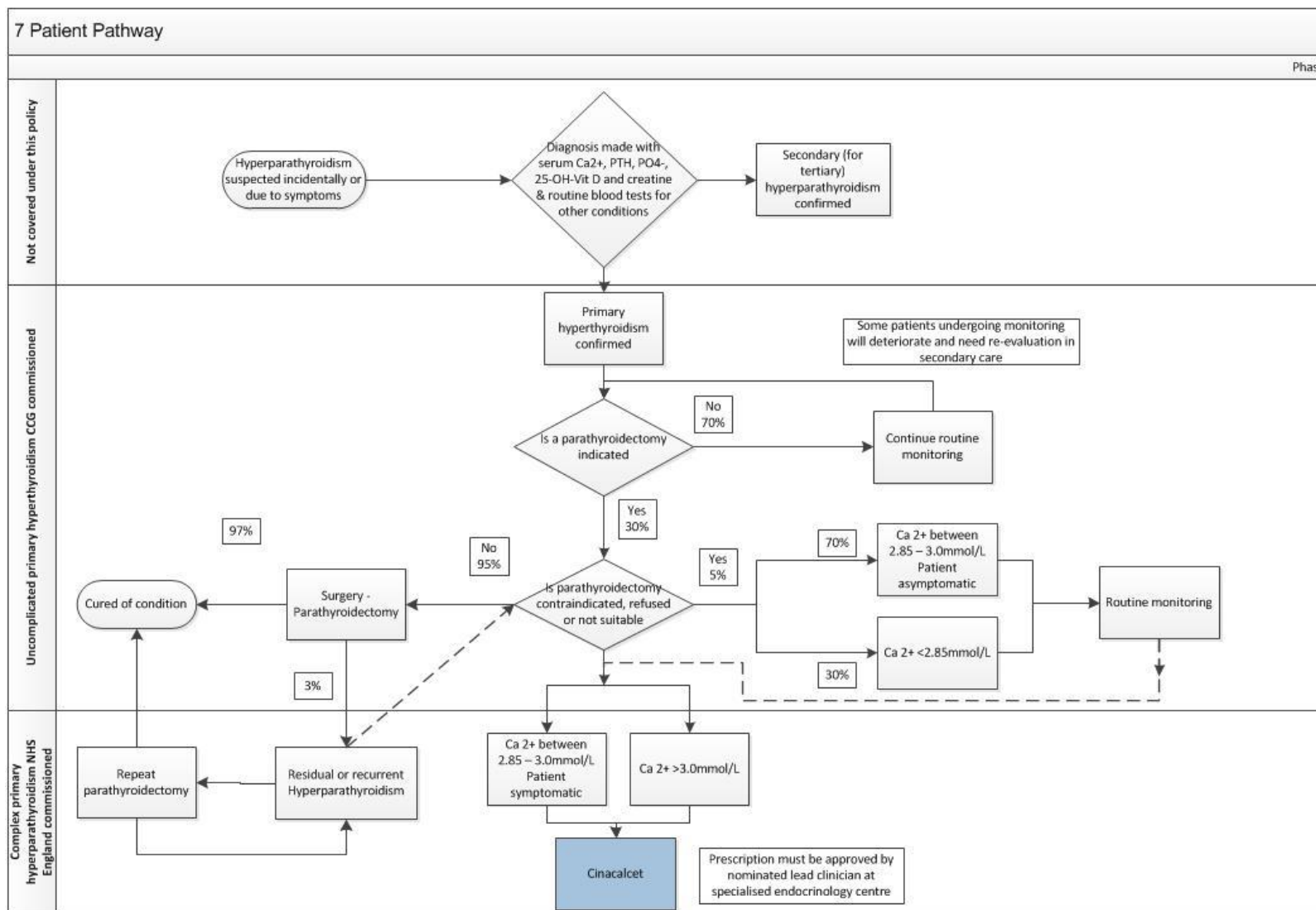
(2) Used in isolation to treat low bone mineral density. In this instance treatment with bisphosphonates are indicated.

(3) Used as sole treatment for PHPT where fracture risk is high, as cinacalcet does not reduce fracture risk.

(4) Prior to parathyroidectomy.

**(5) Cinacalcet has previously been shown to be ineffective for that specific patient (section amended from original – please see explanatory note).**

## 7 Patient Pathway (section amended from original – please see explanatory note)





## **8 Governance Arrangements**

All hospital-based clinical endocrinology services that are compliant for delivering complex calcium and bone diseases services as a component of specialised endocrinology services commissioned by NHS England may prescribe under the arrangements in this policy.

The use of cinacalcet will need prior authorisation from the nominated lead clinician at the specialised endocrinology centre.

## **9 Mechanism for Funding**

Specialised Centres treating complex primary hyperparathyroidism including parathyroid surgery and cinacalcet prescribing in line with the patient pathway will be commissioned through NHS England local specialised commissioning teams.

## **10 Audit Requirements**

The following data will be available to commissioners upon request:

- (1) Baseline pre-treatment data including; serum measures of PHPT activity, bone density, urine calcium excretion, comorbidities and treatment history to date.
- (2) Outcomes of treatment including; sequential serum calcium measurements, fracture data, renal stone incidence, associated comorbidities and mortality.

## **11 Documents which have informed this Policy**

None.

## **12 Date of Review**

This document will be reviewed when information is received which indicates that the policy requires revision

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## Change Notice for Published Specifications and Products developed by Clinical Reference Groups (CRG)

### Amendment to the Published Products

**Product Name**

Clinical Commissioning Policy: Cinacalcet for complex primary hyperparathyroidism in adults

**Ref No**

16034/P

**CRG Lead**

John Wass

### Description of changes required

Describe what was stated in original document	Describe new text in the document	Section/Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
In rare cases, PHPT can occur as a result of inherited genes and the diagnosis is made at a younger age. Very rarely, it is caused by cancer of a parathyroid gland.	In rare cases, PHPT can occur as a result of inherited gene abnormalities and the diagnosis is sometimes made at a younger age. Very rarely, PHPT it is caused by cancer of a parathyroid gland.	Section 2 Definitions	Correct inaccuracies	Prof Neil Gittoes	14 Feb 17
Whilst PHPT is common, its clinical profile has dramatically changed over recent years, shifting from the traditional manifestation described as 'stones, bones, abdominal groans and psychic moans' to a more subtle, asymptomatic form.	Whilst PHPT is common, its clinical profile has dramatically changed over recent years, shifting from the traditional manifestation described as 'stones, bones, abdominal groans and moans' to a more subtle, asymptomatic form.	Section 4 Epidemiology and Needs Assessment	Correct inaccuracies	Prof Neil Gittoes	14 Feb 17
(2b) Who, following prior attempted	(2b) Who, following prior attempted	Section 6 Criteria for	Correct	Prof Neil	14 Feb 17

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parathyroidectomy, have residual or recurrent PHPT that is inaccessible or not amenable to further surgery (e.g. unable to localise parathyroid tissue)	parathyroidectomy, have residual or recurrent PHPT that is inaccessible or not amenable to further surgery.	Commissioning	inaccuracies	Gittoes	
(5) Cinacalcet has previously been shown to be ineffective for that patient.	(5) Cinacalcet has previously been shown to be ineffective for that specific patient.	Section 6 Criteria for Commissioning	Correct inaccuracies	Prof Neil Gittoes	14 Feb 17
Original diagram of Patient Pathway.	Revised diagram of Patient Pathway.	Section 7 Patient Pathway	Correct inaccuracies	Prof Neil Gittoes	14 Feb 17