NHS England

Clinical Commissioning Policy Proposition:

Cinacalcet for complex primary hyperparathyroidism

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Clinical Commissioning Policy Proposition: Cinacalcet for complex primary hyperparathyroidism

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Contents

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Plain Language Summary

Primary hyperparathyroidism (PHPT) is a common disease affecting the parathyroid glands that may cause inappropriately raised levels of parathyroid hormone (PTH) relative to the level of calcium in the body. In turn this causes blood calcium levels to climb. Both raised PTH and calcium are responsible for the symptoms of PHPT. 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. PHPT has also been associated with many other common conditions.

Successful surgical removal of abnormal parathyroid glands by parathyroidectomy (PTx) is the accepted definitive treatment for PHPT. Success rates of parathyroidectomy are high (approximately 97%). There is variance around when and if to undertake PTx but international and UK guidelines exist. However, even if PTx is recommended, some patients refuse surgery, are medically unfit or have residual or recurrent disease inaccessible to further surgery. Some of these patients may be suitable for long-term observation but others require further therapy for management of symptomatic or moderate to severe hypercalcaemia, osteoporosis or kidney stones. This policy specifically relates to the latter group of patients with PHPT. The selection of a suitable therapy for each patient within this subgroup should be individualised to patients' needs.

Cinacalcet is an oral medication that is licensed for use in PHPT where surgery is not clinically appropriate or is contraindicated. It is effective in lowering raised blood calcium levels, thereby reducing symptoms and improving quality of life. It does not however, directly prevent PHPT-associated bone loss or kidney disease.

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of cinacalcet for the treatment of hyperparathyroidism where surgery has not been undertaken.

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 primary hyperparathyroidism.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

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 cinacalcet will be routinely commissioned is planned to be made by NHS England by May 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. The proposed intervention and clinical indication

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 circualting 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 pateints 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. It is effective in lowering raised blood calcium concentrations, thereby reducing symptoms and improving quality of life. It does not however, directly prevent PHPT associated bone loss or kidney disease.

3. Definitions

Primary hyperparathyroidism 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

primary hyperparathyroidism is a non-cancerous tumour called an adenoma (or more than one adenoma) growing on the parathyroid glands, causing it to become overactive. Primary hyperparathyroidism may also result from two or more of the glands becoming enlarged (hyperplasia). In rare cases, primary hyperparathyroidism 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.

Symptoms of high blood calcium levels include:
Polyuria (increased frequency of urination) and polydipsia (increast thirst), dyspepsia - due to calcium-regulated release of gastrin, depression, mild cognitive impairment, muscle weakness, constipation, anorexia and nausea, fatigue, abdominal pain, severe headaches, bone pain, vomiting, dehydration, lethargy, cardiac arrhythmias, shortened QT interval, coma and pancreatitis.

Parathyroidectomy is the surgical procedure of removing one or more parathyroid glands and is effective in 97% of cases. Approximately 30% of patients with PHPT meet the criteria for parathyroidectomy which 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) Adjusted serum calcium (aCa) greater than 0.25mmol/L above the upper limit of reference range
(4) Creatinine clearance less than 60ml/min
(5) Low bone mineral density as evidenced by a T score less than -2.5 or previous fragility fractures
(6) 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. Cinacalcet has been shown to be effective in reducing or normalizing serum calcium levels in several groups of patients with PHPT, including patients with mild to moderate PHPT, intractable PHPT, and parathyroid carcinoma, and in PHPT as a part of multiple endocrine neoplasia type 1. Cinacalcet slightly reduces PTH levels and has no effects on bone mineral density. 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.

4. Aim and objectives

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

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

5. 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, it's 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. 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.

6. 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 hyperparathyroidism where surgery has not been undertaken.

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 > 0.25mmol/L (1.0mg/dl) above upper limits of normal, creatinine clearance <60ml/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 (Mimpara) 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 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, in treating patients with PHPT who either refuse surgery, surgery is contraindicated, deemed inappropriate or have residual disease following previous surgery. 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 doubled blinded RCT comparing cinacalcet with placebo, showed 75.8% (n=25/33) of patients receiving cinacalcet achieved normocalcaemia (from 2.94mmol/L to ≤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 statistical significant changes in Z-aBMD scores at the spine, wrist, femoral neck and total femur, with 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. Further studies are required to evaluate the efficacy of cinacalcet in different disease cohorts of patients with PHPT. These findings are consistent with a large observational study, 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 ≤ 2.56mmol/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 of 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 Arg990Gluc 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 cinaclacet 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. Normal 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.

7. Proposed 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.

OR

(2b) Who, following prior attempted parathyroidectomy, have residual or recurrent PHPT that is inaccessible or not amenable to further surgery (e.g. unable to localise parathyroid tissue).

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)

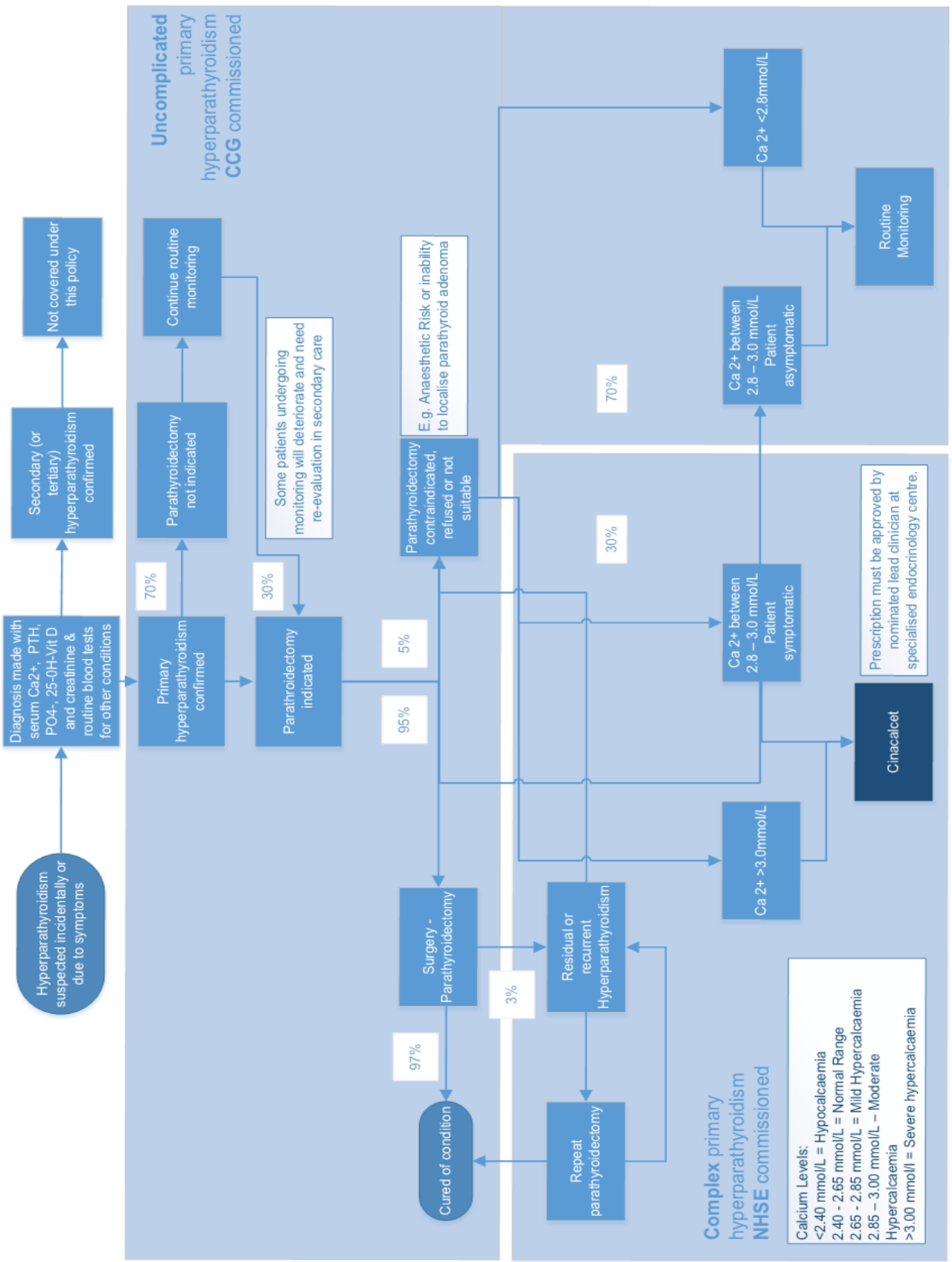
AND

(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 patient.

8. Proposed patient pathway

See diagram below


Hyperparathyroidism suspected incidentally or due to symptoms
Diagnosis made with serum Ca2+, PTH, PO4-, 25-OH-Vit D and creatinine & routine blood tests for other conditions
Secondary (or tertiary) hyperparathyroidism confirmed
Not covered under this policy
Primary hyperparathyroidism confirmed
70%
30%
Parathyroidectomy not indicated
Continue routine monitoring
Some patients undergoing monitoring will deteriorate and need re-evaluation in secondary care
Parathroidectomy indicated
5%
95%
Parathyroidectomy contraindicated, refused or not suitable
E.g. Anaesthetic Risk or inability to localise parathyroid adenoma
Uncomplicated primary hyperparathyroidism CCG commissioned
Surgery - Parathyroidectomy
97%
3%
Residual or recurrent Hyperparathyroidism
Repeat parathyroidectomy
Cured of condition
30%
70%
Ca 2+ between 2.8 – 3.0 mmol/L Patient symptomatic
Ca 2+ between 2.8 – 3.0 mmol/L Patient asymptomatic
Ca 2+ >3.0mmol/L
Ca 2+ <2.8mmol/L
Routine Monitoring
Cinacalcet
Prescription must be approved by nominated lead clinician at specialised endocrinology centre.
Complex primary hyperparathyroidism NHSE commissioned
Calcium Levels:
<2.40 mmol/L = Hypocalcaemia
2.40 - 2.65 mmol/L = Normal Range
2.65 - 2.85 mmol/L = Mild Hypercalcaemia
2.85 – 3.00 mmol/L – Moderate Hypercalcaemia
>3.00 mmol/l = Severe hypercalcaemia

9. Proposed 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 NHSE 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.

10. Proposed mechanism for funding

Complex primary hyperparathyroidism including parathyroid surgery and cinacalcet prescribing in line with the patient pathway will be commissioned via NHSE local specialised commissioning teams.

Uncomplicated primary hyperparathyroidism will continue to be funded by CCGs.

11. Proposed audit requirements

The following data will be available to commisioners 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.

12. Documents which have informed this policy proposition

None

13. 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)