NHS England

Evidence Review:

Cinacalcet for complex primary hyperparathyroidism

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Contents

1. Introduction

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.

2. Summary of results

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 from baseline in PTH 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.

3. Research questions

1. Is cinacalcet clinically effective in the treatment of patients with PHPT who refuse surgery, are medically unfit or have residual or recurrent disease inaccessible to further surgery who require management of symptomatic or moderate to severe hypercalcaemia, osteoporosis or kidney stones?

2. Is cinacalcet more effective than standard treatment in the treatment of patients with PHPT who refuse surgery, are medically unfit or have residual or recurrent disease inaccessible to further surgery who require management of symptomatic or moderate to severe hypercalcaemia, osteoporosis or kidney stones?

3. Is cinacalcet safe to use in the treatment of patients with PHPT who refuse surgery, are medically unfit or have residual or recurrent disease inaccessible to further surgery who require management of symptomatic or moderate to severe hypercalcaemia, osteoporosis or kidney stones?

4. Is cinacalcet a cost-effective treatment option for use in patients with PHPT who refuse surgery, are medically unfit or have residual or recurrent disease inaccessible to further surgery who require management of symptomatic or moderate to severe hypercalcaemia, osteoporosis or kidney stones?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and intervention			Outcomes					Reference	Other		
Grade of evide	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
1+	RCT	67 patients	33 patients in Cinacalcet group. Cinacalcet for ≤ 28 weeks. 30 day screening phase, a 12 week dose titration phase and a 16 week efficacy assessment phase. Initial dose in of 30mg twice daily and increased every 3 weeks in titration phase to a max of 90mg three times daily. During the efficacy phase dose increased or decreased every 4 weeks to maintain serum calcium conc within normal range.	Clinical effectiveness of the intervention	Achievement of a normal mean corrected total serum calcium concentration of ≤ 10.3mg/dl (2.58 mmol/l) during the efficacy phase. Baseline medium serum PTH was 164pg/ml (131, 211) and mean serum Ca2+ was 11.77 (0.46) mg/dl.	25/33 (75.8%) of patients in the Cinacalcet group achieved mean corrected serum calcium ≤ 10.3mg/dl (2.58 mmol/l) during the efficacy assessment phase compared with 0 receiving placebo (P<0.001)	i) achievement of an ≥ 1mg/dl (0.25mmol/l) reduction in mean corrected total serum calcium concentration from baseline to efficacy assessment phase ii) percentage change in corrected total serum calcium phase iii) mean plasma PTH percentage change from baseline to efficacy assessment phase iv) Changes in phosphate, ALP v) treatment failures, defined as corrected calcium >12.5mg/dl (3.12mmol/l) on two occasions or requirement for parathyroidectomy vi) changes from baseline to 28 weeks on health related quality of life (HRQOL) measures using three questionnaire (included parathyroid assessment of symptoms (PAS), medical outcome scores-cognitive functioning (MOS-CF) and short from 36 questionnaire (SF-36)	Secondary endpoints were meet i)mean corrected calcium decreased by ≥ 1mg/dl in 84.8% of Cinacalcet treated when compared to 5.9% of patients in the placebo group (P<0.001). ii) Percentage change in serum calcium from baseline to efficacy phase favoured Cinacalcet -15.21% in the treatment group and -1.66% in the placebo group iii)Percentage change in plasma PTH from baseline during the efficacy assessment phase was -23.8% in the Cinacalcet group and -1.01% in the placebo group. iv) No change in serum phosphorus conc in the placebo group and an increase in Cinacalcet group from 2.66 to 3.54mg/dl. Small increase in ALP in both groups. v) No difference between treatment failures between both groups, occurred in one patient in the treatment group and two in the placebo group (P=0.598) vi) HRQOL indices difference did not reach statistical significance	Khan, Aliya; Bilezikian, John; Bone, Henry; Gurevich, Andrey; Lakatos, Peter; Misiorowski, Waldemar; Rozhinskaya, Liudmila; Trotman, Marie-Louise; Tóth, Miklós. Cinacalcet normalizes serum calcium in a double-blind randomized, placebo-controlled study in patients with primary hyperparathyroidism with contraindications to surgery. Eur. J. Endocrinol. 2015;172(5):527-535.	The number of adverse events reported in each group was similar between both groups (27 cinacalcet vs 20 placebo). 3 serious AE reported in cinacalcet group and 4 in placebo group. One patient in cinacalcet group developed anorexia and another discontinued therapy because of accidental medication overdose. Most common AE were nausea (30% cinacalcet vs 18% in placebo) and muscle spasms (18% cinacalcet and 0% placebo)	Yes	Population: Patients with moderate PHPT, 78% women. Patients were randomised to either Cinacalcet or placebo group, with no difference between sex and race in both groups. Patients in Cinacalcet group were younger. Inclusion criteria: age ≥ 18yrs, total corrected serum calcium >2.83mmol/Ll and ≤ 3.13mmol/L, and plasma PTH>55pg/ml (5.8pmol/l). Patients had to meet one of the following criteria: failed parathyroidectomy, cardiovascular and other comorbid conditions contraindicating parathyroidectomy or parathyroidectomy not considered.. Exclusion criteria included one of the following attributed to hypercalcemia requiring immediate medical intervention, unstable medication conditions or hospitalisation within 30 days, also administrating drugs that may influence serum calcium measurement, prior treatment with Cinacalcet in the last 60 days and if initiated or changed dose of bisphosphonate Overall comments: Double blinded multicentre study. A sample size of 66 was determined to be sufficien.t to provide 90% power to detect a difference of 0.39 in the proportion of subjects achieving the primary endpoint, after adjusting for a 15% dropout/crossover rate. The authors comment as a limitation the duration of study was short, and that a longer trial with bone mineral density and fracture data would be useful to assess the long term effects of cinacalcet on skeletal health.

1-	RCT	10 patients	All patients during a 10 month observational period were started on standard treatment, potassium citrate (50mEq daily) and/or allopurinol 300mg daily. Cinacalcet was started following the observational period and optimised to reduce PTH within normal limits and continued further observation for 10months. Dose of cinacalcet was optimised in order to reduced PTH within normal limits and maintaining normal calcium values. Patients in both groups were give the same diet, with reduction in sodium intake, oxalate rich foods and animal protein, with standard intake of calcium.	Clinical effectiveness of the intervention	i) The number of stones from baseline to the end of the observation period. ii) Whether there is a difference in size of stones form baseline to observation period	i) A significant reduction in the overall number and in the diameter of renal stones found in the cinacalcet group, decreased from 3±2.5 to 2.3±2.8 (P=0.045). Also greater reduction in the cinacalcet group when compared to the non-cinacalcet group, 2.3±2.8 versus 3.2±2.5 (P=0.019) respectively. ii) There was a reduction of the larger diameter of stone in the cinacalcet from baseline 0.81±0.21cm versus 0.47±0.38cm, p=0.002 at the end of the observation period. Also a difference between the cinacalcet vs non-cinacalcet at the end of the observational period, 0.47cm vs 0.78±0.36cm	Endocrine and metabolic parameter changes	In the Cinacalcet group statistically significant reduction in serum calcium, PTH, an increase in serum phosphorus and increase in urinary pH	Brardi, Simone; Cevenini, Gabriele; Verdacchi, Tiziano; Romano, Giuseppe; Ponchietti, Roberto. Use of cinacalcet in nephrolithiasis associated with normocalcemic or hypercalcemic primary hyperparathyroidism: results of a prospective randomized pilot study. Arch Ital Urol Androl 2015;87(1):66-71.	None reported	Yes	Population: Ten patients with active nephrolithiasis associated with primary hyperparathyroidism (4 patients were hypercalcaemic and 6 normocalcemic). Patients were divided equally between males and female. Patients were eligible for study if documented active form of kidney stone disease (2 or more stones during the previous two years) associated to hypercalcaemic or normocalcemic primary hyperparathyroidism with high PTH levels >79.6pg/ml. Excluded patients with known causes of secondary elevation of PTH. Overall comments: Authors report nephrolithiasis is present in 15-20% of patients with hypercalcaemic primary hyperparathyroidism, but also an increased prevalence in patients with normocalcemic primary hyperparathyroidism. Very small non-blinded randomised study, increases heterogenicity, short follow-up period. No power calculation performed - downgraded study

1-	RCT	15 patients	MEN1 patients randomly placed in Cinacalcet and placebo group. 7 patients in cinacalcet group (Group A). Cinacalcet treatment was started on 30mg daily and titrated (increased by increments of 30mg weekly if required) according to serum and ionized calcium and after titration maintained for 3 months. Patient reassessed, following a one month washout period the treatments were switched between groups B/A. All patients were treated with cholecalciferol 300000U every 4-6months and last administration was between 1 and 2 months before start of study. None of the patients received bisphosphonates within 6 months	Clinical effectiveness of the intervention	i) Assess the efficacy on calcium-phosphorus metabolism ii)safety profile of cinacalcet	In Group A mean cinacalcet dose was 40±16mg/day with normalisation of calcium levels in 1- 2weeks. In group B mean dose was 48±27mg/day with minimal effective dose reached in 1-3 weeks. During the cinacalcet phase both plasma ionized and serum albumin-corrected calcium normalised, 1.2±0.6 and 9.5±0.4 respectively with a subsequent significant increase in phosphate (P<0.001), 3.1±0.2mg/dl. Observed a significant statistical reduction in PTH level (median 26.3%, P=0.002) and normalisation in five patients. The dose in the sPHPT was higher to require calcium control when compared to MEN1 patients, 54±25 vs 45±21mg/day, P=0.314. ii) Two patients in group A and two in Group B during the first maintenance phase (3months) withdrew due to personal reasons. In both first and second maintenance phase one patient in each phase reported nausea, although continued with treatment. No patients had hypocalcaemia. 4 patients in the sPHPT experienced nausea, cinacalcet was not discontinued.	Evaluate the possible role of CASR 990Gly polymorphism	In those patients that completed the study 9patients in the MEN1 group (81.8%) were Arg990 homozygotes and 3 were heterozygotes. In the sPHPT group 17 patients (85%) were homozygotes and 3 were heterozygotes. The authors report no significant difference in PTH, serum calcium. phosphorous, nephrolithiasis and osteoporosis in either baseline or after treatment between 990Gly carriers and non-carriers in both MEN1 and sPHPT groups	Filopanti, Marcello; Verga, Uberta; Ermetici, Federica; Olgiati, Luca; Eller-Vainicher, Cristina; Corbetta, Sabrina; Persani, Luca; Beck-Peccoz, Paolo; Spada, Anna. MEN1-related hyperparathyroidism: response to cinacalcet and its relationship with the calcium-sensing receptor gene variant Arg990Gly. Eur. J. Endocrinol. 2012;167(2):157-164.	As per primary outcome	Yes	Population: 15 patients with genetically confirmed MEN1 affected by PHPT. 8 were females and 7 were men. Diagnosis in both MEN1 and sPHPT was made with in the setting of high ionized calcium in the presence of elevated or inappropriately normal serum PTH. All patients met the EMA criteria for cinacalcet treatment, persistent PHPT after surgery or contraindications to surgery (serum Ca level ≥ 1mg above the upper normal limit in all patients). Of the 15 patients, 8 pts had relapse after one or more surgical operations, two patients had contraindications and five refused or postponed surgery for personal reasons). Both ionized calcium and total serum calcium was NS between both MEN1 and sPHPT patients, plasma ionized Ca 1.44±0.5mmol/L vs 1.43±0.6mmol/L and total Ca 2.86 ±0.05mmol/L vs 2.93mmol/L ±0.125mmol/L respectively. Serum PTH was significantly higher in the sPHPT group compared to MEN1, 179.1±126.8pg/ml vs 97.8±18.9, P=0.005 Overall comments: In MEN1 patients due to frequent occurrence of multiple gland hyperplasia and ectopic location success of rate of parathyroid surgery remains low ~50% in experienced centres. Small randomised crossover double-blind study, with a short term follow-up. downgraded

3	Case series	45 patients	Treated initially with 30mg cinacalcet twice daily, and increased in the 12week titration week to 50mg twice daily if calcium levels >10.3mg/dl and maintained on dose for up to 4.5yrs	Clinical effectiveness of the intervention compared to existing interventions	i) Assessment of serum calcium, ii) PTH, iii) phosphate and iv) alkaline phosphatase v) assess areal bone mineral density (aBMD)	i)Normalised elevated serum Ca level within a few weeks and maintained normocalcemia (<10.3mg/dl) for total of 5.5yr of follow-up (1 year from previous RCT). Once maintenance dose established in majority of patients remained stable with 5/41 patients requiring dose adjustments over the next 4 years. ii) Plasma PTH significantly decreased with cinacalcet from baseline (109.8±6.8pg/ml) at 4years (88.6±7.4pg/ml, P=0.01), 5years (87.7±7.3pg/ml, P=0.03), however did not reach normal levels (10-65pg/ml). iii) Within the first 12 weeks serum phosphate increased and then remained constant within normal range throughout the study period (2.6-4.1mg/dl). iv) Overall ALP was stable although slightly increased (upper limit of normal) v) During the 5 year study period no significant changes in Z-aBMD score at the spine, wrist, femoral, neck and total femur, with a nonsignificant increase of Z-scores at the lumbar spine	N/a	N/a	Peacock, Munro; Bilezikian, J. P.; Bolognese, M. A.; Borofsky, Michael; Scumpia, Simona; Sterling, L. R.; Cheng, Sunfa; Shoback, Dolores. Cinacalcet treatment of primary hyperparathyroidism: biochemical and bone densitometric outcomes in a five-year study. J. Clin. Endocrinol. Metab. 2009;94(12):4860-4867.	42 patients (93%) completed the titration phase (wk. 1-12) and entered maintenance phase (wk. 13-287), two patients withdrew consent and one lost to follow up 31 patients completed bw 5 and 5.5yrs at 41 patients at least 2 year follow-up. Two patients died unrelated to medication, metastatic colon cancer and cerebral ischemia. Two patients withdrew unrelated to treatment, with worsening nodular goitre, carcinomas and sepsis. 98% reported at least one mild to moderate adverse events, commonly reported arthralgia (38%), myalgia (27%), diarrhoea (22%), upper respiratory infection (20%) and nausea (20%). 2 patients developed renal stones	Yes	Population: 45 patients with PHPT. Inclusion criteria from the parent study was as follows: Serum calcium >2.56mmol/L and <3.13mmol/L, and plasma PTH >45pg/ml. Exclusion criteria include Creatinine clearance <50ml/min, treatment with bisphosphonates or fluoride in the 90 days before baseline line, familial hypocalciuric hypercalcaemia and fasting urine Ca/Creat ratio <0.05. Overall comments: Open label extension study, of 45 patients from a double blinded controlled 1 year trial continued into this study.

2+	Cohort	43 patients	Two phases, first phase 3 month initiation phase and all patients received cinacalcet 30mg qds with no dose escalations. Subsequently doses were titrated by 30mg every three weeks to achieve normocalcemia. Max dose allowed was 90mg qds. In Cat 1 median daily dose of cinacalcet to maintain normocalcemia was 60mg qds (range 30-120mg).	Clinical effectiveness of the intervention	i) Comparison between both groups in terms of biochemical responses following treatment. ii) Comparison of bone mineral density between both groups	i) Normalisation and long term maintenance of Ca levels was achieved in all patients. At the end of the initiation phase greater proportion of patients achieved normocalcemia in Cat 2 compared to Cat 1 90% vs 56.5% p<0.001. Stable normalisation of PTH in both groups were never achieved. Phosphate increased significantly in both groups. ii) Patients on bisphosphonates were excluded from the BMD analysis. Overall non-significant changes in BMD T-scores in both groups. However in Group 1 a progressive increase in mean BMD-T scores in the lumbar spine and a progressive decrease at the femoral neck site was observed. BMD T-scores in cat 2 were stable throughout the study at both lumbar spine and femoral neck	N/a	N/a	Marotta, Vincenzo; Di Somma, Carolina; Rubino, Manila; Sciammarella, Concetta; Del Prete, Michela; Marciello, Francesca; Ramundo, Valeria; Circelli, Luisa; Buonomano, Pasqualina; Modica, Roberta; Vitale, Mario; Colao, Annamaria; Faggiano, Antongiulio. Potential role of cinacalcet hydrochloride in sporadic primary hyperparathyroidism without surgery indication. Endocrine 2015;49(1):274-278.	None reported	Yes	Population: Patients with sporadic sPHPT were included, excluded patients with familial PHPT. Patients were divided into two groups. Category 1: 23 patients with PHPT with surgical indications. Patients were treated with cinacalcet if surgery was contraindicated, not feasible or refused as per recommendation by the European Medical Agency (EMA) labelling. 20 patients were symptomatic, 6 with nephrolithiasis, 16 with osteoporosis and 4 with fragility fractures. Patients were allow treatment with 25-hydroxyvitamin D only in the follow-up phase. NS difference between both group in terms of age, sex and proportion of post menopausal women. Patients in Cat 1 had higher mean Ca levels (2.9mmol/L vs 2.68mmol/L P<0.001), lower serum phosphate (2.5 vs 2.9mg/dl, p=0.06) and higher mean plasma PTH levels (280.5 vs 182.5 pg/ml, p=0.12). Treatment with bisphosphonates in 13 patients in Cat 1 and one patient in Cat 2. Overall comments: PTH is known to exert a catabolic effect upon cortical bone and a paradoxical anabolic effect on trabecular bone. The authors have commented that the effect on BMD T-scores may be a result of cinacalcet failing to lower PTH levels. In Cat 2 the BMD T-scores were stable which although not normalised in Cat 2, the PTH level at the end of 6 months showed a progressively stronger reduction. The authors report study includes an homogenous cohort of patients, all patients treated and followed up at a single centre. Small cohort study
0	Other	N/a	N/a - Study only referenced in review for demographic data	Other	N/a - Study only referenced in review for demographic data	N/a - Study only referenced in review for demographic data	N./a	N/a	Duntas, Leonidas H.; Stathatos, Nikolaos. Cinacalcet as alternative treatment for primary hyperparathyroidism: achievements and prospects. Endocrine 2011;39(3):199-204.	N/a	N/a	N/a - Study only referenced in review for demographic data

2-	Cohort	24 patients	12 patients received 30mg cinacalcet and 12 patients received 60mg cinacalcet orally	Clinical effectiveness of the intervention	i) To compare single dose cinacalcet testing on PTH secretion with standardised short time calcium load in healthy controls	In healthy controls 60min after intravenous calcium loading PTH levels dropped from 22.6±1.4 to 4.5±0.5ng/l, which corresponded to a 80.2±1.9% drop from basal levels. Similar findings were observed in HC following administration of 60mg of cinacalcet with a decrease to <7ng/l, corresponding to a 84.8±1.9% drop from baseline.	ii) Evaluate the effect of single dose cinacalcet testing on PTH secretion and plasma calcium levels in patient with proven PHPT compared to HC	i) Dose of 30mg cinacalcet. In HC significant decrease (P<0.01) in serum PTH to 7.7±1.1ng/l, corresponding to a 66±4.8% basal drop at 60mins. PTH levels progressively reached baseline levels at 6hrs. Plasma calcium levels decreased from 2.43±0.03 to 2.27±0.3mmol/l (P<0.05), although remained with normal range along the testing. In patients with PHPT serums PTH levels decreased at 60min from 64±13.2 to 38.3±11.6ng/l (P<0.05), corresponding to 44.8±6.9% drops, and no significant change in plasma calcium, ionized calcium or plasma phosphorus was observed. ii) Dose of 60mg cinacalcet: In HC serum PTH levels decreased to 84.8±1.9% from baseline, and at 6hr post PTH level rose progressively although remained significantly lower at 10.2±0.9ng/l P<0.001. Plasma calcium levels decreased but stayed within normal range. Patients with PHPT serum PTH levels decreased to 19.7±3.5ng/l, corresponding to a 58.2±5.2% drops 60mg following intake. Serum PTH was >8ng/l in all patients. Plasma calcium levels decreased progressively from baseline 2.7±0.05mmol to 2.55±0.55mmol/l (P<0.01) at the end of testing, no significant change in plasma ionized calcium levels	Cailleux, A.; Vuillermet, P.; Basuyau, J. P.; Ménard, J. F.; Lefebvre, H.; Kuhn, J. M.; Prévost, G.. A step towards cinacalcet testing for the diagnosis of primary hyperparathyroidism: comparison with the standardized intravenous calcium loading. A pilot study. Clin. Endocrinol. (Oxf) 2015;82(5):663-669.	Reported overall good tolerance. No side effects observed in PHPT group	Yes	Population: 24 patients with PHPT, 7 men and 17 women. Patients studies prior to undergoing surgery. Normal diet as controls, taking no medications to modify calcium homoeostasis. The menopausal women were not taking hormonal replacement therapy. Diagnosis of PHPT association of hypercalcaemia, normal or elevated serum PTH, hypercalciuria and normal serum 25 OH vitamin D. 16/22 patients on imaging had a presence of an adenoma. No patient had MEN-1 syndrome. Basal albumin corrected Ca levels were 2.65mmol/l and PTH 60ng/l Overall comments: Small cohort study, with lower number of HC controls when compared to PHPT patients. All the PHPT patients were not tested with the same three tests as HC, 30mg, 60mg cinacalcet and calcium loading. Authors comment the design of the study was such to avoid delay in surgery.

3	Other	81 patients	Pooled data from three studies, Cinacalcet dose varied from 30-50mg twice daily to 90mg four times daily	Clinical effectiveness of the intervention	i) To evaluate measuring the study including serum Ca, PTH, phosphate, and bone specific ALP, and ii) area bone mineral density (aBMD).	i) Mean serum Ca decreased into normal range by 6 month in all categories and remained normal up to 4 years. Overall no further changes in serum Ca beyond what was observed in the first 6 months of treatment. With mean decrease in Ca from baseline in Croup 1, 2 and 3, being 17.1%, 11.2% and 12.4% respectively P<0.0001. PTH had decreased overall from baseline in each group although in Group 3 levels were lower compared to the other groups at all time points (yearly). No changes in ALP, and mean phosphate levels increased in all groups and remained high during the four year follow-up. ii) Mean BMD remained similar to baseline values in all categories. In Group 2 the decrease at 1 year Z-score at total femur was obsereved (P=0.03)	N/a	N/a	Peacock, Munro; Bilezikian, J. P.; Bolognese, M. A.; Borofsky, Michael; Scumpia, Simona; Sterling, L. R.; Cheng, Sunfa; Shoback, Dolores. Cinacalcet HCl reduces hypercalcemia in primary hyperparathyroidism across a wide spectrum of disease severity. J. Clin. Endocrinol. Metab. 2011;96(1):E9-18.	No serious adverse effects reported. 99% of patients experienced at least one mild or moderate AE. Most common AE reported were nausea (36%), arthralgia (30%), diarrhoea (22%), myalgia (22%) and paraesthesia (22%). 3 patients died unrelated to treatment of drug - metastatic colon cancer, cerebral ischaemia and cardiomyopathy	Yes	Population: Patients with PHPT grouped into three categories, Group 1: 29 patients with history of failed parathyroidectomy, Group 2: 37 patients meeting one or more criteria for parathyroidectomy but without prior surgery Group 3: 15 patients with mild asymptomatic PHPT without meeting criteria for either above category. Pooled data from three studies. Three disease categories balanced in terms of sex, age and race. Group 1 and 2 had higher mean serum Ca (2.95mmol/L and 2.75mmol/L respectively) and mean PTH (163 and 125pg/ml) when compared with asymptomatic patients (Ca 2.63mmol/L and PTH 103pg/ml). Group 3 had nonsignificant higher mean BMD Z-score than the other two groups at the hip (femur) and wrist (distal one third radius) and significantly higher at the lumbar spine (P<0.05). Overall comments: Pooled analysis of data from three multicentre clinical trials, one double blinded placebo controlled trial, and the other two studies open label single arm trials. Retrospective study of pooled analysis. Low level study
3	case series	33 patients	Cinacalcet dose of 30mg/daily orally and during titration phase to a maximum of 60-90mg/daily. In 15 patients (45.5%) dose increased to 60mg/day and in one patient increased up to 90mg/day	Clinical effectiveness of the intervention	i) To evaluate the effect of cinacalcet on serum calcium and PTH. Response to treatment was observed as complete if serum calcium and/or PTH normalised, partial if serum calcium and/or PTH decreased >5% without falling within the normal range. Persistent or progression if <5% drop or increase in serum calcium and PTH	No statistical significant difference in terms of response to cinacalcet between the two groups of patients, those who received at primary treatment and in those as a result of persistent/recurrent disease following surgery. At 12 months an average decrease of serum calcium from 10.9mg/dl to 9.8mg/dl, P<0.001. No significant changes in urinary calcium excretion or serum PTH levels. At 12 months 25/28 patients (89.3%) had a complete response and 1/28 a partial response and disease persistence in 2/28 patients	To assess the effect of cinacalcet on i) bone turnover makers, ii) bone mineral density iii) neuroendocrine MEN1-related hormones iv) parathyroid size	i) Bone turnover indirectly evaluated by measuring formation, BALP and resorption DPD markers. Both BALP and urinary DPD was not significantly changed after a year of cinacalcet therapy and remained within normal range during study duration. ii) At baseline 33% of patients were osteoporotic and 54.5% osteopenic at lumbar spine. At 12 months no significant changes in BMD T-score and Z-score values iii)At 12 months no significant changes in the pituitary and gastroenteropancreatic hormones. iv)At baseline 27/33 patients showed enlarged parathyroid gland upon neck ultrasound evaluation and 21/33 showing hyper functioning parathyroid disease following scintigraphy assessment. Remained unchanged at 12 months	Giusti, Francesca; Cianferotti, Luisella; Gronchi, Giorgio; Cioppi, Federica; Masi, Laura; Faggiano, Antongiulio; Colao, Annamaria; Ferolla, Piero; Brandi, Maria Luisa. Cinacalcet therapy in patients affected by primary hyperparathyroidism associated to Multiple Endocrine Neoplasia Syndrome type 1 (MEN1). Endocrine 2015;0(0):0.	Well tolerated by 28 patients (85%), 5 patients complained of heartburn and nausea. All completed the study	Yes	Population: Patients with PHPT and MEN 1(confirmed by genetic analysis). 22 patients started cinacalcet therapy as an alternative to surgery and 11 patients opted for therapy after onset of persistent post surgical primary hyperparathyroidism. 10 males and 23 females. Patients had normal liver and kidney function. 7 patients (21%) had symptomatic PHPT (history of kidney stones) and 12 patients (37%) were asymptomatic and diagnosed during biochemical screening. Overall comments: Multicentre phase IV prospective open label non-comparative trial in patients with MEN1-PHPT. Prospective short term study. Low level evidence.

3	case series	303 patients	At started of treatment the mean cinacalcet dose was 43.9mg/day and at 12 months mean dose was 51.3mg/day, with a median dose of 30mg/day. 55.4% of patients were taking cinacalcet once daily and 38.9% twice daily.	Clinical effectiveness of the intervention	i) To describe the clinical profiles of adults with PHPT receiving cinacalcet ii) to evaluate the effect of cinacalcet on serum calcium	219 patients (72%) completed 12 months of treatment. 40 patients (13%) discontinued therapy as underwent a parathyroidectomy. Reasons for prescribing cinacalcet were: surgery deemed inappropriate (35%), patient declined surgery (28%) and surgery failed or contraindicated (22%). ii) At 12months in 60% of patients reduced in calcium levels of ≥1mg/dl was observed. 9.9% of patients at baseline had an albumin corrected Ca of ≤10.3mg/dl. The percent of patients at 3,6 and 12 months that had Ca of ≤10.3mg/dl were 63, 69 and 71% respectively.	N/a	N/a	Schwarz, P.; Body, J. J.; Cáp, J.; Hofbauer, L. C.; Farouk, M.; Gessl, A.; Kuhn, J. M.; Marcocci, C.; Mattin, C.; Muñoz Torres, M.; Payer, J.; Van De Ven, A.; Yavropoulou, M.; Selby, P.. The PRIMARA study: a prospective, descriptive, observational study to review cinacalcet use in patients with primary hyperparathyroidism in clinical practice. Eur. J. Endocrinol. 2014;171(6):727-735.	27% of patients (81 patients) reported adverse events, commonly nausea (41 patients). Five patients reported hypocalcaemia and paraesthesia. Three serious ADRs were reported in two patients:hypocalcaemia and muscles spasms (patient was receiving cinacalcet 60mg daily) and circulatory collapse (patient receiving cinacalcet 30mg twice daily). 7.6% of patients discontinued therapy as a result of adverse events.	Yes	Population: Patients with PHPT who received Cinacalcet treatment for the first time. Majority of patients (79.5%) were female (n=241), and 64% were >65years of age. 134 patients (44%) were symptomatic, majority complaining of bone pain (58) or renal stones (50). At baseline the mean albumin corrected serum calcium (ACSC) was 2.9mmol/L (11.4mg/dl). Overall comments: Prospective multicentre observational study. Limitations include the lack of long term follow-up, no control group for comparison, non-randomised, did not evaluate bone mineral density nor bone turnover markers. Low level evidence study.

3	Case series	135 patients	In 64% of sPHPT and 91% of fPHPT cinacalcet was started at 30mg daily and titrated to achieve normocalcaemia. Final dose range between 15 -120mg daily.	Clinical effectiveness of the intervention	i) Evaluating prescription of cinacalcet following European Medicine Agency (EMA) labelling. EMA defined prescription criteria for cinacalcet 'reduction in hypercalcaemia in patients for whom PTx is not clinically appropriate or is contraindicate.'	i) 53% of sPHPT and 26% of fPHPT patients met EMA labelling. In 96% of sPHPT patients cinacalcet was prescribed in 34% of patients with high surgical risk, 19% with negative preoperative imaging ,24% for control of hypercalcaemia following parathyroidectomy (PTx) and 19% who refused PTx. In 79% of fPHPT indications were as follows: in 34% of patients was an initial treatment, 31% as result of persistent/relapsing PHPT after surgery and 14% refusal of PTx	To assess the effect of cinacalcet in each group sPHPT and fPHPT on i) calcium and PTH ii)BMD changes	i)In the sPHPT group at the final observation calcium significantly decreased from 2.90±0.27mmol to 2.55±0.22mmol/l (P<0.0001). 65% (65pts) became normocalcaemic. Serum PTH declined (-22%) from 18pmol/l to 14pmol/l (P=0.038). In the fPHPT group the reduction in serum Ca was from 2.75±0.17mmol to 2.47±0.15mmol/l (P<0.001), and 80% of patient became normocalcaemic. PTH did not significantly change from 13pmol/l to 12pmol/l (P=0.757) ii) in sPHPT follow-up data on BMD changes in 26/100 patients of which 13 pts were treated with bisphosphonates, with mean final T score significantly higher than baseline -1.71 to -2.0, P=0.003, no significant difference in non-bisphosphonate group when data was further analysed.	Saponaro, Federica; Faggiano, Antongiulio; Grimaldi, Franco; Borretta, Giorgio; Brandi, Maria Luisa; Minisola, Salvatore; Frasoldati, Andrea; Papini, Enrico; Scillitani, Alfredo; Banti, Chiara; Del Prete, Michela; Vescini, Fabio; Gianotti, Laura; Cavalli, Loredana; Romagnoli, Elisabetta; Colao, Annamaria; Cetani, Filomena; Marcocci, Claudio. Cinacalcet in the management of primary hyperparathyroidism: post marketing experience of an Italian multicentre group. Clin. Endocrinol. (Oxf) 2013;79(1):20-26.	In the sPHPT (n=100) 15 patients reported upper GI adverse effects and as a result withdrew from treatment. One patient had symptomatic hypocalcaemia (decreased to 2.10mmol/l) and withdrew. In fPHPT group (n=35) overall treatment well tolerated with 6 patients reporting mild symptomatic hypocalcaemia. Two patients experienced hypocalcaemia with one patient requiring to withdraw from treatment	Yes	Population: 100 patients with sporadic sPHPT and 35 patients with familial PHPT (fPHPT), 32 patients with MEN-1 and 3 with familial isolated PHPT. 112 women and 23 men Diagnosis of PHPT based on elevated ionized or total serum calcium with increased or inappropriate normal intact PTH. Majority of patients (n=96) were symptomatic of PHPT and 38 were asymptomatic. At baseline the mean adjusted Ca was 2.85±0.25mmol/L, median PTH and 25OHD was 16pmol/l and 48nmol/l respectively. Overall comments: Authors conclude that the study illustrates a wide heterogeneity in the use of cinacalcet in patients with PHPT in Italy and that EMA labelling is not always followed. Retrospective analysis of 8 Italian centres. Authors recognise no long term study on evaluating the safety profile of cinacalcet. Low level evidence study.
3	case series	34 patients	Initial dose of cinacalcet was 30mg twice daily in 94% of patients and 30mg daily in 6% of patients. 41% of patients required a dose adjustment, 7 pts a dose escalation and in 4 pts a reduction.	Clinical effectiveness of the intervention	i) To evaluate the effect of cinacalcet on serum calcium, PTH and phosphorus.	20/34 patients completed treatment up to 12 months. Treatment discontinued in 13 patients, 4 because of adverse events and 9 when surgery was performed. In 55% of patients normocalcemia was achieved (<10.2mg/dl). After 3 months of cinacalcet serum Ca significantly decreased from 11.73mg/dl to 10.7mg/dl, serum phosphorus increased from 2.41mg/dl to 2.63mg/dl p=0.004 and no significant change occurred in PTH, 181.91pg/ml to 195.47pg/ml, p=0.695. No significant change from 3 to 6 months. At 12 months PTH decreased significantly from baseline to 152.47pg/ml p=0.028 and serum calcium decreased 10.2mg/dl p<0.001 and phosphorus significantly increased 2.71mg/dl, p=0.01.	N/a	N/a	Luque-Fernández, Inés; García-Martín, Antonia; Luque-Pazos, Alessandra. Experience with cinacalcet in primary hyperparathyroidism: results after 1 year of treatment. Ther Adv Endocrinol Metab 2013;4(3):77-81.	17.6% of patients had at least one mild to moderate adverse event, commonly reported were nausea and vomiting.	Yes	Population: 20/34 patients completed 12 months of treatment. 29 women and 5 men Patients with PHPT, with reasons for starting cinacalcet treatment were refusal to have parathyroidectomy (n=8), surgery not possible due to comorbidities (n=5) and progressive hypercalcemia prior to surgery (n=21). Arterial hypertension present in 67.6% of patients with type 2 diabetes in 29.4% and impaired glucose levels in 8.82%. 19 patients had sporadic PHPT and one multiple endocrine neoplasia type I syndrome. Overall comments: Authors conclude cinacalcet is an effective alternative in the nonsurgical treatment of PHPT. Small sample size, short follow-up time. Low evidence study.

3	case series	14 patients	Cinacalcet dose was titrated 2 weekly to achieve normocalcaemia and then maintained. Median dose was 30mg twice daily (range 30mg daily to 60mg twice daily)	Clinical effectiveness of the intervention	i) To evaluate the efficacy of cinacalcet in reducing serum calcium in patients with PHPT	Serum calcium decrease by 1mg/dl in all patients and normalised in 10 patients. Average decrease of Ca from baseline was from 12.2mg/dl to 9.9±0.2mg/dl (P<0.001). Similar result observed for serum ionized calcium. PTH decreased by 17.1% compared to baseline (269pg/ml to 223pg/ml) although never reached normal range.	ii) Evaluate BMD changes	8 patients had BMD T score below -2.5 at any site or previous fragility fracture and had received concomitant treatment with bisphosphonates. At one year follow-up in 7 patients BMD monitoring did not show any significant changes.	Cetani, F.; Saponaro, F.; Banti, C.; Cianferotti, L.; Vignali, E.; Chiavistelli, S.; Viccica, G.; Pinchera, A.; Marcocci, C.. Cinacalcet efficacy in patients with moderately severe primary hyperparathyroidism according to the European Medicine Agency prescription labeling. J. Endocrinol. Invest. 2012;35(7):655-660.	6 patients (43%) experienced adverse events, 5 patients nausea and one vomiting. Two patients experienced severe symptoms and withdrew from the trial. Two patients experienced hypocalcaemia one at 2 weeks from starting treatment and the other at 12 weeks. In both patients normocalcaemia was achieved by decreasing the dose.	Yes	Population: Patients with PHPT where parathyroidectomy is indicated according to serum calcium levels but surgery is contraindicated (n=7) or not clinically appropriate (n=4) because of recurrent or persistent PHPT after multiple surgery. 3 patients refused after a prior white cervicotomy. Baseline serum calcium was 3.05±0.08mmol/L. 8 patients received bisphosphate therapy during the study Overall comments: Prospective open label single centre study. Small study, with short term follow-up. Low level evidence study

3	case series	70 patients	Cinacalcet prescribed twice daily for all patients. The dose ranged from 60 to 120mg daily in divided doses. All patients underwent surgery within 2 months of referral	Clinical effectiveness of the intervention	To evaluate i) effect on calcium and PTH levels ii) assessment of bone density iii) symptoms of PHPT	i) In 83% of patients calcium levels decreased into normal range (p<0.001) at calcium levels for patients taking treatment for more than one month decreased from 11.7±1.1 to 10.2±0.4 (p<0.05). Mean decrease in serum serum PTH in patients taking cinacalcet for >6months was 15.4%. ii) 59/70 patients had baseline DEXA scans. 23 patients had taken cinacalcet for >1.5years,and 14 of these patients showed significant decrease in bone density T scores (P<0.05) with 5 patients having more than 1 SD decrease in Z scores. 40% of patients were taking concomitant bisphosphonate therapy. iii) 3 patients (6%) reported improvement in symptoms whilst on cinacalcet and 11 patients (21.6%) felt worse. The number of symptoms reported at baseline (at least 2 weeks of cinacalcet) were 5.3±2.1, whilst on cinacalcet treatment 6.8±2.8 and 2 months post operatively 3.2±2.4. Most common symptoms reported were fatigue, memory loss, insomnia, bone pain, nephrolithiasis, muscle cramps, depression and irritability.	To evaluate reasons for discontinuing cinacalcet	Patients referred for surgery and reasons for stopping medical treatment: 19 patients (27%) discontinued as a result of nausea/vomiting, 3 patients (4%) cost of medication, 18pts (26%) because the felt the same or worse, in 8patients the new doctor ceased the medication, 7 patients self referred for surgery, 1 patient had symptomatic hypocalcaemia and 14 patients (20%) had worsening osteoporosis	Norman, James; Lopez, Jose; Politz, Doug. Cinacalcet (Sensipar) provides no measurable clinical benefits for patients with primary hyperparathyroidism and may accelerate bone loss with prolonged use. Ann. Surg. Oncol. 2012;19(5):1466-1471.	4 patients (6%) required hospitalisation for IV calcium following treatment resulting in symptomatic cinacalcet.	Yes	Population: PHPT patients established on cinacalcet therapy as an alternative to surgery. 7 patients (10%) had persistent symptoms following parathyroid surgery, 24% started because physician felt inappropriate (age), 9% because of increased risk of surgery in view of co-morbidity (atrial fibrillation, prior stroke). Predominately female patients (n=51), 73%. Overall comments: 59 patients were prescribed cinacalcet by 51 different endocrinologists and 11 patients by 8 different nephrologists. Authors report the justification for starting cinacalcet was determined by reviewing the clinic notes for each patient. Small study with significant bias as selective group of patients that were started on cinacalcet and referred for surgical procedure. In additions symptoms of PHPT were defined as baseline as min of two weeks off cinacalcet, baseline was established post cinacalcet therapy. The data for cinacalcet therapy is predominately retrieved from case notes and retrospectively, no clear defined protocol followed to ensure consensus of treatment. Low level evidence study.

3	case series	3 patients	Cinacalcet prescribed	Clinical effectiveness of the intervention	To evaluate the effect of cinacalcet in a cohort of elderly patients	Patient 1: 84 year old, with raised ionised calcium 1.46mmol/l, PTH 14pmol/l and symptomatic complaining of low back pain, nausea, cognitive disorders, mood changes and weakness. Spiral MR showed old wedge fractures and sestabmibi scan parathyroid adenoma. Started on treatment with cinacalcet and within 3 week readmitted because of worsening nausea and underwent parathyroidectomy, with normalisation of Ca and PTH levels. ii) Patient 2: 79 year old woman with PTHT and secondary osteoporosis with a hip fracture, no parathyroid abnormalities evident upon imaging. Normalisation of ionised Ca from 1.48mmol/l to 1.16mmol/l following treatment with cinacalcet. Also improvement of cognitive function and mobility. iii) 87 year old woman with multiple bone fractures, cardiovascular co-morbidity and confusion and upon imaging revealed a parathyroid adenoma. Underwent force saline hydration without sufficient reduction in Ca level, when onto to have cinacalcet in normalisation of calcium and underwent surgery two weeks later	N/a	N/a	Jacobs, L.; Samson, M. M.; Verhaar, H. J. J.; Koek, H. L.. Therapeutic challenges in elderly patients with symptomatic hypercalcaemia caused by primary hyperparathyroidism. Neth J Med 2012;70(1):35-38.	Patient 1 suffered severe nausea	Yes	Population: Four elderly patients with symptomatic hypercalcaemia as a result of PHPT. Three patients had a parathyroid adenoma shown on imaging. Overall comments: Very small case series dose of cinacalcet not described. Low level evidence study

3	Case series	23 patients	10 patients received cinacalcet and alendronate and 13 patients cinacalcet alone. Cinacalcet hydrochloride started at dose of 30mg daily, increased by 30mg until normocalcaemia was achieved, with a max dose of 90mg a day. Alendronate was administered at a dose of 70mg a week. Cholecalciferol was started in patients if 25 hydroxy vitamin D <20ng/ml once normocalcemia was achieved.	Clinical effectiveness of the intervention	Evaluate the effect of cinacalcet on i) serum calcium, PTH, phosphorus, ii) 24hour urinary calcium and phosphorus iii) BMD	After 3 months treatment serum Ca significantly decreased, serum phosphorus significantly increased compared to baseline (P<0.001). At 3 months no change in serum PTH, although after 6 months serum PTH significantly decreased as compared to baseline (P<0.001). Results were maintained after 12 and 24months of therapy with cinacalcet. At 12 months the serum calcium and PTH concentrations were within normal range in 100% and 43% respectively. No difference in rate of serum calcium and PTH decreases between patients with cinacalcet and alendronate, and those who were treated with cinacalcet alone. ii) 24hour urine calcium excretion and 24h urine calcium: creatinine ratio significantly decreased from baseline (P<0.001). iii)16 patients (65%) received replacement treatment with cholecalciferol. In the cinacalcet alone group no change in BMD. Patients in the cinacalcet and alendronate group T score increased by 9.6% at lumbar spine and 3.9% at femur level (P<0.01).	N/a	N/a	Faggiano, A.; Di Somma, C.; Ramundo, V.; Severino, R.; Vuolo, L.; Coppola, A.; Panico, F.; Savastano, S.; Lombardi, G.; Colao, A.; Gasperi, M.. Cinacalcet hydrochloride in combination with alendronate normalizes hypercalcemia and improves bone mineral density in patients with primary hyperparathyroidism. Endocrine 2011;39(3):283-287.	0	Yes	Population: Patients with sPHPT, 8 patients did not meet current guidelines for surgery, 15 patients fulfilled the criteria for parathyroid surgery, 5 patients contraindicated to surgery and 10 patients refused to be operated. All patients showed parathyroid enlargement. 78% of patients with a history of bone abnormalities, osteopenia in 13, osteoporosis in 5 vertebral fractures in 3 patients. 52% of patients had a history of kidney stones, 6 with nephrolithiasis and 6 microlithiasis. All patients had a normal renal function. Overall comments: Retrospective study, with no comparative group. Observational study. Low level evidence study.
3	case series	3 patients	Started on cinacalcet on 30mg twice daily and advised to avoid calcium intake and consume up to to 2 litres of calcium poor mineral water	Clinical effectiveness of the intervention	To evaluate the efficacy of cinacalcet in setting of severe hypercalcaemia prior to ambulatory surgery	Serum calcium normalised in two patients and failed to normalise in one patient to safe levels. In 2 patients elective surgery was performed	N/a	N/a	Rostoker, Guy; Bellamy, Jean; Janklewicz, Philippe. Cinacalcet to prevent parathyrotoxic crises in hypercalcaemic patients awaiting parathyroidectomy. BMJ Case Rep 2011;2011(0):0.	0	Yes	Population: 3 patients referred with severe nephrolithiasis (bilateral and recurrent phosphocalcic stones). All patients had hypercalciuria, severe hypercalcaemia at least >3mmol/l (>12mg/dl) and elevated 1-84 parathyroid levels. Within a week parathyroid adenoma was identified and patients awaiting elective surgery. Patients were not admitted to hospital for rehydration and intravenous bisphosphonates to be followed by emergency parathyroidectomy. Started on cinacalcet Overall comments: Authors reports cinacalcet may be safe and beneficial in severely hypercalcaemic patients awaiting primary hyperparathyroidism.

3	Case report	2 patients	Cinacalcet at a dose of 30mg daily	Clinical effectiveness of the intervention	Effect of Cinacalcet on calcium and PTH levels	Serum calcium and PTH levels normalised after 1 and 6 months of starting therapy and remained with normal range at least 50 months post follow-up	N/a	N/a	Del Prete, M.; Marotta, V.; Ramundo, V.; Marciello, F.; Di Sarno, A.; Esposito, R.; Carratù, A. C.; De Luca Di Roseto, C.; Di Somma, C.; Colao, A.; Faggiano, A.. Impact of cinacalcet hydrochloride in clinical management of primary hyperparathyroidism in multiple endocrine neoplasia type 1. Minerva Endocrinol. 2013;38(4):389-394.	Well tolerated and no adverse events reported	Yes	Population: Two MEN1 patients from the same family (mother and daughter) with PHPT. Patients refused surgical intervention. Mother already a had a previous partial parathyroidectomy Overall comments: Low level evidence study
3	Case report	1 patient	Cinacalcet initially started on 30mg daily and decreased to 45mg daily as a result of nausea	Clinical effectiveness of the intervention	To evaluate the efficacy of cinacalcet	7 months following treatment calcium normalised to 10mg/dl from 11.6mg/dl and PTH from 649pg/ml to 339pg/ml. Bone density improved 11.8% at right forearm, 31.7% at lumbar spine and 24.1% at left hip	N/a	N/a	Ogrin, C.. Evaluation of parathyroid levels and bone densitometry after cinacalcet treatment in severe primary hyperparathyroidism. Minerva Endocrinol. 2013;38(3):337-338.	Nausea and dose decreased	Yes	Population: Patient with a 15 year history of primary hyperparathyroidism and on no treatment, presented to accident and emergency with a pathological wrist fracture. She was not taking Vit D and Ca supplements and had refused a parathyroidectomy. Following admission initially started on Vit D3 and Calcium supplements although no significant improved and was started on oral Ibandronate. Calcium levels improved after intravenous Ibandronate but could not achieve normocalcaemia and cinacalcet was started. Overall comments: Bone density did increase although patients were on treatment with bisphosphonates, calcium and vit D supplements. Low level evidence study.
N/a - Study only referenced in review for demographic data	Other	N/a	N/a - Study only referenced in review for demographic data	Other	N/a - Study only referenced in review for demographic data	N/a - Study only referenced in review for demographic data	N/a - Study only referenced in review for demographic data	N/a - Study only referenced in review for demographic data	Ning Y., Donnan P.T., Murphy M.J., Leese G.P.. Epidemiology of primary hyperparathyroidism in Tayside, Scotland, UK.. Clinical Endocrinology 2009;71, 485-493.	N/a - Study only referenced in review for demographic data	N/a - Study only referenced in review for demographic data	N/a - Study only referenced in review for demographic data.

N/a	Other	N/a	Summary statement of international guidelines. Included as reference for clinical guidelines. Not reviewed as evidence.	Other	N/a	N/a	N/a	N/a	Bilezikian J.P., Brandi M.L., Eastell R., Silverberg S.J., Udelsman R., Marcocci C., Potts J.T. Jr.. Guidelines for the management of asymptomatic primary hyperparathyroidism : summary statement from the Fourth International Workshop.. Journal of Clinical Endocrinology and Metabolism 2014;99(10): 3561-9.	N/a	N/a	Summary statement of international guidelines. Included as reference for clinical guidelines. Not reviewed as evidence.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	Original search terms provided by NHS England (where applicable)
Updated search terms - Population	Primary hyperparathyroidism PHPT
Updated search terms - Intervention	Cinacalcet Sensipar Mimpara
Updated search terms - Comparator	Parathyroidectomy Bisphosphonates
Updated search terms - Outcome	N/a
Inclusion criteria	General inclusion criteria
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	N/a
Exclusion criteria	General exclusion criteria
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) 7. Narrative / non-systematic reviews (relevant referenced studies to be included)
	Specific exclusion criteria
	N/a