# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

# Overview

# Cinacalcet hydrochloride for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the first Appraisal Committee meeting, it is prepared before the Institute receives consultees' comments on the assessment report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

## 1 Background

### *1.1 The condition*

The parathyroid glands regulate calcium and phosphate levels in the circulation by secreting parathyroid hormone (PTH). PTH raises calcium levels and lowers phosphate levels. It increases calcium levels through three actions: indirectly stimulating osteoclasts to release calcium from bones, stimulating reabsorption of calcium in the renal tubules, and stimulating renal hydroxylation of inactive 25-hydroxyvitamin D to the active form calcitriol, which in turn enhances intestinal absorption of calcium. PTH lowers phosphate levels by reducing reabsorption in the renal tubules.

Regulation of PTH secretion is complex. High levels of phosphate stimulate PTH synthesis and secretion. Low levels of calcitriol lead to insufficient activation of vitamin D receptors on the parathyroid cells, which also results in increased secretion of PTH. However, the interaction of calcium with specific calcium-sensing receptors on the parathyroid cell membranes is the most potent factor influencing PTH secretion: low circulating levels of calcium decrease the activation of calcium-sensing receptors on the parathyroid cells, resulting in rapid secretion of PTH.

Secondary hyperparathyroidism is a common complication of impaired renal function. It begins early in the course of the disease, when renal function is only mildly to moderately impaired. Almost all people whose kidney function has declined to the point where they need dialysis have secondary hyperparathyroidism. Two UK studies have estimated the annual incidence of end-stage renal disease to be 132 and 148 per million population.

Both failure of the excretory function of the kidney (impaired excretion of phosphate and impaired reabsorption of calcium) and of the endocrine function of the kidney (reduced hydroxylation of inactive forms of vitamin D to the active form, calcitriol) contribute to the development of secondary hyperparathyroidism.

Hyperphosphataemia plays an important role in the development of secondary hyperparathyroidism (de Francisco 2004). In the early stages of renal impairment, as the glomerular filtration rate falls, phosphate excretion is reduced. Initially hyperphosphataemia does not occur because increased secretion of PTH stimulates the kidneys to excrete more phosphate. When renal impairment progresses to the moderate stage, the kidneys are unable to eliminate phosphate in response to PTH and phosphate levels begin to rise. Hyperphosphataemia suppresses the renal hydroxylation of inactive 25-hydroxyvitamin D to calcitriol. Low levels of calcitriol lead to reduced intestinal absorption of calcium, leading in turn to hypocalcaemia. Hypocalcaemia, low calcitriol levels and hyperphosphataemia all independently stimulate PTH synthesis and secretion.

As these chronic stimuli persist, the parathyroid glands become enlarged and begin to function autonomously, continuing to secrete PTH even if hypocalcaemia is corrected. PTH levels become extremely elevated and this causes further quantities of calcium and phosphate to be released from bone. Hyperphosphataemia is exacerbated and hypercalcaemia may occur. When the parathyroid no longer adequately responds to calcium levels, the condition is referred to as ‘tertiary’ or ‘refractory’ hyperparathyroidism. At this advanced stage, the hyperparathyroidism is refractory to medical treatment.

Secondary hyperparathyroidism is associated with both skeletal and non-skeletal clinical consequences.

### 1.1.1 Bone disease in chronic renal failure

Bone disease (renal osteodystrophy) is present in about 70% of people starting dialysis. It manifests as bone pain, deformity and pathological fracture and is a major cause of disability in people with end-stage renal disease (ESRD).

Renal osteodystrophy is a multifactorial disease but secondary hyperparathyroidism and calcitriol deficiency are important contributors to its development. The assessment report refers to two main forms (see section 3.3.1.1): high turnover bone disease, associated with high levels of PTH, alkaline phosphatase and other markers of high bone turnover; and low turnover disease associated with low levels of PTH. However, PTH levels are not sufficient to establish the type of osteodystrophy in an individual patient (Hruska 2000). Bone biopsy is required for characterisation of bone lesions, although this is not standard clinical practice. The main types of lesion are described in Table 1 below.

A study of 40,538 people on haemodialysis found that serum phosphorous concentration was significantly related to hospitalisation for fracture (Block et al. 2004; see assessment report page 32–33). Time on dialysis was also strongly associated with hospitalisation for fracture. As expected, the following risk factors were also significantly associated with fracture-related hospitalisation: advanced age, female sex, white race, and lower body weight.

**Table 1 Bone lesions in renal disease**

| Bone lesion | Description |
|---|---|
| Osteitis fibrosa | This is the most common form of renal bone disease. It is primarily caused by secondary hyperparathyroidism. It is characterised by increased frequency of bone remodelling. Increased osteoclasts, osteoblasts, and fibroblast-like cells result in abnormal bone resorption, abnormal bone formation, and marrow fibrosis. This leads to bone porosity with or without deposition of fibrous tissues. Cysts may develop. |
| Osteomalacia | This is a disparity between the rate of bone matrix synthesis and mineralisation resulting in increased unmineralised osteoid and a weakened skeleton. Bone turnover is low. In the past, osteomalacia in renal disease was commonly caused by aluminium toxicity. Because aluminium is now no longer commonly used as a phosphate binder and is no longer present in high concentrations in treated water for dialysis, the incidence has declined. Calcitriol deficiency is also a potential cause of osteomalacia in people with renal disease. |
| Mixed lesions | A combination of osteitis fibrosa and osteomalacia. |
| Adynamic bone disease | This is associated with low levels of PTH (for example, after parathyroidectomy) or normal levels of PTH. It is characterised by reduced osteoclasts and osteoblasts, and bone turnover is markedly low. It appears that PTH levels in the region of 3–5 times the upper range of normal are required for normal bone turnover in people with end-stage renal disease, indicating skeletal resistance to PTH. Treatment of hyperparathyroidism, for example with calcitriol, has been found to slow bone turnover to abnormal levels. The consequences of adynamic bone disease principally relate to the risk of hypercalcaemia and calcification of extraskeletal tissues because of the reduced ability of the bone to sequester calcium. It is unclear whether there is an increased risk of fracture. |

### 1.1.2 Extraskeletal complications

Cardiovascular disease is the leading cause of death in people with ESRD. Cardiovascular mortality rates are several times higher than in the general population even after adjusting for age, sex, race and the presence of diabetes (Chertow 2003).

Hyperphosphataemia is associated with elevated risk of cardiovascular mortality. The assessment report notes a US study in 40,538 people on thrice weekly dialysis that reported an increased risk of death with serum phosphate levels above 1.61 mmol/litre after adjustment for age, race or ethnicity,

diabetes, time since initiation of dialysis and various laboratory variables (assessment report, page 31). In the same study, higher adjusted serum calcium concentrations were also associated with an increased risk of death. There was a weaker relationship between PTH and mortality. Moderate to severe hyperparathyroidism (PTH levels 600 pg/ml or more) was associated with an increased risk of death, while more modest increases in PTH were not.

Also, the renal registry has reported increased mortality hazard for elevated levels of phosphate, calcium and calcium phosphorus product (Ca x P) for people on haemodialysis or peritoneal dialysis (see appendix 8.1 in the assessment report).

Cardiac and vascular calcification is thought to underlie these increases in risk of mortality. Hyperphosphataemia and elevated Ca x P are associated with cardiovascular calcification, including the aorta, carotid and coronary arteries, the cardiac valves, and myocardial muscle (Qunibi 2004). Calcification can also be seen in other soft tissues including the lung, the conjunctiva, periarticular tissues, and the breast.

Calciphylaxis (calcific uraemic arteriolopathy) is a rare but serious complication that can occur in people with ESRD. It appears as painful, red cutaneous nodules (singular or numerous) that can often progress rapidly to ulceration, necrosis and sepsis. On biopsy, arteriolar calcification of the subcutaneous fat and dermis is seen. Mortality is high, rates of between 45% and 65% have been reported (Qunibi 2004).

## *1.2 Current management*

The aim of treatment is to re-establish normal levels of phosphate, PTH and calcium. In the UK the Renal Association, and in the US the National Kidney Foundation, have set standards for these parameters in ESRD (see assessment report, page 35).

Conventional therapy includes dietary modification to reduce phosphate intake, the use of phosphate binders, hydroxylated vitamin D sterols (calcitriol,

alfacalcidol) or the synthetic vitamin D analogue paricalcitol, and modification of the dialysis regimen. In severe hyperparathyroidism, parathyroidectomy is required.

Reducing phosphate in the diet is difficult to achieve while maintaining adequate nutritional intake, because many sources of protein are also high in phosphate. Phosphate binders can be taken with meals to reduce phosphate absorption from the gut. In the past, aluminium hydroxide was commonly used as a phosphate binder, but concern about aluminium toxicity in people receiving dialysis means that it is no longer widely used for this purpose. Calcium acetate and calcium carbonate are the most commonly used phosphate binders, but calcium salts are contraindicated in hypercalcaemia. Sevelamer is a non-calcium containing phosphate binding agent, but it is relatively expensive (average dose of nine tablets a day costs £2240 per year) and is associated with gastrointestinal adverse effects. Lanthanum carbonate is another non-calcium containing phosphate binder. It is on the market elsewhere in Europe, but not in the UK.

Vitamin D compounds that do not require renal hydroxylation for activation have been used in the treatment of secondary hyperparathyroidism in ESRD. However, doses that are capable of suppressing PTH secretion may lead to hypercalcaemia and a decline in renal function. By increasing intestinal absorption of calcium and phosphate, the risk of vascular calcification may be increased. In some people, PTH may be oversuppressed leading to adynamic bone disease (see Table 1 above).

Improved phosphate clearance can be achieved by intensifying the dialysis regimen. The most usual haemodialysis prescription is for 4 hours three times per week. Slow prolonged dialysis (over 8 hours or more nocturnally) or more frequent (daily) dialysis improves phosphate loss. Limitations on the availability of dialysis facilities mean that this option may be feasible only for some patients on home dialysis.

Surgical parathyroidectomy can be subtotal, total, or total with some parathyroid tissue reimplanted in a site such as the arm. As noted in the

submission from the Royal College of Physicians, perioperative risk is greater in people with renal failure than in people with normal renal function, and there is the additional risk that any remaining parathyroid tissue will become hyperplastic and require repeat surgery. Parathyroidectomy can lead to hypoparathyroidism and the problems associated with adynamic bone disease (see Table 1 above)

# 2 The technology

**Table 2 Summary description of technology**

| | | | |
|---|---|---|---|
| Generic name | Cinacalcet | | |
| Proprietary name | Mimpara | | |
| Manufacturer | Amgen Ltd | | |
| Dose | Starting dose 30 mg once daily, titrated every 2–4 weeks against intact or biointact PTH levels to a maximum of 180 mg once daily | | |
| Acquisition cost excluding VAT ('British national formulary' edition 51) | 30 mg tablets | 28-tablet pack | £126.28 |
| | 60 mg tablets | 28-tablet pack | £232.96 |
| | 90 mg tablets | 28-tablet pack | £349.44 |

Cinacalcet is a calcimimetic agent, that is, it increases the sensitivity of the calcium-sensing receptor to extracellular calcium ions, thereby inhibiting the release of PTH.

The licensed indication in renal disease is as follows: treatment of secondary hyperparathyroidism in patients with ESRD on maintenance dialysis therapy. It may be used as part of a therapeutic regimen including phosphate binders and/or vitamin D sterols, as appropriate.

Since cinacalcet lowers calcium levels, it is contraindicated when serum calcium (corrected for albumin) is below the lower limit of the normal range.

Cinacalcet was licensed in the EU in October 2004. Prescription cost analysis (PCA) data for 2005 indicate that there were 805 prescriptions for cinacalcet dispensed in the community in England at a total net ingredient cost of £199,700. This does not include prescribing in secondary care, where prescriptions are usually dispensed by the hospital pharmacy.

# 3 The evidence

## *3.1 Clinical effectiveness*

The systematic review carried out by the Assessment Group identified seven published reports of randomised controlled trials (RCTs) of cinacalcet versus standard care (vitamin D and phosphate binders) in people with hyperparathyroidism secondary to ESRD who were receiving dialysis. Most of these publications reported on one or more of four RCTs sponsored by Amgen, although three smaller RCTs were also identified (one of which included a subgroup of patients from Amgen trial 188). More comprehensive data relating to the four Amgen trials was reported on the website of the US Food and Drug Administration (FDA). The Assessment Group stated that the manufacturer's submission reported limited clinical effectiveness data from the same trials and also presented some data on the clinical effectiveness of comparator treatments (vitamin D and phosphate binders). In addition, the manufacturer submitted information on an as yet unpublished study relating to a phase IIIb RCT designed to evaluate optimal levels of concomitant vitamin D and phosphate binders in patients receiving standard care with or without cinacalcet.

The Assessment Group used the Amgen trial reports submitted to the FDA as the primary source for its review of clinical effectiveness. The reasons for this were as follows: more details in terms of methodology and outcomes were available in the FDA medical review than in the published papers, pooled data across the three main trials were reported for a number of outcomes, there were some small differences in reported numbers between the FDA medical review and the published papers and it was considered preferable to use a single source.

### 3.1.1 Study characteristics

A summary of the characteristics of the RCTs identified in the Assessment Group's systematic review is given in Table 3 below. The studies all comprised two phases: a titration phase and a maintenance phase during which efficacy was assessed. All studies were designed to assess

biochemical endpoints (namely changes in serum PTH, calcium, phosphate and calcium phosphorus product [Ca x P]). The study by Lien et al. also reported on bone mineral density.

**Table 3 Summary of study characteristics**

| Study | Design | Intervention[a] | Comparator[a] | Length of treatment |
|---|---|---|---|---|
| Amgen 172 | Phase III RCT | Cinacalcet 30 mg with titration to 60, 90, 120 and 180 mg (n = 205) | Placebo (n = 205) | 26 weeks (12-week dose titration and 14-week efficacy assessment) |
| Amgen 183 | Phase III RCT | Cinacalcet 30 mg with titration to 60, 90, 120 and 180 mg (n = 166) | Placebo (n = 165) | 26 weeks (12-week dose titration and 14-week efficacy assessment) |
| Amgen 188 | Phase III RCT | Cinacalcet 30 mg with titration to 60, 90, 120 and 180 mg (n =294) | Placebo (n = 101) | 26 weeks (16-week dose titration and 10-week efficacy assessment) |
| Amgen 141[b] | Phase II RCT | Cinacalcet 30 mg with titration to 50, 90, 120 and 180 mg (n = 32) | Placebo (n = 16) | 52 weeks (24-week dose titration and 28-week efficacy assessment) |
| Lien 2005 | Subgroup from Amgen 188 and another study | Cinacalcet 30 mg with titration to 60, 90, 120 and 180 mg (n = 8) | Placebo (n = 6) | 26 weeks (12-week dose titration and 14/18-week efficacy assessment) |
| Lindberg 2003 | RCT | Cinacalcet 20 mg with titration to 30, 40, and 50 mg (n =39) | Placebo (n = 39) | 18 weeks (12-week dose titration and 6 week efficacy assessment) |
| Quarles 2003 | RCT | Cinacalcet 25 mg with titration to 50, 75, and 100 mg (n = 36) | Placebo (n = 35) | 18 weeks (12-week dose titration and 6 week efficacy assessment) |

[a] patients in both arms received concomitant vitamin D sterols and phosphate binders
[b] patients also received concomitant calcium supplements

A post hoc analysis of pooled safety data from the four Amgen trials (Cunningham et al. 2005) reported on clinical outcomes of mortality, cardiovascular hospitalisation, all-cause hospitalisation, fracture and parathyroidectomy. This study also reported on health-related quality of life.

### 3.1.2 Study quality

The Assessment Group considered that the individual studies were generally well designed. Adequate steps to minimise bias appear to have been taken,

although the Assessment Group noted that the rates of attrition were higher in the cinacalcet arms than in the control arms (see assessment report page 67). Patient characteristics were generally similar across arms.

The Assessment Group raised several further issues with regard to the Cunningham analysis. In particular, they noted that three of the four included trials provide only a 6-month follow up, and question whether effects observed during such a short follow-up period can be extrapolated to the longer term (especially given that that absolute number of events is small). For some participants 12-month data is provided but this is taken from the smaller RCT and from participants in the 6-month trials who agreed to an extension, and is therefore potentially subject to bias. The Assessment Group also noted a lack of transparency with regard to censoring, with different numbers of patients reported to be at risk for different outcomes at the same time point.

### 3.1.3 Clinical effectiveness results

The clinical trials reported on a number of outcomes. Prespecified subgroup analyses by baseline PTH, calcium, phosphate and Ca x P level and duration of dialysis were presented for some endpoints. Where pooled results for Amgen trials 172, 183 and 188 are available, the individual results from each of these trials are not reported in this section. A full breakdown of all results from all trials can be found in the assessment report, pages 74–92.

***Percentage of patients achieving a mean PTH level of ≤ 26.5 pmol/litre***

In all trials that reported this outcome, a statistically significantly greater proportion of patients receiving cinacalcet achieved a mean PTH level of 26.5 pmol/litre or less when compared with patients receiving placebo. It is unclear why 26.5 pmol/litre (250 pg/ml) has been adopted as the standard threshold, although it does fall within the target range recommended in the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (15.90 to 31.80 pmol/litre or 150 to 300 pg/ml)

A pooled analysis of the three largest Amgen trials (172, 183, 188) showed that 40% of patients randomised to cinacalcet achieved target PTH levels versus 5% of patients receiving placebo ($p < 0.001$). The resultant odds ratio

(OR) was 12.33, 95% confidence interval (CI) 7.96 – 19.09. Similar results were seen in the other studies (Amgen 141: 53% versus 6%, p-value not reported; Quarles et al: 44% versus 20%, p = 0.029).

A stratified analysis by baseline PTH levels in the pooled analysis referred to above suggested that the effect was most pronounced in patients with moderately high (between 53.0 and 84.8 pmol/litre) PTH at baseline (OR 23.83, 95% CI 8.28–68.58) compared with OR of 10.85 in those with higher or lower PTH levels at baseline (see table 17 in the assessment report). However, it should be noted that the confidence intervals overlapped with those of the other subgroups. No statistical tests for interaction were reported. There were no significant effects when results were analysed by baseline calcium, phosphate, Ca x P or dialysis vintage.

***Achievement of a reduction in mean PTH levels from baseline of at least 30%***

In all studies where this outcome was investigated, significantly more patients who were treated with cinacalcet achieved a reduction of at least 30% in mean PTH levels compared with those receiving standard care alone. In the pooled analysis of Amgen trials 172, 183 and 188, 62% of patients treated with cinacalcet achieved this target, versus 11% in the placebo arm (p = 0.029). Results were also reported by Lindberg et al. (38% versus 8%, p = 0.001) and Quarles et al. (53% versus 23%, p = 0.009).

Achievement of a 30% or greater reduction did not appear to be influenced by baseline PTH, calcium or phosphate or dialysis vintage. However, the results of the subgroup analysis did suggest that higher baseline Ca x P (> 5.65 $mmol^2/litre^2$) may be associated with greater mean PTH reduction in patients treated with cinacalcet.

***Percentage change from baseline in mean PTH, serum calcium, phosphate and Ca x P***

Table 4 summarises the changes in mean levels of PTH, calcium, phosphate and Ca x P observed in the trials. The differences between arms were all statistically significant, with the exception of the results from Amgen study 141 and the percentage change in serum phosphate reported in Quarles et al.

Generally, patients receiving cinacalcet achieved decreases from baseline for all four measures, with placebo treated patients experiencing increases or in some cases decreases of lower magnitude. However, for change in serum phosphate, Amgen 141 (n = 48) showed a non-significant difference in the opposite direction to the other studies, with patients receiving placebo demonstrating a greater reduction.

The FDA review of Amgen trials 172, 183 and 188 noted that changes in serum calcium and phosphate were not correlated with changes in PTH.

**Table 4 Percentage change in mean serum levels of PTH, calcium, phosphate and Ca x P**

| Study | % change mean PTH | | % change mean calcium | | % change mean phosphate | | % change mean Ca x P | |
|---|---|---|---|---|---|---|---|---|
| | Cinacalcet | Placebo | Cinacalcet | Placebo | Cinacalcet | Placebo | Cinacalcet | Placebo |
| Amgen 172, 183, 188 | -41.5 | +8.1 | -6.7 | +0.5 | -7.8 | -0.3 | -13.8 | +0.1 |
| Amgen 141 | -54 | +36 | -5 | +2 | -10 | -14 | NR | NR |
| Lindberg et al., 2003 | -26 | +22 | -4.7 | 0 | -7.5 | +10.9 | -11.9 | +10.9 |
| Quarles et al., 2003 | -32.5 | +3.0 | -4.6 | +2.6 | -2.6* | +7.0 | -7.9 | +11.0 |

*Not significant, p value = 0.217 versus placebo

The results from Amgen trials 172 and 183 indicate that approximately 90% of people treated with cinacalcet achieved both a mean PTH of 26.5 pmol/litre or less and a reduction from baseline in Ca x P.

***Achievement of KDOQI standards***

A study by Moe and colleagues combined data from Amgen trials 172, 183 and 188 to establish the proportion of patients achieving KDOQI targets at baseline and during the maintenance phase. For all outcomes, a statistically significantly greater proportion of patients receiving cinacalcet achieved the recommended targets. The results are summarised in Table 5 below.

**Table 5 Percentage of patients achieving KDOQI standards**

| Target | % achieving target | |
|---|---|---|
| | Cinacalcet | Placebo |
| **Mean PTH < 31.8 pmol/litre** | | |
| Baseline | <1 | <1 |
| Maintenance phase | 56 | 10 |
| **Mean serum calcium 2.10–2.37mmol/litre** | | |
| Baseline | 32 | 33 |
| Maintenance phase | 49 | 24 |
| **Mean serum phosphate 1.13–1.78 mmol/litre** | | |
| Baseline | 33 | 31 |
| Maintenance phase | 46 | 33 |
| **Mean Ca x P < 4.44 mmol$^2$/litre$^2$** | | |
| Baseline | 37 | 34 |
| Maintenance phase | 65 | 36 |
| **Mean PTH < 31.8 pmol/litre and mean Ca x P < 4.44 mmol$^2$/litre$^2$** | | |
| Baseline | 0 | 0 |
| Maintenance phase | 41 | 6 |

***Impact of cinacalcet on bone mineral density***

The study by Lien et al. (2005) conducted in a subgroup of patients from Amgen 188 and another study (n = 14) reported a statistically significant increase in femoral bone mineral density from baseline in patients receiving cinacalcet, compared with a statistically significant decrease from baseline in those receiving placebo. No significant difference in lumbar bone mineral density was observed.

***Impact of cinacalcet on cardiovascular events, fracture parathyroidectomy and death***

The analysis by Cunningham et al. (2005) used adverse event data from the four Amgen trials (172, 183, 188 and 141) to assess the effect of cinacalcet on the clinical outcomes of fracture, cardiovascular events, hospitalisation and mortality compared to placebo. No significant difference was seen in overall mortality or all-cause hospitalisation. However, significant differences were observed in fracture, cardiovascular hospitalisation, and parathyroidectomy based on follow-up of 6–12 months. Table 6 provides a summary of the results.

**Table 6 Impact of cinacalcet on risk of clinical outcomes**

| Outcome | Event count | | Events per 100 patient years | | RR (95% CI) | P-value |
|---|---|---|---|---|---|---|
| | Cinacalcet n = 697 | Placebo n = 487 | Cinacalcet | Placebo | | |
| Mortality | NR | NR | 5.2 | 7.4 | 0.81 (0.45–1.45) | 0.47 |
| Cardiovascular hospitalisation | 72 | 77 | 15.0 | 19.7 | 0.61 (0.43–0.86) | 0.005 |
| All-cause hospitalisation | NR | NR | 67.0 | 71.0 | 1.03 (0.87–1.22) | 0.74 |
| Fracture | 12 | 20 | 3.2 | 6.9 | 0.46 (0.22–0.95) | 0.04 |
| Parathyroidectomy | 1 | 12 | 0.3 | 4.1 | 0.07 (0.01–055) | 0.009 |

***Quality of life***

The Cunningham study also reports combined data on health related quality of life, based on the SF-36 instrument, from Amgen studies 172, 183 and 188. Significant changes over time in the scores for the physical and bodily pain components were reported for people treated with cinacalcet versus those treated with placebo. No significant differences were found for the other domains. There was no overall difference between the study arms in self-assessed decline in physical status, although more people in the cinacalcet arm reported an increase of 5 points or more.

***Adverse events***

There was no significant difference in the number of deaths or the incidence of serious adverse events between study arms in Amgen trials 172, 183 and 188. No individual serious adverse event occurred in more than 2% of patients. The most common serious adverse events included: vascular access thrombosis, pneumonia, sepsis and non-cardiac chest pain. Cardiac arrest occurred in 1% of patients in each treatment arm and was fatal in three patients receiving placebo and eight patients receiving cinacalcet.

Pooled data for all adverse events were not reported; however, the rates of adverse events between the trial arms seem similar in Amgen trials 172, 183, and 188. Adverse event rates in cinacalcet treated patients were 90%, 93% and 91% in each of the trials respectively versus 95%, 93% and 93% in patients receiving placebo. The pooled analysis of Amgen trials 172, 183, 188,

indicates that the two most frequently reported adverse events were nausea (31% in cinacalcet treated patients versus 19% in placebo treated patients, $p < 0.001$) and vomiting (27% in cinacalcet treated patients versus 15% in placebo treated patients, $p < 0.001$). There was a higher incidence of hypocalcaemia in patients randomised to cinacalcet versus placebo treated patients (65% versus 25% having at least one serum calcium measurement < 2.1mmol/litre). There was also a greater incidence of seizures in patients randomised to cinacalcet (2% versus 0.4%).

A higher proportion of patients receiving cinacalcet than those receiving placebo withdrew from trials 172, 183 and 188 because of adverse events (15% versus 8%, $p = 0.005$). The most frequently cited reason for withdrawal was nausea and/or vomiting.

***Impact of cinacalcet on dose of vitamin D and phosphate binders***

The manufacturer's submission reported as yet unpublished results from the OPTIMA study. This was an open-label post-marketing study which randomised participants to standard care with or without cinacalcet. The primary endpoint was the proportion of patients achieving a mean iPTH of 300pg/ml. In contrast to previous trials, the OPTIMA study allowed the adjustment of doses of vitamin D sterols and phosphate binders in accordance with treatment algorithms (doses had been held constant in other RCTs to minimise the potential for confounding). The primary endpoint was achieved by 71% of patients in the cinacalcet arm versus 22% of patients receiving standard care alone ($p < 0.001$). Although the proportion of patients taking vitamin D sterols increased in both arms (66% to 81% in the standard care arm, 68% to 73% in the cinacalcet arm), the mean relative dose of vitamin sterol decreased by 22% in the cinacalcet arm, whereas a 3% increase occurred in the standard care arm. No significant differences in the doses of phosphate binders were observed.

### 3.1.4 Summary of clinical effectiveness section

The results from the clinical trials indicate that cinacalcet is effective at modifying levels of serum PTH, calcium, phosphate and Ca x P. The effect of cinacalcet on clinical outcomes such as fracture, cardiovascular events and

mortality is less clear. To date, only one study (Cunningham et al., 2005) has examined this question. This was based on a post-hoc analysis of adverse event data from studies that were designed and powered to assess biochemical endpoints and that had follow-up of only 6–12 months.

Pooled data from Amgen trials 172, 183, and 188 showed a statistically significant improvement in the summary score for the physical component of SF-36 measure of quality of life.

There is some evidence that patients treated with cinacalcet may be able to achieve target levels of PTH with lower doses of vitamin D sterols than patients receiving standard care.

## *3.2 Cost effectiveness*

The systematic review carried out by the Assessment Group did not identify any published cost effectiveness studies relevant to the scope of this appraisal. An economic model and separate cost consequence analysis were submitted by the manufacturer of cinacalcet. The Assessment Group developed its own economic model.

Both models were cost-utility analyses comparing cinacalcet in addition to standard care (vitamin D and phosphate binders) with standard care only in patients with hyperparathyroidism (PTH > 31.6 pmol/litre) who were receiving dialysis. Both analyses adopted the perspective of the NHS and generally similar cost and resource use assumptions were used. There were, however, major differences between the models with regard to the assumptions driving effectiveness.

### 3.2.1 Manufacturer's model

The model submitted by Amgen incorporated health states reflecting patients' status in relation to adverse events associated with secondary hyperparathyroidism. Clinical events included in the analysis were cardiovascular hospitalisations, fractures (major and minor), parathyroidectomies and death. A direct effect of cinacalcet on these outcomes was modelled.

The manufacturer's model resulted in an incremental cost effectiveness ratio (ICER) of £35,600 per quality adjusted life year (QALY) gained. Subgroup analyses in patients with moderate (PTH 31.6 to 84.2 pmol/litre) and severe (PTH > 84.2 pmol/litre) secondary hyperparathyroidism resulted in ICERs of £30,400 and £48,300 per QALY gained respectively.

A range of one-way sensitivity analyses were conducted. The results of these indicated that the ICER was most sensitive to variation in the dose of cinacalcet. A probabilistic sensitivity analysis was also carried out. This indicated that the probability that cinacalcet is cost effective at a willingness of to pay of £20,000 per additional QALY is approximately 30%, rising to approximately 43% at a willingness to pay of £30,000.

Although the Assessment Group felt that the manufacturer's economic analysis was generally well conducted, a number of weaknesses were identified. A detailed critique of the manufacturer's model is given in paragraph 5.3.2.3 of the assessment report.

Amgen also conducted a cost consequence analysis. Drug costs per responder were calculated for patients receiving standard care and standard care plus cinacalcet. The analysis was based on prospectively collected data from the OPTIMA study in which patients receiving standard care plus cinacalcet had achieved PTH targets with lower average doses of vitamin D sterols compared with patients receiving standard care alone. For the primary endpoint of the trial (mean PTH ≤ 31.6 pmol/litre), the drug costs per responder were similar in both arms. Costs per responder in relation to other outcomes are given in section 5.3 of the manufacturer's submission.

### 3.2.2 Assessment Group's model

The Assessment Group adopted a different approach to the manufacturer by modelling the effect of treatment on biochemical measures and then relating these intermediate endpoints to clinical events. In the base case analysis, patients in both arms were stratified by PTH levels: controlled (PTH ≤ 32 pmol/litre), uncontrolled (PTH between 33pmol/litre and 84 pmol/litre) or very uncontrolled (PTH ≥ 85 pmol/litre) and according to whether or not they had

undergone parathyroidectomy (with or without adverse events). Within each stratum, patients were able to move between health states reflecting their status in relation to clinical outcomes (cardiovascular events, fracture, parathyroidectomy, death). Patients also moved between strata if their levels of PTH increased.

The baseline distribution of patients at the various PTH levels following the titration phase was based on pooled data from three of the clinical trials of cinacalcet. Deterioration in PTH control over time was based on assumptions by the authors, including that there was no loss of control over time for patients taking cinacalcet (see assessment report pages109-110). Adverse events included cardiovascular events and fractures, and the probabilities of these occurring at different PTH levels were derived based on a variety of different sources, mostly large cohort studies. These rely on a number of assumptions and are subject to uncertainty. A wide range of sensitivity analyses were therefore conducted. The costs of dialysis were excluded in the base case analysis and included in a sensitivity analysis. Resource-use and unit costs included in the analysis are detailed in Section 5.5.3 of the assessment report (pages 124–132). Health-related utility for event-free survival and the disutility associated with adverse events were estimated from the published literature. Having uncontrolled PTH was assumed to have no impact on health-related utility and having very uncontrolled PTH was assumed to lead to 15% reduction in utility. Costs and QALYs were discounted at 3.5%.

The Assessment Group’s analysis resulted in an ICER of £61,890 per QALY gained when dialysis costs were excluded, and increased to £74,443 when dialysis costs were included. A subgroup analysis in patients with uncontrolled and very uncontrolled PTH levels resulted in ICERs of £57,442 and £81,479 respectively (excluding dialysis costs).

One-way sensitivity analyses carried out by the Assessment Group indicated that the model was most sensitive to the cost of cinacalcet, the relative risk of mortality for people with very uncontrolled PTH versus those with controlled PTH and the inclusion of costs associated with dialysis. A probabilistic

sensitivity analysis indicated that cinacalcet was likely to be more cost effective than standard care only at a willingness to pay of at least £62,000 per additional QALY.

The Assessment Group also modelled two further scenarios. In the first of these the intermediate marker of PTH level was removed and a direct effect of treatment on clinical outcomes was simulated. This permitted a more direct comparison with the manufacturer's submission and, as far as possible, effectiveness data were taken from the same source (Cunningham et al. 2005). This analysis resulted in an ICER of £42,999 excluding dialysis costs. The second additional analysis assumes that the effect of cinacalcet is mediated by levels of both PTH and Ca x P. This produced an ICER of £38,555 per QALY gained, excluding dialysis costs.

### 3.2.3 Summary of key points

The economic evaluations carried out by the manufacturer and the Assessment Group both indicate that the ICER of cinacalcet versus standard care (vitamin D and phosphate binders) is greater than £30,000 per QALY gained.

Both economic analyses suggest that cinacalcet may be more cost effective in a subgroup of patients with moderate secondary hyperparathyroidism but that the ICER is likely to remain above £30,000 in these patients.

The base case ICER obtained by the Assessment Group was more than 70% higher than that reported by the manufacturer (dialysis costs excluded), due to higher incremental costs and lower incremental QALYs. The difference may be attributable to the different model structures used. An ICER more similar to that calculated by the manufacturer was obtained when the Assessment Group assumed a direct effect of cinacalcet on clinical outcomes; however, the cost per QALY gained obtained remained in excess of £40,000. The Assessment Group noted that differing patterns of state occupancy were a key factor in the different costs and QALYs generated by the two models (see assessment report, pages 177–182, for a detailed breakdown).

A thorough comparison of the two models and a discussion of possible reasons for the different results is given on pages 176 to 183 of the assessment report.

# 4 Issues for consideration

- Do the improvements in biochemical measures observed in clinical trials translate into benefits in terms of health outcomes? If so, can the relationship be characterised from the current evidence base?
- Are the benefits of cinacalcet observed in clinical trials of relatively short duration (maximum length 52 weeks) likely to continue in the longer term?
- How should possible interaction between the key biochemical measures affected by secondary hyperparathyroidism (PTH, calcium, phosphate and calcium phosphorus product) be taken into account given the paucity of evidence in this area?
- Can serum PTH level be singled out as the sole driver of relevant clinical outcomes or are other factors (such as levels of calcium and phosphate) likely to have an influence?
- Are the associations between PTH levels and clinical outcomes assumed by the Assessment Group robust?
- Do patients receiving cinacalcet require lower doses of vitamin D in order to reach Renal Association / KDOQI targets (as observed in the OPTIMA trial)? If so, how would this affect cost effectiveness?
- Should consideration be given to the question of compliance in a disease area where patients are already prescribed a large number of medications?
- Is it possible to define and identify responders? Could cost effectiveness be more favourable if a 'stopping rule' were applied?
- Recognising that the cost of cinacalcet is prohibitive and likely to result in poor cost effectiveness, a number of consultees have suggested that its use should be restricted to the subgroup of patients with very uncontrolled secondary hyperparathyroidism. How should this be taken into account, given that this is the group in which cinacalcet appears to be least cost-effective?

- Should the costs of dialysis be included in the assessment of cost effectiveness, given that it is implicitly considered to be an acceptable use of NHS resources despite its poor cost-effectiveness?
- How should the difficulties surrounding accurate detection of PTH levels (overestimation of PTH due to inactive PTH build up in secondary hyperparathyroidism, variation between assays) be taken into account? (See assessment report page 35).

# 5 Ongoing research

The submission from the Royal College of Physicians indicates that there are ongoing trials of cinacalcet in patients with early hyperparathyroidism. However, it is unclear whether these studies will be directly relevant to the scope of this appraisal because the patients are unlikely to be undergoing dialysis.

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# Appendix A: Sources of evidence considered in the preparation of the overview

A The Assessment Report: Garside R, Pitt M, Anderson R et al. (Peninsula Technology Assessment Group). 'The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end stage renal disease patients on dialysis: a systematic review and economic evaluation'. March 2006.

B Submissions from the following organisations:

I Manufacturers/sponsors:

- Amgen Ltd.

II Professional/specialist and patient/carer groups:

- British Renal Society
- Kidney Research UK (National Kidney Research Fund)
- National Kidney Federation
- Royal College of Nursing
- Renal Association
- Royal College of Physicians
- Society of Endocrinology
- UK Renal Pharmacy Group

III Commentator organisations (without the right of appeal):

- None received

C Additional references used:

Block GA, Klassen PS, Lazarus JM, et al. (2004) Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 8: 2208–18.

Chertow GM (2003) Slowing the progression of vascular calcification in hemodialysis. *J Am Soc Nephrol* 14(9, Suppl 4): S310–4.

Cunningham J, Danese MD, Olson KA et al. (2005) Effects of the calcimimetic cinacalcet HCI on cardiovascular disease, fracture, and health related quality of life in secondary hyperparathyroidism. *Kidney Int.* 68: 1793–800

de Francisco ALM (2004) Secondary hyperparathyroidism: review of the disease and its treatment*. Clin Ther* 26:1976–93

Hruska K (2000) Pathophysiology of renal osteodystrophy *Pediatr Nephrol* 14: 636–40.

Qunibi WY (2004) Consequences of hyperphosphatemia in patients with end-stage renal disease (ESRD). *Kidney Int Suppl.* 90: S8–12.