NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final Appraisal Determination

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

1 Guidance

1.1 Cinacalcet is not recommended for the routine treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy.

1.2 Cinacalcet is recommended for the treatment of refractory secondary hyperparathyroidism in patients with end-stage renal disease (including those with calciphylaxis) only in those:

- who have 'very uncontrolled' plasma levels of intact parathyroid hormone (defined as greater than 85 pmol/litre [800 pg/ml]) that are refractory to standard therapy, and a normal or high adjusted serum calcium level, **and**
- in whom surgical parathyroidectomy is contraindicated, in that the risks of surgery are considered to outweigh the benefits.

1.3 Response to treatment should be monitored regularly and treatment should be continued only if a reduction in the plasma levels of intact parathyroid hormone of 30% or more is seen within 4 months of treatment, including dose escalation as appropriate.

2 Clinical need and practice

2.1 The parathyroid glands produce parathyroid hormone (PTH), which controls the levels of calcium in the blood. Excessive production of this hormone is

called hyperparathyroidism. When this is caused by another condition, it is called secondary hyperparathyroidism. Secondary hyperparathyroidism is a common complication of impaired renal function. Almost all people with end-stage renal disease (ESRD) have secondary hyperparathyroidism. Two UK studies have estimated the annual incidence of ESRD to be 132 and 148 per million population. A high proportion of people with ESRD receive dialysis; it is estimated that approximately 100 people per million population begin dialysis each year.

2.2 The development of secondary hyperparathyroidism in people with impaired renal function is complex. It occurs as a result of 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 [1,25-dihydroxyvitamin D]). In the early stages of renal impairment, phosphate excretion is reduced. Initially, this does not lead to high levels of phosphate in the blood (hyperphosphataemia) because increased secretion of PTH stimulates the kidneys to excrete more phosphate. When renal impairment progresses to the moderate stage, the kidneys can no longer eliminate more phosphate in response to increased PTH secretion, and phosphate levels begin to rise. Hyperphosphataemia suppresses the renal hydroxylation of inactive calcidiol (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. This condition is referred to as ‘refractory’ hyperparathyroidism and is also sometimes called ‘tertiary’ hyperparathyroidism. PTH levels become extremely elevated and this causes calcium and phosphate to be released from bone. Hyperphosphataemia is exacerbated and hypercalcaemia may occur.

2.3 Secondary hyperparathyroidism is associated with clinical complications involving the bones and other tissues. Bone disease (renal osteodystrophy) is present in about 70% of people starting dialysis. It is a multifactorial disease but secondary hyperparathyroidism is an important contributor to its development. Renal osteodystrophy manifests as bone pain, bone deformity and pathological fracture, and is a major cause of disability in people with ESRD. A study conducted in the USA including 40,538 people on haemodialysis found that the serum phosphorous concentration was statistically significantly related to the rate of hospitalisation for fracture. Time on dialysis was also strongly associated with hospitalisation for fracture.

2.4 People with kidney disease have a much higher risk of cardiovascular disease and associated mortality compared with the general population. This is a result of multiple factors, but derangements in calcium and phosphate homoeostasis appear to contribute. Hyperphosphataemia and elevated calcium–phosphorus product (Ca x P; the multiple of the serum levels of calcium and phosphorus) are associated with cardiovascular calcification affecting the aorta, the carotid and coronary arteries, the cardiac valves and myocardial muscle.

2.5 Calcification can also occur 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/purple cutaneous nodules (singular or numerous), and often progresses rapidly to ulceration, necrosis and sepsis of the skin and subcutaneous tissues. On biopsy, arteriolar calcification of the subcutaneous fat and dermis is seen. Mortality is high; rates of between 45% and 65% have been reported in people with this complication.

2.6 The aim of treatment in secondary hyperparathyroidism is to manage levels of phosphate, PTH and calcium. 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, total or partial surgical removal of the parathyroid glands may be needed.

2.7 Reducing phosphate in the diet while maintaining adequate nutritional intake is difficult, 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.

2.8 Vitamin D compounds that do not need renal hydroxylation for activation have been used in the treatment of secondary hyperparathyroidism in patients with ESRD. However, doses that are capable of suppressing PTH secretion may lead to hypercalcaemia and a decline in renal function. Vitamin D compounds are contraindicated in hypercalcaemia. By increasing intestinal absorption of calcium and phosphate, the risk of vascular calcification may be increased.

2.9 Phosphate clearance can be improved by intensifying the dialysis regimen. The most usual haemodialysis prescription is for 4 hours three times per week. Slow prolonged dialysis (over the course of 8 hours or more at night) or more frequent (daily) dialysis increases phosphate removal. Limitations on the availability of dialysis facilities mean that this option may be feasible only for some patients on home dialysis.

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

3 The technology

3.1 Cinacalcet (Mimpara: Amgen Ltd) is a calcimimetic agent which increases the sensitivity of calcium-sensing receptors to extracellular calcium ions, thereby inhibiting the release of PTH. It is licensed for the 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. It is initiated at a dose of 30 mg once daily, titrated every 2–4 weeks to a maximum of 180 mg once daily to achieve a target level of intact PTH of between 15.9 and 31.8 pmol/litre (150–300 pg/ml).

3.2 Because cinacalcet lowers calcium levels, it is contraindicated if serum calcium is below the lower limit of the normal range. The most commonly reported adverse effects in clinical trials were nausea and vomiting. These were mild to moderate in nature and transient in most cases. For full details of side effects and contraindications, see the summary of product characteristics (SPC).

3.3 The drug costs of treatment with cinacalcet are between £1646 and £9110 per year depending on the dose administered (excluding VAT; 'British national formulary' edition 51). Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 The systematic review carried out by the Assessment Group (appendix B) identified seven published reports of randomised controlled trials (RCTs) of cinacalcet versus placebo 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 the manufacturer of cinacalcet, although three smaller RCTs were also identified. In addition, the manufacturer submitted information on an unpublished study relating to an RCT designed to evaluate optimal levels of concomitant vitamin D and phosphate binders in patients receiving standard care with or without cinacalcet. All studies were designed to assess biochemical endpoints (namely changes in plasma PTH, serum calcium, serum phosphorus and Ca x P). One small study (n = 14) also reported on bone mineral density. Seven of the RCTs had durations of 26 weeks or less, with dose titration phases of between 12 and 16 weeks and efficacy assessment phases of between 6 and 14 weeks. The remaining study was 52 weeks long, with a 24-week dose titration period followed by a 28-week efficacy assessment.

4.1.2 Improvements in mean levels of PTH, calcium, phosphorus and Ca x P observed in the trials were statistically significantly greater in the cinacalcet groups in most of the studies that reported these endpoints. Generally, patients receiving cinacalcet had decreases from baseline for all four measures, with placebo-treated patients experiencing increases or, in some cases, decreases of lower magnitude. However, in two studies that reported changes in serum phosphorus levels (n= 71 and n = 48), differences in changes between the groups were not statistically significant, and in the smaller of these two studies patients receiving placebo had a greater reduction in phosphorus compared with those receiving cinacalcet. However, these two studies were not designed or powered to detect clinically meaningful differences in serum phosphorus.

4.1.3 A pooled analysis of the three largest RCTs (n = 1136) showed that target mean intact PTH levels were reached in 40% of patients randomised to cinacalcet, compared with 5% of patients receiving placebo ($p < 0.001$). In these studies, a target intact PTH level was defined as lower than 26.5 pmol/litre (250 pg/ml). Similar results were seen in another two studies that measured this endpoint. In these two studies the proportions of patients with target intact PTH levels were 53% versus 6% (n = 48, statistical

significance not reported) and 44% versus 20% (n = 71, p = 0.029) for patients receiving cinacalcet and placebo respectively.

4.1.4 Statistically significantly more patients who were treated with cinacalcet had a reduction of at least 30% in mean intact PTH levels compared with those receiving standard care alone in all RCTs that reported this outcome. In the pooled analysis of the three largest studies, 62% of patients treated with cinacalcet had a reduction of at least 30%, versus 11% in the placebo arm (p = 0.029). This endpoint was reported in two other studies, which also favoured cinacalcet over standard care. In these studies the proportions of patients with a reduction of at least 30% in mean intact PTH levels were 38% versus 8% (n = 78, p = 0.001) and 53% versus 23% (n = 71, p = 0.009) for patients receiving cinacalcet and placebo respectively.

4.1.5 A post-hoc analysis of pooled data from four RCTs designed to investigate changes in biochemical markers (n = 1184) assessed the effects of cinacalcet compared with placebo on the clinical outcomes of fracture, cardiovascular hospitalisation, all-cause hospitalisation, parathyroidectomy and mortality. No statistically significant difference was seen in overall mortality or all-cause hospitalisation. However, statistically significant differences were observed in fracture (relative risk [RR] 0.46; 95% confidence interval [95% CI], 0.22–0.95), cardiovascular hospitalisation (RR 0.61; 95% CI, 0.43–0.86), and parathyroidectomy (RR 0.07; 95% CI, 0.01–0.55) based on follow-up of 6–12 months.

4.1.6 The same analysis also reported combined data on health-related quality of life, based on the SF-36 health survey. At baseline in both treatment groups the scores on the eight domains of the scale were approximately half to one standard deviation below the general population means. For the physical component summary score there was a 0.5-unit improvement in the cinacalcet arms compared with a 0.8-unit decrease in the control arms (p = 0.01); for the bodily pain scale there was a 0.6-unit improvement in the cinacalcet arms compared with a 1.0-unit decrease in the control arms

(p = 0.03); and for the general health perception scale there was a 0.2-unit improvement in the cinacalcet arms compared with a 1.0-unit decrease in the control arms (p = 0.02). No statistically significant differences were found for the other domains. The Committee heard from the patient experts that bone pain could result in considerable disability and that reduction in bone pain was an important benefit of treatment.

4.1.7 The Assessment Group reported subgroup analyses by baseline plasma intact PTH, serum Ca x P, serum calcium, serum phosphorus and dialysis duration for a variety of biochemical endpoints. However, most of these did not indicate statistically significant differences between subgroups. The Assessment Group noted that some results suggested that cinacalcet may be more effective in less advanced disease, but were cautious about interpreting these findings.

4.1.8 The manufacturer's submission reported unpublished results of an open-label post-marketing study (n = 552) that randomised participants to standard care with or without cinacalcet. The primary endpoint was the proportion of patients with a mean plasma intact PTH level of 31.8 pmol/litre (300 pg/ml) or less during a 7-week efficacy phase, following a 16-week titration phase. In contrast to previous trials, this study allowed the adjustment of doses of vitamin D sterols and phosphate binders in accordance with treatment algorithms (in other RCTs doses were held constant to minimise the potential for confounding). The primary endpoint was reached 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 D sterol decreased by 22% in the cinacalcet arm, whereas a 3% increase occurred in the standard care arm. The proportions of patients taking phosphate binders in the two groups were similar throughout the study. The proportion of patients taking calcium-containing phosphate binders or calcium supplements remained

stable over the study period in the standard care group and increased in the group of patients receiving cinacalcet.

4.2 Cost effectiveness

4.2.1 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, and the Assessment Group developed its own economic model. Both models were cost–utility analyses comparing cinacalcet in addition to standard care (using vitamin D and phosphate binders) with standard care only in patients with secondary 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, differences between the models in the assumptions driving effectiveness.

4.2.2 The model submitted by the manufacturer 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. The effect of cinacalcet on the relative risks for these outcomes was based on the pooled results of four clinical trials. 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. Various one-way sensitivity analyses were conducted. The results of these indicated that the ICER was most sensitive to variations in the dose of cinacalcet.

4.2.3 The Assessment Group's approach differed from that of the manufacturer in that they modelled the effect of treatment on PTH levels and then related this intermediate endpoint to clinical events. In the base-case analysis, patients in

both arms were stratified by PTH levels. These were defined as 'controlled' (PTH 32 pmol/litre or less), 'uncontrolled' (PTH 33 to 84 pmol/litre) or 'very uncontrolled' (PTH 85 pmol/litre or more). Patients in the 'very uncontrolled' group were stratified further according to whether or not they had undergone parathyroidectomy (with or without adverse surgical events). Clinical events included cardiovascular events, fractures and death, and the probabilities of these occurring at different PTH levels were derived from a variety of different sources, mostly large cohort studies. These estimates of probability rely on a number of assumptions and are subject to uncertainty. The reduction in utility associated with an adverse event was greater in the 3 months after the event than in subsequent cycles of the model. Utility increased for subsequent cycles, but to a level that was lower than the utility before the event. The costs associated with cinacalcet, the treatment of adverse events, parathyroidectomy, monitoring of patients and concomitant medications were included in the model. It was assumed that a proportion of patients with 'very uncontrolled' PTH levels, and no patients with 'controlled' or 'uncontrolled' PTH levels, would be taking non-calcium-based phosphate binders. A wide range of sensitivity analyses were conducted. The costs of dialysis were excluded from the base-case analysis but included in a sensitivity analysis.

4.2.4 The results of the base-case analysis found that the ICER for cinacalcet was £61,900 per additional QALY. 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' versus those with 'controlled' PTH levels, and the inclusion of costs associated with dialysis. The inclusion of dialysis costs increased the ICER by more than £10,000 per QALY.

4.2.5 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 enabled a more direct comparison with the manufacturer's submission and, as far as possible, effectiveness data were taken from the same source (pooled data from four

RCTs). This analysis resulted in an ICER of £43,000 per QALY gained, excluding dialysis costs. The second additional analysis assumed that the effect of cinacalcet is mediated by levels of both PTH and Ca x P. This produced an ICER of £38,900 per QALY gained, excluding dialysis costs.

4.2.6 In an additional analysis conducted after the submission of the assessment report, the Assessment Group examined the cost effectiveness of two strategies for discontinuing cinacalcet in people whose PTH levels were not controlled by treatment. In the first scenario it was assumed that people with 'very uncontrolled' PTH levels after 3 months of treatment with cinacalcet (titration phase) would discontinue the treatment and receive standard care only. In this scenario, the ICER was reduced to £57,400 per QALY. In the second scenario it was assumed that only those people whose PTH levels reached a target of 32 pmol/litre would continue treatment. In this scenario the ICER was £44,000 per QALY.

4.2.7 Following consultation on the preliminary guidance, the manufacturer submitted a revised analysis based on the Assessment Group's modelling approach. This analysis identified strategies for using cinacalcet that could be considered more cost effective, based on applying rules for discontinuing treatment in those people for whom the drug produces an inadequate response, and for limiting the maximum dose of the drug that may be used when adjustments are made according to PTH levels. Two subgroups were considered: people with 'very uncontrolled' baseline PTH levels and people with 'uncontrolled' PTH levels. It was proposed that the subgroup of people with 'very uncontrolled' PTH levels could be treated cost-effectively as follows. The initial regimen is adjusted during the first 3 months up to a maximum of 120 mg cinacalcet per day. Those people whose PTH levels remain 'very uncontrolled' at the end of this titration period then discontinue treatment. Those whose PTH levels are now defined as 'controlled' may continue at a dose of up to 120 mg. Those who are now in the 'uncontrolled' state may continue treatment, but only at a dose of up to 60 mg. The second subgroup, that is people who start with 'uncontrolled' levels of PTH, are given cinacalcet

at a dose of 30 mg daily. If at the end of 3 months their PTH levels have become 'controlled' at a dose of 30 mg, they may continue treatment. Otherwise treatment is discontinued.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of cinacalcet, having considered evidence on the nature of the condition and the value placed on the benefits of cinacalcet by people with hyperparathyroidism secondary to ESRD, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.3.2 The Committee noted that the clinical trials of cinacalcet showed that it was effective in reducing levels of PTH and other biochemical markers, including serum calcium and phosphorus. It acknowledged that a reduction in adverse clinical outcomes associated with raised PTH levels, such as bone fracture and cardiovascular hospitalisation, had been observed in a post-hoc analysis of pooled safety data from several trials. However, it noted that these trials were not designed to demonstrate the clinical benefits of treatment in terms of a reduction in adverse events, and also noted that there was a lack of data relating to long-term treatment with cinacalcet. The Committee was aware of observational evidence to suggest that there is a relationship between levels of PTH, calcium and phosphate, and adverse clinical outcomes. However, it noted that there is considerable uncertainty about the extent to which intervening to correct derangements in the levels of PTH, calcium and phosphate (in particular by lowering PTH levels) is effective in reducing the risk of the adverse outcomes. The Committee also noted that many other factors relating to ESRD and its underlying causes contribute to the increased risk of serious adverse events for people on dialysis, and that these add to the uncertainty in predicting clinical benefits from changes in surrogate markers.

4.3.3 In addition to the possible risk of major adverse events associated with raised PTH levels, the Committee heard from the clinical specialists and patient

experts that the biochemical disturbances associated with secondary hyperparathyroidism produce symptoms, such as pruritus, pain and muscle weakness, that reduce quality of life and may interfere with sleep and daily activities. However, the Committee heard that although cinacalcet could help to reduce the severity of these symptoms, it did not replace the need for dietary restrictions and the use of other medications such as phosphate binders and vitamin D sterols.

4.3.4 Although acknowledging the uncertainties involved with using surrogate markers, the Committee accepted the approach taken by the Assessment Group in using PTH levels as a marker of risk of adverse events in its cost-effectiveness analysis. The Committee also agreed that the additional complexity of the model, incorporating additional states to reflect different degrees of control of PTH levels, provided the best available characterisation of the course of the disease. Furthermore, this approach allowed the incorporation of health-related utilities to reflect a reduction in quality of life resulting from symptoms of 'very uncontrolled' hyperparathyroidism. The Committee accepted the validity of the Assessment Group's approach to incorporating the reduction in health-related quality of life associated with an adverse event, followed by some degree of recovery. On the basis of the cost-effectiveness analyses submitted, the Committee concluded that cinacalcet was unlikely to be a cost-effective use of NHS resources in the treatment of secondary hyperparathyroidism in patients with ESRD.

4.3.5 The Committee discussed whether cinacalcet could be used more cost-effectively by applying 'stopping rules' if the response to treatment was inadequate. In particular, the Committee considered carefully whether the strategies proposed by the manufacturer for the more cost-effective use of cinacalcet were practicable. The Committee noted that these suggested treatment strategies were based on the wide ranges of PTH levels that were specified in the model. While accepting the Assessment Group's approach to modelling the decision problem, the Committee recognised that the ranges of PTH levels that defined health states in the model were arbitrary and were not

intended to define the goals of a treatment strategy. The Committee therefore considered that the use of these ranges by the manufacturer in defining treatment strategies did not reflect clinically appropriate treatment goals and was not consistent with the dose-titration regimen described in the SPC. For example, the Committee noted that the strategies required doses of cinacalcet not to be increased above 120 mg per day, despite the 'Posology and methods of administration' section of the SPC indicating that the dose should be increased to a maximum of 180 mg per day to achieve individual treatment goals, specifically a reduction of intact PTH levels to between 150 and 300 pg/ml (15.9–31.8 pmol/litre). In addition, the proposed strategies required the cinacalcet dose to be reduced in patients who had achieved a partial response to a dose of 120 mg and yet remained in the 'uncontrolled' state. The Committee was therefore not persuaded that these treatment strategies were clinically practicable, and did not consider them an acceptable approach to maximising the clinical and cost effectiveness of treatment with cinacalcet.

4.3.6 The Committee heard from the clinical specialists that there may be a small subgroup of people with refractory hyperparathyroidism for whom cinacalcet may be an alternative to surgical parathyroidectomy. The Committee noted that there was no RCT evidence on the effectiveness of cinacalcet in people with refractory hyperparathyroidism, but considered that clinical experience existed for this subgroup of patients. The Committee noted that surgical parathyroidectomy was a treatment option for some patients with refractory disease, but there was no evidence on the clinical effectiveness or cost effectiveness of cinacalcet compared with surgical parathyroidectomy. The Committee concluded that cinacalcet should not be recommended as an alternative to parathyroidectomy.

4.3.7 The Committee were persuaded by the patient experts and clinical specialists that patients with refractory hyperparathyroidism with very high PTH levels may experience a very poor quality of life compared with those with better-controlled levels of PTH. In addition, they understood that the mortality and

overall prognosis in this patient group are also significantly worse, particularly for patients with calciphylaxis. Furthermore, the Committee heard from healthcare professionals and patients that there are some people with refractory hyperparathyroidism in whom the risks of surgical parathyroidectomy are considered to be so high as to rule it out as an acceptable treatment option. The clinical specialists reported some success with cinacalcet in this subgroup of patients.

4.3.8 The Committee considered that if the high risk of adverse consequences and the poor quality of life experienced by the subgroup of patients described in 4.3.7 (in whom surgical parathyroidectomy is not possible) were taken into account, it was likely that the ICER for cinacalcet would be reduced to the extent that it could be considered a cost-effective use of NHS resources. The Committee concluded that the benefits of cinacalcet were likely to be sufficient to recommend its use in these extreme situations. However, the Committee considered that if cinacalcet does not produce an adequate response in these situations, treatment should be stopped. For these purposes the Committee proposed that an adequate response to cinacalcet treatment should be defined as a 30% or greater reduction in the plasma concentration of intact PTH after 4 months of treatment, including dose escalation as appropriate. This definition of an adequate response is based on the clinical endpoints reported in the RCTs of cinacalcet.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in ‘Standards for better health’ issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX). *[Note: list to be added. Tools will be available when the final guidance is issued]*

6 Recommendations for further research

6.1 The Committee identified a need for long-term clinical studies that are designed to evaluate the effects of cinacalcet on clinical outcomes (in particular, fracture and cardiovascular events) in people with ESRD. Studies to establish the multivariate relationship between biochemical disruption in secondary hyperparathyroidism and these clinical outcomes are also recommended.

6.2 The Committee also noted that more research is needed on the effects of cinacalcet in people with ESRD with particular clinical needs, specifically people with refractory secondary (or tertiary) hyperparathyroidism, people awaiting kidney transplants from living donors, people with calciphylaxis, people with recurrent hyperparathyroidism after parathyroidectomy, and people in whom surgical parathyroidectomy is contraindicated.

7 Related guidance

7.1 NICE has issued the following related technology appraisal guidance.

Renal failure: home versus hospital haemodialysis. *NICE technology appraisal guidance* no. 48 (2002). Available from: www.nice.org.uk/TA048

7.2 NICE is in the process of producing the following clinical guideline.

Kidney disease: early identification and management of adults with chronic kidney disease in primary and secondary care (publication expected September 2008).

8 Review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in December 2009.

David Barnett
Chair, Appraisal Committee
October 2006

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam
Radiologist, St George's Hospital, London

Professor A E Ades
MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Amanda Adler

Consultant Physician,

Consultant Physician, Addenbrooke’s Hospital, Cambridge

Dr Tom Aslan

General Practitioner, Stockwell, London

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain

Lay Member

Dr Karl Claxton

Health Economist, University of York

Dr Richard Cookson

Senior Lecturer in Health Economics, School of Medicine, Health Policy and Practice, University of East Anglia

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital

Professor Christopher Eccleston

Director, Pain Management Unit, University of Bath

Dr Paul Ewings

Statistician, Taunton and Somerset NHS Trust, Taunton

Professor John Geddes

Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston

Director of Finance, Barts and the London NHS Trust

Mr Adrian Griffin

Health Outcomes Manager, Johnson & Johnson Medical

Ms Linda Hands

Consultant Surgeon, John Radcliffe Hospital, Oxford

Dr Elizabeth Haxby

Lead Clinician in Clinical Risk Management, Royal Brompton Hospital, London

Dr Rowan Hillson

Consultant Physician, Diabeticare, The Hillingdon Hospital, Uxbridge

Dr Catherine Jackson

Clinical Senior Lecturer in Primary Care Medicine, University of Dundee

Professor Richard Lilford

Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Ms Judith Paget

Chief Executive, Caerphilly Local Health Board, Wales

Dr Katherine Payne

Health Economist, The North West Genetics Knowledge Park, University of Manchester

Dr Ann Richardson

Independent Research Consultant

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Professor Andrew Stevens (Vice Chair)

Professor of Public Health, University of Birmingham

Dr Cathryn Thomas

General Practitioner, Sutton Coldfield, West Midlands; Associate Professor, Department of Primary Care and General Practice, University of Birmingham

Simon Thomas

Consultant Physician, General Medicine and Clinical Pharmacology, Newcastle Hospitals NHS Trust

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Professor Mary Watkins

Professor of Nursing, University of Plymouth

Dr Paul Watson

Medical Director, Essex Strategic Health Authority

B. NICE Project Team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Kate Burslem

Technical Lead

Louise Longworth

Technical Adviser

Janet Robertson

Technical Adviser

Alana Miller
Project Manager

Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Peninsula Technology Assessment Group.

Garside R, Pitt M, Anderson R, et al. *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 The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and Appraisal Consultation Document (ACD). Consultee organisations have the opportunity to appeal against the Final Appraisal Determination (FAD).

I Manufacturers/sponsors:

- Amgen Ltd (cinacalcet)

II Professional/specialist and patient/carer groups:

- British Kidney Patient Association
- British Thyroid Foundation
- Kidney Alliance
- Long-Term Medical Conditions Alliance
- National Kidney Federation
- Association of Renal Industries
- Association of Renal Technologists
- British Dietetic Association
- British Renal Society
- British Thyroid Association
- National Kidney Research Fund
- Renal Association
- Renal Pharmacy Group

- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Surgeons
- Royal Pharmaceutical Society
- Society for District General Hospital Nephrologists
- Society for Endocrinology
- Department of Health
- Huntingdonshire Primary Care Trust
- North Eastern Derbyshire Primary Care Trust

III Commentator organisations (without the right of appeal):

- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- British National Formulary
- Welsh Assembly Government

C The following individuals were selected from clinical specialist and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on cinacalcet for the treatment of hyperparathyroidism secondary to impaired renal function by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Neil Gittoes, Consultant Endocrinologist, nominated by the Royal College of Physicians – clinical specialist
- Dr Alastair Hutchison, Consultant Renal Physician, nominated by the Royal College of Physicians – clinical specialist

- Christopher Payne, nominated by the National Kidney Federation – patient expert
- Steve Rowe, nominated by the National Kidney Federation – patient expert