On behalf of the

THE ROYAL COLLEGE OF PHYSICIANS

Submission to NICE, Health Technology Appraisal

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

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Licensed Indication

Cinacalcet is licensed for treatment of secondary hyperparathyroidism in adult patients (over 18 years) with end-stage renal disease on dialysis, and also for the treatment of hypercalcaemia in parathyroid carcinoma.

Dosage and Administration

The recommended starting dose is 30mg once daily adjusted every 2 to 4 weeks to a maximum of 180mg daily. Tablets are available in 30mg, 60mg and 90mg strengths.

Costs

30mg tablets	£4.51 each	£4.51 per 30mg
60mg tablets	£8.32 each	£4.16 per 30mg
90mg tablets	£12.48 each	£4.16 per 30mg

Therefore one year's treatment with cinacalcet costs £1,646 (30mg daily) to £9,110 (180mg daily).

Background Information

Secondary hyperparathyroidism, is a common complication of chronic kidney disease, characterized by increased circulating levels of parathyroid hormone (PTH). The most widely recognized complication of secondary hyperparathyroidism is renal osteodystrophy [1,2]. The accompanying abnormalities in bone metabolism, together with the abnormal mineral metabolism that result from secondary hyperparathyroidism, are *associated* with poor quality of life, fractures, and increased mortality [3–7]. These associations are largely based on retrospective, cross-sectional studies, the results of which have not been

confirmed in large scale prospective interventional studies, and therefore one must be circumspect in drawing from them any firm conclusions.

Current treatment addresses the prevention and reduction of secondary hyperparathyroidism through dietary phosphate restriction, administration of calcium or noncalcium-containing phosphate binders, phosphate removal by dialysis, maintenance of adequate serum calcium concentrations, and the administration of calcitriol or other vitamin D sterols to suppress PTH. Surgical parathyroidectomy is required in cases of uncontrolled, severe, symptomatic secondary hyperparathyroidism, and without such intervention patients suffer a variety of very debilitating and life-shortening symptoms including bone fracture, muscle pain, anaemia, and occasionally life-threatening calciphylaxis. Parathyroidectomy in patients with renal failure is not without risk however, and for many reflects a failure in medical therapy. Peri-operative risks are greater in this group of patients than those with normal kidneys and there is the additional risk that any remnant tissue (or re-implanted tissue) will become hyperplastic and require later excision which can often represent a significant surgical challenge. Furthermore, total parathyroidectomy leads to problems associated with hypoparathyroidism and adynamic bone which may predispose the patient to ectopic and vascular calcification.

In patients undergoing maintenance dialysis therapy, increased serum phosphate concentrations and calcium–phosphate product are associated with an increased risk of cardiac, visceral and vascular calcifications [8,9], and an increased risk of cardiovascular death [10–14]. Unfortunately, these complications also frequently arise in response to therapy with vitamin D and/or calcium-based phosphate binders, requiring withholding treatment for safety considerations. Repeated interruptions in therapy lead to inadequate PTH control and disease progression [6,15]. However, no interventional study has yet demonstrated that correcting these biochemical abnormalities is associated with reduced risk of death. Nevertheless, recognition of the complications of abnormal bone and mineral metabolism has led in the USA to the proposal of new National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKFK/ DOQI) targets (sponsored by pharmaceutical companies; Amgen, Abbott and Genzyme) for PTH (150–300 pg/ml),

serum calcium (8.4–9.5 mg/dl), phosphate (3.5–5.5 mg/dl) and calcium–phosphate product (<55mg2/dl2) [16]. These targets are difficult to achieve in most patients receiving dialysis, with an estimated 50% of dialysis patients not achieving guideline targets for PTH concentrations [1,17]. The guidelines are mostly opinion-based because of the lack of prospective interventional studies and are not fully accepted by many European nephrologists. Whilst it is beyond dispute that new therapies are needed to treat the complex abnormalities that make up renal osteodystrophy, it is not clear that there are benefits associated with treatment of mild to moderate hyperparathyroidism (PTH 300 – 800 pg/ml) at this time.

Cinacalcet HCl is a calcimimetic agent that acts as an allosteric modulator of the calcium-sensing receptor present on the surface of parathyroid cells. By targeting the calcium-sensing receptor, cinacalcet provides a new means of regulating PTH secretion by amplifying the receptor's sensitivity to extracellular calcium and reducing PTH concentrations.

Clinical Efficacy

Results from clinical trials examining single and multiple doses up to 180 mg once daily suggest that treatment with cinacalcet not only reduces plasma PTH concentrations but also leads to a concomitant decrease of serum calcium and phosphate in patients with secondary hyperparathyroidism receiving haemodialysis [9,18–20]. Its efficacy appears to be similar in both haemodialysis and peritoneal dialysis patients [21]. It reduces PTH to within k/DOQI targets in 44 – 56% of patients with a greater number (~60%) achieving at least a 30% reduction in serum PTH from baseline [18-21].

Analyses of combined data from randomized, blinded, placebo-controlled, 6- to 12-month studies of cinacalcet versus standard care for secondary HPT showed statistically significant and clinically meaningful reductions in the risks of parathyroidectomy, fracture, and cardiovascular hospitalization. Although the individual clinical studies were designed to assess changes in biochemical parameters and not *a priori* clinical end points, the

prospective and interventional nature of the combined data lends credibility to the clinical relevance of biochemical control in secondary HPT and suggests that therapy with cinacalcet may lead to beneficial effects on clinical outcomes [22]. Long-term treatment has been shown to effectively sustain reductions in PTH for up to 3 years [23].

In association with the reduction in PTH, more modest reductions of serum phosphate, calcium and calcium x phosphate product have been noted in a secondary analysis of three large randomised, placebo controlled 26 week studies [24]. Retrospective assessments of data gathered by large dialysis providers in the USA suggest that elevated serum calcium and phosphate levels are independent risk factors for mortality in general and cardiovascular mortality in particular among patients undergoing haemodialysis, possibly by aggravating arterial calcification [7-10].

Adverse Effects

741 haemodialysis patients with inadequately controlled PTH levels were randomised to placebo or cinacalcet for 6 months [20]. Nausea (32% vs 19%) and vomiting (30% vs 16%) occurred significantly more often in the cinacalcet group than in the placebo group. The frequency of nausea was unrelated to dose, but vomiting occurred more frequently at higher doses. Hypocalcaemia (< 1.90 mmol/L) occurred significantly more frequently in cinacalcet-treated than placebo-treated patients (5% vs 1%). In the titration phase of this study more cinacalcet-treated patients than placebo-treated patients withdrew (15% vs 7%), and just less than another 5% of patients later withdrew from treatment as a result of these adverse effects [20].

Personal experience

Having been involved in some of the studies referenced below, and having had the opportunity to use cinacalcet for a number of ‘named patients’, we would like to highlight its use in patients with severe symptomatic hyperparathyroidism where surgical intervention is not possible.

Case 1 A 64 year old patient on haemodialysis who suffered partial vocal chord paralysis at the time of previous surgical parathyroidectomy (a well recognised complication), was found to have recurrent hyperparathyroidism some years later (PTH >1500pg/ml). He was significantly symptomatic with bone pain, muscle ache and general malaise. Conventional treatments with phosphate control and vitamin D had been unsuccessful. The likelihood of further damage to the recurrent laryngeal nerve was felt to be too high to risk re-operation and isotope scans had failed to demonstrate active parathyroid tissue. Venous sampling of the neck veins was similarly unhelpful. Cinacalcet was started at 60 – 90mg daily which over the following 6 months reduced the PTH level to a stable figure of around 100pg/ml with complete resolution of symptoms. PTH remains stable at this level.

Case 2 A 30 year old patient who had had renal failure since childhood and two previous parathyroidectomies, now on haemodialysis, was found to have recurrent symptomatic hyperparathyroidism for a third time. An isotope scan showed multiple small areas of parathyroid tissue throughout his neck, presumably 'seeded' from previous surgery. Surgical removal of these areas was thought to be impossible because of their size and number. Treatment with cinacalcet quickly reduced his PTH to a stable level of between 100 and 200 pg/ml which was sustained until he received a renal transplant in 2003.

Case 3. A 74 year old woman who had been on haemodialysis for 7 years developed uncontrollable hyperparathyroidism due to non-compliance with phosphate binders. She also had significant ischaemic heart disease but despite this underwent total parathyroidectomy uneventfully. She had been disabled by bone pain and this rapidly resolved post-operatively, only to return when she developed recurrent hyperparathyroidism. All attempts to locate the parathyroid tissue failed on the first attempt and imaging using standard techniques and venous sampling, but eventually using combined CT and isotope imaging techniques tissue was located behind the aortic arch. By now she was wheelchair bound and unable to rise to her feet without help. Her PTH was above the upper limit of detection but the operative risks were considered to be too high. Cinacalcet was started and within days she noticed that her bone pain began to improve. After 6 months, during which the cinacalcet was titrated up to a dose of 90 mg

per day, her PTH had returned to within the desired range and bone enzymes normalised. She was able to demonstrate her re-found ability to arise from chair without help. Although she occasionally suffered some nausea at dose changes she tolerated the drug well and remains on it almost a year later.

Case 4. A 22 year old patient presented acutely with end-stage renal disease requiring urgent dialysis. He had been needle and doctor phobic and had been lost to follow-up having been known to have reflux nephropathy as a child. He had severe secondary and then tertiary hyperparathyroidism with hypercalcaemia unless managed on low calcium dialysate. He almost refused to contemplate any form of dialysis because of his phobia of the medical profession, but eventually agreed to haemodialysis and gradually his phobia of clinicians settled. However, he refused to consider parathyroidectomy or a renal transplant. By the time he started to get very symptomatic from his hyperparathyroid bone disease, cinacalcet had been licensed and we were no longer able to provide him with the compassionate use supply that Amgen had made available to the Oxford unit. He therefore decided to fund the drug privately and has improved considerably, although his PTH has not returned yet to the desired range.

Conclusions

Cinacalcet provides a new therapeutic intervention for secondary hyperparathyroidism in dialysis patients. It has been shown to effectively lower plasma PTH levels and favourably influence calcium and phosphate levels, but prospective studies to examine the effect of these changes on patient outcomes do not yet exist. Its use in patients with severe hyperparathyroidism who are unsuitable for surgery is of particular note.

There is some randomised controlled study evidence that the parathyroidectomy rate can be significantly reduced and our own, albeit anecdotal, experience would support this. On this basis, the county Priorities Forums in the Thames Valley Health Authority region, have started agreeing to fund the use of cinacalcet in patients who otherwise would be referred for parathyroidectomy (according to agreed guidelines for this procedure). This limits its use to a relatively small number of patients per year (the Oxford unit with a

dialysis population of 470 performs 25 parathyroidectomies per year). The bigger question (in terms of funding consequences) is to consider the cost-effectiveness of earlier intervention with cinacalcet, as it may be possible to use much smaller doses in early hyperparathyroidism, thereby preventing the sort of disease leading to parathyroidectomy and the associated morbidity. Current studies nearing completion should throw more light on this.

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