



UK RENAL PHARMACY GROUP

SUBMISSION TO THE NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE on CINACALCET HYDROCHLORIDE FOR THE TREATMENT OF SECONDARY HYPERPARATHYROIDISM IN PATIENTS WITH END-STAGE RENAL DISEASE ON MAINTENANCE DIALYSIS THERAPY

The UK Renal Pharmacy Group would like to thank NICE for the opportunity to contribute to the appraisal process for the use of Cinacalcet Hydrochloride for the treatment of secondary hyperparathyroidism in patients with end stage renal disease on maintenance dialysis therapy.

It is intended that this submission should adopt the following format:-

- Background
- Clinical effectiveness
- Cost effectiveness
- The wider implications for the NHS,

Background

Chronic kidney disease (CKD) alters the regulation of calcium and phosphate homeostasis, leading to secondary hyperparathyroidism, metabolic bone disease, soft tissue calcification and other metabolic derangements that have a significant impact on morbidity and mortality. The organ chiefly responsible for regulating these adaptive responses is the parathyroid gland, and one of the major goals of treatment in patients with CKD involves suppression of parathyroid hormone (PTH) secretion, and avoidance of the development of hypertrophy and hyperplasia of this gland.

Traditional standard therapy includes the use of phosphate binders, and of Vitamin D and its analogues. However, use of Vitamin D is often accompanied by an increase in serum calcium and phosphate concentrations, a problem that often limits their use. Treatment of persistent uncontrollable hyperparathyroidism in patients with end stage renal disease usually involves parathyroidectomy, with all the associated risks of surgery.

About a decade ago, the calcium-sensing receptor (CaR) was identified as the most important factor regulating parathyroid gland function, leading to the development of allosteric modulators of CaR, called calcimimetic agents, which act on the calcium-sensing receptor to increase its sensitivity towards calcium, and thereby reduce PTH secretion.

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) has established guidelines [1] for the treatment of secondary hyperparathyroidism. However, these targets are very stringent, and less than 10% of dialysis patients manage to achieve all three (PTH, Calcium and Phosphate) of the required targets. Clinical trials with cinacalcet have demonstrated suppression of circulating PTH levels without increments in the calcium-phosphate (Ca x P) product, making it easier to achieve these targets.

NKF – K/DOQI Bone Metabolism Guidelines

Parameter	Target Range
PTH	150 – 300 pg/mL OR 16.5 – 33.0 pmol/L
Ca x P	< 55 mg ² / dL ² OR < 4.51 mmol ² / L ²
Serum Phosphate (P)	3.5 – 5.5 mg / dL OR 1.10 – 1.78 mmol/L
Serum Calcium (Ca)	8.4 – 9.5 mg / dL OR 2.10 – 2.37 mmol / L

Clinical Effectiveness

1. An early study showed that Cinacalcet effectively reduced PTH levels and improved Ca x P homeostasis in patients receiving haemodialysis who have uncontrolled secondary hyperparathyroidism despite receiving current best therapy. [2] In this study, patients who were receiving haemodialysis and who had inadequately controlled secondary hyperparathyroidism even from standard treatment were randomly assigned to receive Cinacalcet or placebo for 26 weeks.

Doses were titrated upwards to achieve PTH levels of 250 pg/L or less. The study showed that 43% of the Cinacalcet group reached the primary end point, compared with 5% in the placebo group. The mean PTH value decreased 43% in those receiving Cinacalcet, and increased 9% in the placebo group. This is a statistically significant result (p<0.001). The total serum Ca x P product declined by 15% in the Cinacalcet group but remained unchanged in the placebo group. (p<0.001). A further analysis showed a ten-fold reduction in the frequency of parathyroidectomy and a two-fold reduction in fracture rate during the course of this study.

2. The ability of Cinacalcet treatment to improve achievement of NKF - K/DOQI target levels for PTH, Ca, P, and Ca x P product were investigated in three placebo-controlled, double blind, 26-week studies with similar designs that randomised 1136 subjects on dialysis to receive traditional therapy plus either Cinacalcet (titrated from 30mg to 180mg / day) or placebo [3].

PTH – 56% cinacalcet-treated patients compared with 10% placebo patients achieved a mean PTH < 300 pg/mL (31.8 pmol/mL) (p<0.001).

Ca – 49% cinacalcet patients compared to 24% placebo patients achieved a serum calcium in the range 2.10-2.37 mmol/L (8.4-9.5 mg/dL) (p<0.001).

P – 46% cinacalcet patients compared to 33% placebo patients achieved a serum phosphate in the range 1.13-1.78 mmol/L (3.5-5.5 mg/dL) (p<0.001).

Ca x P product - 65% cinacalcet patients compared to 36% placebo patients achieved a Calcium-Phosphate Product $< 4.44\text{mmol}^2/\text{L}^2$ ($55\text{ mg}^2/\text{dL}^2$) ($p<0.001$).

In addition, 41% cinacalcet patients compared to 6% placebo patients achieved **both** a Ca x P product $< 4.44\text{mmol}^2/\text{L}^2$ ($55\text{ mg}^2/\text{dL}^2$) ($p<0.001$) **and** a serum PTH $< 300\text{ pg/mL}$ (31.8 pmol/mL) ($p<0.001$).

3. Another multicentre, randomised, placebo-controlled, double-blind study evaluated the efficacy and safety of cinacalcet in haemodialysis (HD) and peritoneal dialysis (PD) patients with PTH $\geq 300\text{ pg/mL}$ despite traditional therapy [4]. A total of 395 patients received cinacalcet (260 HD, 34 PD) titrated from 30mg to 180mg daily to achieve a target PTH $\leq 250\text{ pg/mL}$, or placebo (89 HD, 12 PD). During a 10-week efficacy assessment phase, 46% cinacalcet patients versus 9% placebo patients achieved a PTH level $\leq 300\text{ pg/mL}$, 65% cinacalcet patients versus 13% placebo patients achieved a reduction in PTH $> 30\%$ from baseline, and the cinacalcet group had a greater proportion of patients achieving a reduction in PTH levels of 20%, 40% and 50% from baseline compared to the placebo group. In addition, cinacalcet exhibited comparable efficacy in both HD and PD patients, and also significantly reduced serum calcium, phosphate and Ca x P product levels compared with control treatment.

3. Since hyperparathyroidism induces mineralised bone loss, one study investigated the effects of cinacalcet treatment on bone mineral density (BMD) in 14 patients with secondary hyperparathyroidism due to CKD [5]. A dual energy X-ray absorptiometry was performed to measure the BMD of subjects' proximal femurs and lumbar spine (L2-L4) before and after 26 weeks of treatment. It was found that cinacalcet treatment increased proximal femur BMD from $0.945 \pm 0.169\text{ g/cm}^2$ to $0.961 \pm 0.174\text{ g/cm}^2$ ($p<0.05$), but did not affect lumbar spine BMD.

4. One randomised, double-blind, placebo-controlled 18-week study looked at the use of cinacalcet in patients with CKD not yet receiving dialysis in a bid to reduce poor outcomes [6]. A total of 54 patients with a GFR between 15 and 50 mL/min and a PTH level $> 130\text{ pg/mL}$ were enrolled, and randomised to receive either cinacalcet (30mg titrated up to 180mg daily) or placebo in addition to standard treatment. Baseline results – mean PTH levels were 243 pg/mL in the cinacalcet group ($n=27$) and 236 pg/mL in the placebo group ($n=27$). During the efficacy-assessment phase, 56% of the cinacalcet group versus 19% of the placebo group achieved a 30% or greater reduction in PTH levels ($p=0.006$), and mean PTH levels decreased by 32% in the cinacalcet group but increased by 6% in the placebo group.

5. On an anecdotal level, at one large renal centre in London, 8 patients with severe renal bone disease refractory to standard treatment and awaiting parathyroidectomy were prescribed cinacalcet. Within 6 months, all 8 had improved to such an extent that surgery was no longer deemed to be necessary and all 8 were removed from the parathyroidectomy waiting list.

6. Concordance – renal patients are often required to take up to 40 tablets each day, including anywhere between 2 and 5 phosphate binders (which are extremely unpalatable) before each meal. Consequently it is not surprising that compliance with the prescribed regimen is frequently poor, with an accompanying worsening of their secondary hyperparathyroidism. Cinacalcet not only lowers PTH levels without raising Ca and P

levels, but also usually allows the doses of phosphate binders to be reduced, which should aid concordance.

7. It should be noted that Cinacalcet needs to be used with caution in patients with underlying hepatic impairment. Studies were done in patients undergoing haemodialysis, and the most frequently reported events were nausea, vomiting and diarrhoea. Myalgia and dizziness were also experienced in a small number of patients.

Cost Effectiveness

It is not disputed that Cinacalcet therapy is extremely expensive (between £1500 and £8400 / patient / year), and there are no large long-term studies looking at the cost benefit of adding Cinacalcet to standard therapy for secondary hyperparathyroidism in patients with CKD. However, current treatment strategies for renal bone disease involve the use of high-dose Vitamin D therapy to suppress PTH, which in turn raises serum calcium and phosphate levels, increasing the risk of soft tissue calcification and thereby necessitating the use of expensive non-calcium containing phosphate binders such as Renagel® (average cost £2000-£3000 / patient / year), which patients are loathe to take, and which are not very effective. Even given the limited data available, it would seem that Cinacalcet is effective, is a much smaller tablet burden for the patient, and in many cases allow a reduction in the dose of phosphate binder required, thereby off-setting some of the cost of the Cinacalcet. Since the alternative is parathyroidectomy, with its associated costs and risks, it would seem that there is a place in therapy for Cinacalcet in the treatment of patients with very advanced renal bone disease.

It should be noted that while most hospitals with renal units are able to negotiate discounted prices for many drugs, this discount is often offset by the fact that they pay VAT on these drugs. Typically, dialysis patients attend the hospital for dialysis, but their day-to-day care is managed in the community. The hospital nephrologist will have the clinical responsibility of monitoring blood levels of PTH, calcium and phosphate, and changing doses accordingly, but all other management of the patient is amenable to a shared-care protocol between the renal unit and the GP. Unfortunately, there is an increasing trend for GPs to refer total management of and prescribing for the patient back to the renal unit, particularly where the patient has been prescribed a new and unfamiliar drug. This is inconvenient for the patient, and an added cost pressure on the drugs budget of the renal unit.

Wider NHS Implications

Treatment of secondary hyperparathyroidism with the concomitant minimisation of renal bone disease and soft tissue calcification are major factors determining patient morbidity and mortality in the dialysis population. Unsuccessful management of this condition has a profound impact on the utilisation of limited financial resources for the renal unit.

It is vital that we maintain the clinical freedom to individualise drug therapy for each patient with CKD. By targeting renal bone disease therapy in those patients with refractory secondary hyperparathyroidism, we can ensure that these patients receive optimum benefit from their treatment, ensuring the long-term preservation of skeletal

integrity, but at the same time, minimising undesirable side-effects such as soft tissue calcification. Ultimately, the greater extent to which these aims are achieved, the longer patients with CKD will survive, the better will be their quality of life, and the better condition they will be in for subsequent transplantation. Severe soft tissue calcification damages blood vessels to such an extent it renders some patients untransplantable. In order for the treatment of advanced renal bone disease to move forward, we would strongly urge the committee to recommend that Cinacalcet should be available for the limited cohort of patients with refractory secondary hyperparathyroidism who are awaiting parathyroidectomy..

Summary

1. Cinacalcet offers a new therapeutic option for controlling secondary hyperparathyroidism in patients with chronic kidney disease on dialysis.
2. The calcimimetic agents are an adjunct to, rather than a replacement to current treatment options for secondary hyperparathyroidism in patients with CKD. Given the cost of the newer, non-calcium containing phosphate binders now available, the additive cost pressure of Cinacalcet could prove to be a major barrier to its widespread use in clinical practice.
3. Cinacalcet's place in therapy should initially be limited to those patients with severe secondary hyperparathyroidism refractory to all standard treatments who require parathyroidectomy.
4. Cinacalcet would be amenable to a shared care scheme between the renal unit and GP. Treatment would be initiated within the renal unit, and whilst haemodialysis patients do have to attend hospital three times a week to dialyse, those on peritoneal dialysis generally only come to clinic every few months. Patients are more likely to be adherent if they do not have to make regular visits to hospital just to collect their tablets, and it would be easier for the patient if they were able to obtain repeat prescriptions from their GP.

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