

**Appraisal of cinacalcet hydrochloride for the treatment of  
secondary hyperparathyroidism in patients with end-stage  
renal disease on maintenance dialysis therapy**

**Society for Endocrinology Submission to the National  
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## **Background**

Mineral metabolism is a closely integrated process involving kidneys, intestine, parathyroid glands, and bone. Parathyroid hormone (PTH) is the key regulator of calcium homeostasis and small fluctuations in serum calcium are sensed by the parathyroid gland by virtue of the cell surface calcium sensing receptor (CaR) which modulates PTH secretion. The primary targets for PTH to effect changes in calcium concentration are bone (calcium mobilized from skeleton) and kidney (conversion of inactive 25-hydroxy-vitamin D to biologically active 1,25-dihydroxy-vitamin D via  $1\alpha$ -hydroxylation). In the setting of progressive deterioration in renal function there is inadequate synthesis of activated vitamin D, a concomitant fall in serum calcium leading to secondary hyperparathyroidism, and associated hyperphosphataemia.

Cinacalcet hydrochloride is a calcimimetic agent that binds the calcium-sensing receptor (CaR) of parathyroid cells, resulting in diminished PTH secretion [1]. Cinacalcet acts by allosterically modulating the CaR, enhancing the sensitivity of the CaR to extracellular calcium and thus exerts a suppressive effect on PTH secretion [1]. Cinacalcet offers a novel and effective means of treating the key pathogenic factor in secondary hyperparathyroidism in the context of chronic renal impairment.

## **Shortcomings in the current management of secondary hyperparathyroidism**

- Traditional therapies for secondary hyperparathyroidism have been targeted at correcting or replacing biochemical abnormalities rather than addressing the root cause of the problems.
- Administration of active forms of vitamin D, calcium supplementation, and phosphate restriction are at best moderately effective in achieving agreed clinical standards and are prone to unacceptable side-effects.
- Conventional therapies for secondary hyperparathyroidism can contribute to hypercalcaemia and hyperphosphataemia [2-4], which are recognized biochemical features associated with increased mortality in end-stage renal disease (ESRD; [5-8]).
- Hyperphosphataemia and secondary hyperparathyroidism significantly increase the risk of cardiovascular disease and fracture [6].
- Vitamin D sterols are capable of suppressing PTH [9-11] but a large fraction of ESRD patients have refractory hyperparathyroidism [8] that is difficult to reverse [12]. Tertiary hyperparathyroidism may ensue in ESRD, leading to hypercalcemia and progressive bone disease. Surgical intervention in the form of parathyroidectomy is frequently required.
- In some patients, vitamin D sterols are overly effective in suppressing PTH causing a low bone turnover state [13,14].

## **Bone disease in secondary hyperparathyroidism**

- Bone pathology in chronic renal impairment is complex and multifactorial.
- Renal bone diseases represent a spectrum of skeletal disorders ranging from high turnover states arising predominantly from excess PTH secretion to low turnover states of diverse etiology that are typically associated with normal or reduced plasma PTH levels.
  - Both states are associated with increased fracture rates [15,16].
  - The only effective way to differentiate high from low turnover states is with bone biopsy, an invasive procedure.
- The management of increased fracture risk differs between high and low turnover states.
  - Anti-catabolic agents are used in high turnover states.
    - Anti-catabolic agents used in low turnover states may increase fracture risk by further suppressing bone turnover.
  - Anabolic agents may be more appropriate for low turnover states.
  - Patients with ESRD rarely have bone biopsies performed to determine the specific form of renal bone disease.
    - Patients with renal bone disease and increased fracture risk often are not treated with specific bone-active drugs for fear of exacerbating the underlying skeletal state and further increasing fracture risk.
- A more effective means of managing secondary hyperparathyroidism-induced renal bone disease is required that can supplant the issues of low and high turnover states in ESRD.
  - Cinacalcet is able to suppress PTH hypersecretion and its use should supersede the requirement for use of vitamin D sterols and phosphate binders that can exacerbate the complex metabolic bone diseases seen in patients with secondary hyperparathyroidism and ESRD.

## **Vascular calcification in secondary hyperparathyroidism**

- Calcification in the vascular system is common in patients with chronic renal failure and is associated with serious adverse clinical outcomes including cardiovascular disease and high mortality rates from cardiovascular causes [17].
- Vascular calcification in part is related to disturbances in mineral metabolism such as phosphorus retention and hyperphosphataemia. Episodes of hypercalcaemia and calcium retention caused by the use of large amounts of calcium as a phosphate-binding agent and from the administration of large doses of vitamin D sterols also contribute.
- Current treatments for secondary hyperparathyroidism associated with ESRD exacerbate the already exaggerated cardiovascular risk profile seen in this patient group. A more effective means of managing secondary hyperparathyroidism is required that does not increase cardiovascular risk and ideally is able to reduce cardiovascular morbidity and mortality.

## **The value of cinacalcet**

- In contrast with vitamin D, when using cinacalcet, the reduction in PTH secretion is accompanied by simultaneous reduction of the calcium/phosphorus product, serum calcium, and phosphorus [18][19][20][21][22]; all of which are hallmark features of increased risk of cardiovascular disease and mortality in patients with end-stage renal disease.
- The phase 2 and phase 3 studies comparing cinacalcet with placebo administered to subjects receiving standard care for hyperphosphataemia and secondary hyperparathyroidism were powered to answer questions related to biochemical end points.
  - Phase 2 and all phase 3 clinical trials were not individually designed to evaluate the effects of cinacalcet on morbidity (e.g. fracture), mortality, or other outcomes believed to be related to the severity of secondary HPT.
- In a combined analysis of safety data (parathyroidectomy, fracture, hospitalizations, and mortality) from 4 similarly designed randomized, double-blind, placebo-controlled clinical trials that enrolled 1184 subjects (697 cinacalcet, 487 control) with ESRD and uncontrolled secondary hyperparathyroidism, randomization to cinacalcet resulted in significant reductions in the risk of parathyroidectomy (RR 0.07, 95% CI 0.01–0.55), fracture (RR 0.46, 95% CI 0.22–0.95), and cardiovascular hospitalization (RR 0.61, 95% CI 0.43–0.86) compared with placebo [23].
- In a small clinical study, suppression of PTH with cinacalcet reversed bone loss in the proximal femur [24].
- Experimental evidence suggests that calcimimetic agents may also impede the development of parathyroid gland hyperplasia, an integral component of secondary hyperparathyroidism caused by chronic renal failure [25].

## **Conclusions**

Cinacalcet offers an effective means of treating secondary hyperparathyroidism in ESRD. Current standard treatments for secondary hyperparathyroidism in ESRD exacerbate risks of cardiovascular events and of fractures. Use of cinacalcet in place of standard treatment should negate this excess risk. While high quality data relating to clinically relevant end points are currently lacking, pooled safety data from 4 large randomized controlled trials suggest that in addition to its desirable effects on PTH and mineral metabolism, cinacalcet causes an improvement in clinical outcomes including parathyroidectomy, fracture, and cardiovascular hospitalization. Given the available data and the clear clinical need for improved management of secondary hyperparathyroidism in ESRD, the Society for Endocrinology advocate the use of cinacalcet in patients fulfilling the criteria laid out in the final scope document.

## **Development**

This Document was developed by Dr Neil Gittoes (University of Birmingham) on behalf of the Clinical Committee of the Society for Endocrinology. If there are any questions resulting from this submission, please address them to Tom Parkhill, External Relations Manager at the Society for Endocrinology ([tom.parkhill@endocrinology.org](mailto:tom.parkhill@endocrinology.org), or 01454 642206).

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