1. Executive Summary

Cinacalcet is a new treatment for patients with hyperparathyroidism secondary to chronic kidney disease (CKD). It acts by modulating the calcium-sensing receptor, a key regulator of the parathyroid gland, thereby opening up new possibilities for management of the uncontrolled mineral metabolism seen in secondary hyperparathyroidism (sHPT). At present, patients have to rely on inadequate drug therapies that frequently fail to control all dimensions of sHPT and have potential long-term adverse consequences. Those of most concern are related to hypocalcaemia and/or hyperphosphataemia - biochemical disturbances thought to be key contributors to the process of vascular calcification and to the excess morbidity and mortality observed in end-stage renal disease (ESRD).

In 2003, about 19,000 patients in England and Wales received renal replacement therapy with dialysis. An additional 3,000 patients are expected to require dialysis in 2006, due to the rising incidence of diabetes. Patients with ESRD on dialysis carry a substantial burden of illness with almost unparalleled rates of morbidity and mortality, including a nine-fold increase in cardiovascular death and a life expectancy that is 16% to 37% lower than that of the general population. Approximately 15 of every 100 dialysis patients in the UK are expected to die in any given year.

Failing kidneys are unable to synthesize sufficient amounts of active vitamin D, phosphate levels rise and calcium levels decrease as more calcium is bound to phosphate and less is absorbed via the gut. The parathyroid glands, four pea-sized organs behind the thyroid, secrete parathyroid hormone (PTH) in response to the lack of calcium and vitamin D, and increased phosphate levels. Continuous stimulation of parathyroid glands leads to sHPT - excessive secretion of PTH accompanied by diffuse gland hyperplasia.

Excess PTH mobilizes calcium from bone to maintain calcium homeostasis, which leads to renal osteodystrophy, a serious bone disorder that can result in fracture and disability. In the presence of high phosphate levels, continuous mobilization of calcium can lead to increased deposition of calcium-phosphate crystals in blood vessels. These changes will manifest in the development of excessive and progressive vascular calcification - one of the mechanisms thought most likely to explain the increased cardiovascular mortality observed in dialysis patients.

Increasing evidence points to measures of sHPT as important independent risk factors for the development of cardiovascular disease with subsequent clinical consequences, including mortality. Compared with the independent effects of individual markers, a combination of elevated levels of PTH, calcium and phosphate, and an increased calcium/phosphate product (CaxP) has a much stronger association with the increase in cardiovascular events and deaths observed in patients with sHPT.

Unlike most key risk factors in this patient population, uncontrolled mineral metabolism is clearly modifiable. However, current therapies rarely achieve adequate control of multiple sHPT measures.

Current interventions to treat sHPT are limited to dietary restriction of phosphate, administration of phosphate binders and active vitamin D compounds, and parathyroidectomy.

Dietary phosphate restriction involves limiting protein intake as much as possible without dropping below adequate levels. This, along with poor compliance, makes the strategy difficult to implement in practice. Ca-containing phosphate binders effectively lower phosphate levels in the blood, but frequently lead to unacceptably high Ca levels. Non-Ca containing phosphate binders have a similar effect on phosphate levels, while influencing neither PTH levels nor calcium homeostasis.

Active vitamin D compounds influence the synthesis of PTH at a genetic transcription level and suppress the cyclical secretion of PTH. With persistent over suppression of PTH, the parathyroid gland is unable to play its role in bone remodelling, potentially contributing to the development of adynamic bone disease. Doses of vitamin D necessary to suppress PTH raise the intestinal absorption of calcium and phosphate and pose a risk of hypocalcaemia and hyperphosphataemia, both of which are contraindications for continuation with vitamin D, and in clinical practice often lead to suspension of its administration.

Parathyroidectomy is a treatment option in patients with persistent, or refractory, hypersecretion of PTH and who fail to respond to all other available therapies. However, it is considered a last resort and is associated with a peri-operative mortality that precludes it being recommended to all patients with sHPT.

Professional bodies such as the UK Renal Association and the National Kidney Foundation (NKF) recognize the importance of improving the quality of care for patients with dialysis and sHPT, and both have published clinical practice guidelines based on target levels of PTH, calcium, phosphate and the calcium-phosphate product.

Understanding of the pathophysiology of sHPT advanced significantly following the cloning, in 1993, of the calcium-sensing receptor, which plays a central role in maintaining the normal integrity of the PTH response to imbalances of mineral metabolism. Calcimimetics were subsequently developed to modulate the activity of the calcium-sensing receptor and inhibit the secretion of PTH.

Cinacalcet is the first calcimimetic to become commercially available. It fulfils an important unmet medical need in that it addresses the entire spectrum of uncontrolled mineral metabolism in the ESRD population, and promises to significantly reduce the incidence of death and potentially devastating complications of sHPT, such as CV events, fractures, and parathyroidectomy.

Randomized clinical trials of up to 1 year in duration have been conducted with cinacalcet among more than 1,100 dialysis patients whose sHPT remained uncontrolled despite traditional therapy. Cinacalcet was shown to simultaneously lower not only PTH but also calcium and phosphate, despite the previous failure of ongoing treatment with active vitamin D analogues and P-binders. The comparative benefit was confirmed in a systematic review of the controlled clinical trial literature. Addition of cinacalcet to currently available therapeutic options will allow nephrologists to reach recommended targets for the control of mineral metabolism.

More specifically, a randomized trial in 552 patients with moderate sHPT (PTH levels of 31.6-84.2 pmol/L or 300-800 pg/mL) confirmed that 71% of those treated with cinacalcet in addition to routine care were able to meet UK renal association PTH targets, while lowering concomitant prescription of vitamin D and phosphate binders. Only 22% of patients given routine care alone were able to meet the same targets, despite increased dosages of vitamin D and phosphate binders. A post-hoc analysis of pooled 1-year safety data from four randomized controlled trials of cinacalcet confirmed that achieving recommended treatment targets has the potential to significantly reduce the risk of serious clinical consequences of sHPT:

- The risk of fracture was reduced by 54%
- The risk of a CV event was reduced by 39%
- The risk of parathyroidectomy was reduced by 93%
- There was a trend towards a 19% reduction in mortality

These data add to the existing evidence in support of making cinacalcet more widely available for patients with ESRD, and of maintaining research to elucidate the causative relationship between surrogate markers of mineral metabolism and final outcomes.

Economic analyses indicate that treating sHPT patients with cinacalcet is cost-effective under a variety of circumstances, and particularly so when treating moderate sHPT (PTH 31.6-84.2 pmol/L [300-800 pg/mL]). Importantly, severe sHPT patients with no treatment options other than parathyroidectomy respond favourably to higher doses of cinacalcet.

Cinacalcet is associated with an incremental cost-effectiveness ratio (ICER) of £35,600 per QALY gained when included as part of the routine care in England and Wales of all patients with PTH target thresholds of >31.6 pmol/L or 300 pg/mL (34% of all patients with ESRD in the UK). These cost effectiveness ratios are significantly reduced to £30,400 per QALY when the analysis is limited to a pre-specified subgroup of patients with moderate sHPT and PTH levels of 31.6-84.2 pmol/L or 300-800 pg/mL (10% of all patients with ESRD). Conversely, cost-effectiveness ratios increase to £48,300 per QALY for patients with severe sHPT and levels of PTH >84.2 pmol/L (800 pg/mL). Sensitivity analyses show that the ICERs are most sensitive to variation in dose, the relative reduction in mortality, and the baseline utility for patients with ESRD.

Analysis of drug cost per responder in moderate patients with sHPT found that the addition of cinacalcet to standard of care (active vitamin D and/or P-binders) translated into costs per responder gained that were similar to those of standard treatment, despite the higher drug acquisition cost of cinacalcet.

Budgetary impact calculations for the UK for patients with sHPT indicate that cinacalcet would lead to 5-year incremental costs of £76.0m (£6.2 in 2006, £20.2 in 2010). The total 5-year impact would be £46.3 and £29.1m, respectively, when limiting treatment to patients with moderate sHPT or severe sHPT. The average annual impact would amount to no more than 4% of the £450 Mio NHS annual budget currently estimated to be earmarked for the management of patients with ESRD. Importantly, the small increase to accommodate cinacalcet is estimated to result in the following annual health gains: 233 deaths avoided, 698 CV hospitalisations avoided, 304 fractures prevented and 312 parathyroidectomies avoided.

The economic results are sensitive to dosage assumptions for cinacalcet. In the phase 3 clinical trials, relatively high doses were required to achieve more stringent targets than are currently recommended. Implementation of current treatment goals (PTH 15.8-31.6 pmol/L [150-300 pg/mL]) in more recent clinical trials and in current UK clinical practice confirms that lower doses are sufficient to keep patients controlled. These data suggest that using an average daily dose of 71 mg in economic models best reflects clinical practice in patients with sHPT.

This is the first attempt to estimate the cost-effectiveness of cinacalcet based on clinical outcomes. The finding that it appears to be reasonably cost-effective in patients with moderate sHPT supports early administration to prevent progression towards more severe sHPT, and suggests that broad access would improve the quality of care offered to patients with ESRD. While patients with severe sHPT are most in need of medical care, the budgetary impact in patients with severe sHPT may be significantly reduced if progression is slowed.

Providing patients with ESRD access to cinacalcet presents an opportunity to significantly influence uncontrolled mineral metabolism and avert its associated morbidity and mortality. As patients taking cinacalcet are more likely than those given existing therapies alone to reach current clinical practice guideline targets, increased availability will result in improvements in the overall quality of care.

Taken together, the clinical and economic findings presented in this submission support a recommendation to offer cinacalcet to all patients with sHPT, with the goal of slowing the progression of the disease towards severe manifestations. Amgen firmly believes that use of cinacalcet in this way meets the requirements of acceptable clinical utility and cost-effectiveness.