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Alana Miller,
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July 12th 2006.

Dear Alana,

NICE Appraisal of Cinacalcet Hydrochloride for the Treatment of Secondary Hyperparathyroidism in Patients with End-stage Renal Disease on Maintenance Dialysis Therapy

Please find attached our response to the ACD for this technology appraisal. We would like to draw your attention to the new health economic analysis that is based upon an amended version of the PenTAG HE model. This analysis shows that a group of patients can be identified, where cinacalcet is cost-effective, if a set of simple stopping rules are applied that restricts the amount of cinacalcet patients are placed on. We would encourage the Appraisal Committee to consider this analysis and we will be sending a working version of the model to NIHCE next week.

We would also like the Appraisal Committee to note that denying patients access to cinacalcet will mean patients with uncontrolled secondary hyperparathyroidism may only have parathryoidectomy left as the remaining treatment option. This procedure has a number of known complications and a significant proportion of patients undergoing this surgery require further medical or surgical intervention. In a patient population with numerous co-morbidities and generally poor quality of life, the recommendations in the ACD would represent an inappropriate restriction of patient choice.

Could you please confirm you have received this document?

Yours sincerely

Philip Booth

Head of HTA

Amgen Response to Issues Raised in the ACD Relating to the Cinacalcet Clinical Data

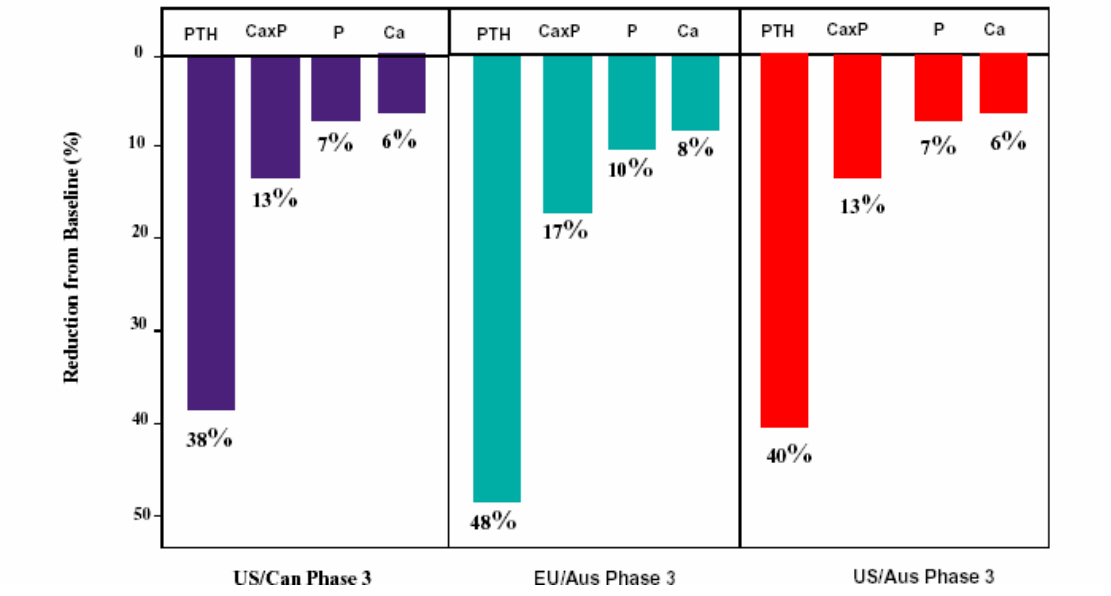
Section 4.1.2

The ACD highlights two studies (20010141, n=48 and study number 990740, n=71 patients) where the changes in serum phosphate were not statistically significantly different between cinacalcet treated patients and placebo treated patients. These 2 studies were not designed nor powered to detect clinically meaningful differences in serum phosphate between cinacalcet treated patients compared to placebo treated patients.

However, data from a pooled analysis of the three largest RCTs, n=1136 subjects (Moe et al. Kidney International 2005; 67(2):760-771) demonstrated statistically significant improvements in all 4 biochemical parameters (PTH, calcium, phosphate and Ca x P) in patients treated with cinacalcet compared with those treated with placebo. It is the first time that a therapy has been demonstrated to reduce all of these 4 clinically important biochemical parameters in this patient population.

The phase III RCTs of cinacalcet were appropriately designed, randomised, prospective, double-blind, placebo controlled trials which demonstrated consistent reductions in biochemical parameters for patients treated with cinacalcet compared to patients treated with placebo. The consistency of results as presented below clearly demonstrates the robustness of the clinical effect of cinacalcet across all of these clinical studies.

Mean Reduction in PTH, Ca x P, Phosphorus, and Calcium in the Three Pivotal Phase 3 Studies of Cinacalcet in Patients with Secondary HPT Receiving Dialysis Therapy



Section 4.1.3

The ACD states that it is unclear why a threshold of target intact PTH <26.5 pmol/litre (250pg/ml) was chosen in the phase III trials. It is important to note that the trials were designed prior to publication of the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines. The actual target threshold was < 200pg/ml, which explains the

high dosage of cinacalcet observed in the trials. The threshold was based on consensus opinion from a panel of clinical experts at the time the study was initiated and was discussed extensively with the FDA.

Section 4.1.7

The ACD states that most of the subgroup analyses did not indicate statistically significant differences in biochemical endpoints. However, as shown below, an analysis of the pooled phase III data (Block et al. N Eng J Med: 350 (15)), clearly shows statistically significant benefits across subgroups confirming cinacalcet is effective in reducing biochemical markers compared to placebo.

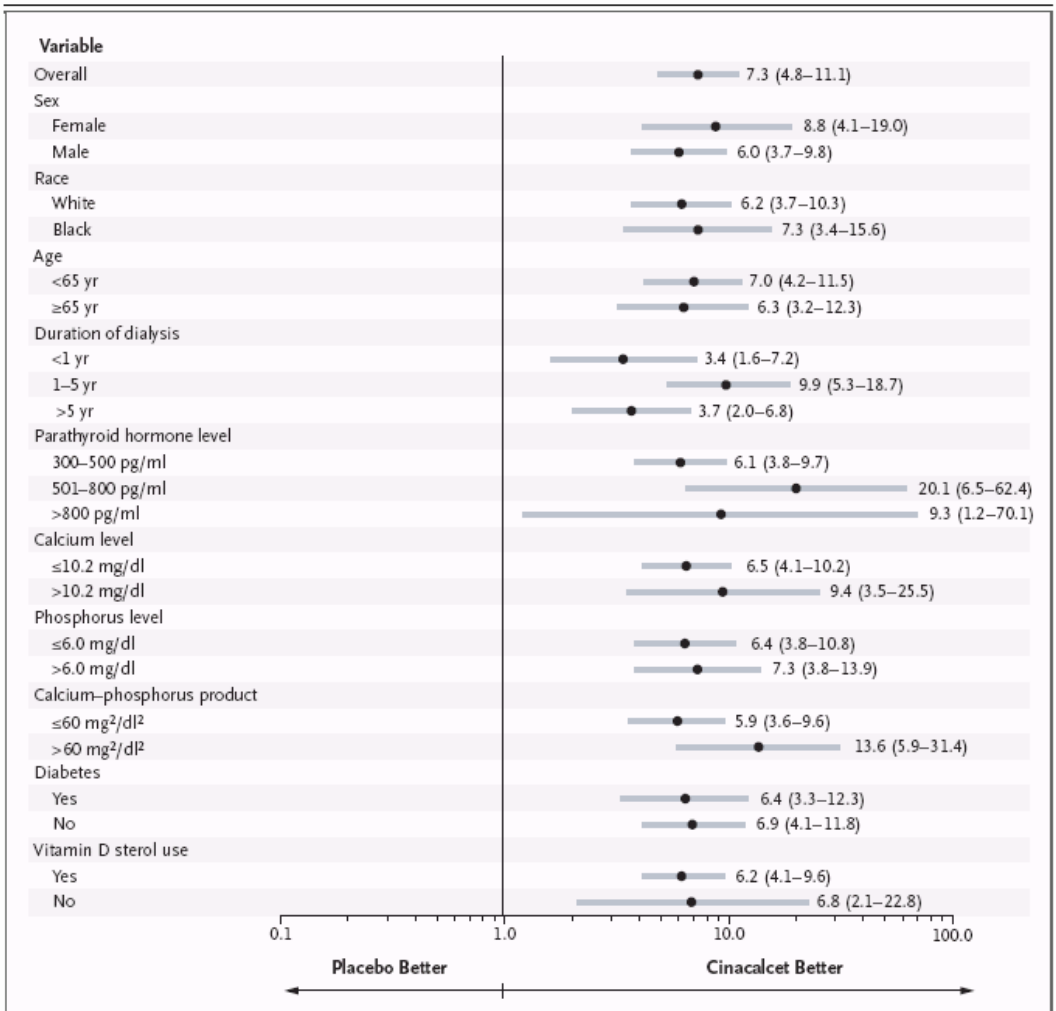


Figure 3. Stratified Analysis of the Likelihood of Achieving a Parathyroid Hormone Level of 250 pg per Milliliter or Less in the Cinacalcet Group as Compared with the Placebo Group.

The analysis was adjusted for the base-line parathyroid hormone level and the calcium–phosphorus product. Values in parentheses are confidence intervals.

Section 4.3.2

The ACD questions the relevance of data obtained from a large observational study that demonstrated a positive relationship between levels of PTH, calcium and phosphate and adverse clinical outcomes. The understanding of this clinical relationship underlies both guidance and treatment regimes in this area. The large Fresenius database is well established and methodologically well respected, having generated many important papers over 10 years or more under the leadership of Block and colleagues. This data provides the best evidence for estimating the likely clinical outcomes over a long period of controlling different levels of these biomarkers. It is inappropriate to reject this information especially when compared to similar evidence accepted and used in other Technology Appraisals. It would be impossible, in any reasonable timescale, to obtain such good information through clinical trials.

The importance of this data is also evident given; it is used in the economic modelling conducted by PenTAG; it is one of the parameters monitored and assessed within the Renal Registry and the Renal Association have published standards for PTH, Ca and P showing the significance of these in the treatment of end stage renal disease (ESRD) patients on dialysis.

Recent analyses from multiple large observational dialysis databases suggest that elevated serum calcium, phosphorus, Ca x P, and PTH are each independently associated with the risk of all-cause mortality (Figure 1) and that secondary HPT constitutes a risk factor of equal importance to that of other cardiovascular risk factors such as diabetes and anaemia (Figure 2).

Figure 1. Elevated Phosphorus, Ca x P, Calcium, and PTH are Associated with Increased Mortality Risk

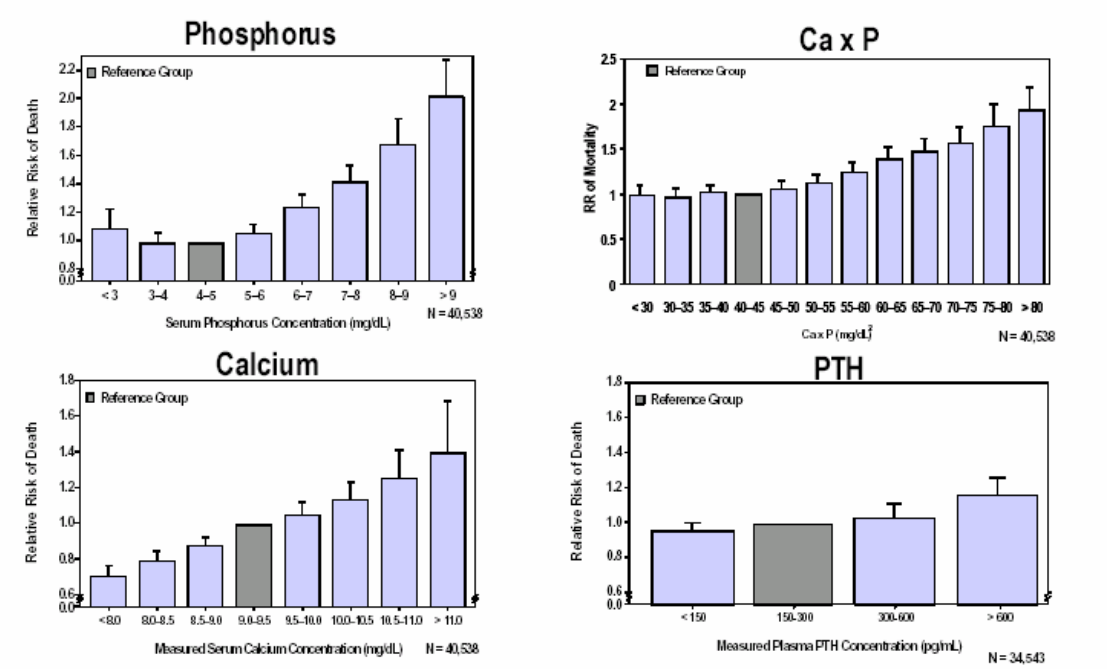
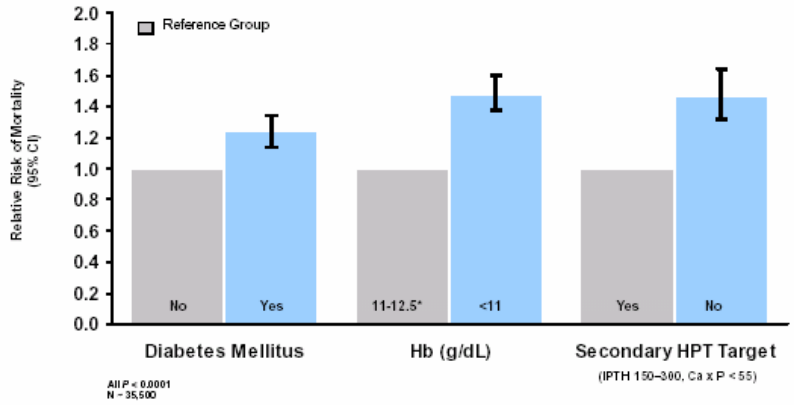


Figure 2. Secondary HPT Constitutes a Risk Factor of Equal Importance to That of other Cardiovascular Risk Factors Such as Diabetes and Anemia



Note: Cox model adjusted for age, sex, race, BMI, vintage, URR, and albumin
Adapted from Block GA, et al. *J Am Soc Nephrol*. 2003;14:474A. Abstract SA-PO801 and poster.

The need for therapeutic interventions targeted toward cardiovascular outcomes is highlighted by the 10- to 30-fold risk of cardiovascular events, including death, among patients with stage 5 CKD receiving dialysis compared to the general population. Given this increased cardiovascular risk, it is unfortunate that even traditional cardiovascular therapies have either not been rigorously tested in this patient population or, when tested, have not shown a benefit. Of the many non-traditional risk factors that may play a role in the increased burden of cardiovascular disease (e.g., malnutrition, inflammation, anaemia, etc), secondary HPT and disordered mineral metabolism stand out as one of the few factors that can clearly be modified by medical therapy.

In addition, further evidence has recently been published that highlights the positive effect of actively changing PTH levels (Melamed et al. Kidney International; online publication May 31st 2006). The CHOICE cohort of 1000 patients on dialysis was prospectively followed for up to 4 years. In this study the time-dependent association between PTH levels > 300pg/ml and death was at times statistially significant and associated with a 23% to 68% increased incidence of death. Moreover, PTH levels < 150pg/ml were associated with an even lower risk of death than being between 150pg/ml and 300pg/ml

Section 4.3.4

There is a contradiction in the ACD such that while section 4.3.2 calls into question the link between biochemical parameters and adverse clinical outcomes, the approach taken by the Assessment Group in their cost effectiveness analysis is accepted. Surely it is inconsistent to reject this approach from a clinical perspective but to accept it as the basis of the PenTAG health economic modelling? As such, we ask that the positive link between biochemical parameters and adverse clinical outcomes as reported in the literature is considered valid in the context of the clinical assessment of cinacalcet.

Amgen Response to Issues Raised in the ACD Relating to the Cinacalcet Health Economic Data

1.0 Background

The Peninsula Technology Assessment Group (PenTAG) prepared a health economic model to examine the cost-effectiveness of cinacalcet for secondary hyperparathyroidism in patients with end stage renal disease (ESRD) who are on dialysis. A Markov (state transition) model was developed that compared cinacalcet to current standard treatment with phosphate binders and vitamin D. The model estimates the incremental cost-utility of giving cinacalcet to patients who fail the current standard treatment of secondary hyperparathyroidism (SHPT) in ESRD. Simulated cohorts of 1000 people aged 55 with SHPT were modelled. Incremental costs and quality adjusted life years (QALYs) were calculated.

Within narrow bounds parathyroid hormone (PTH) regulates homeostatic control of serum calcium and phosphate levels. As kidney function deteriorates, the combined effects of reduced serum calcium, increased serum phosphate and decreased vitamin D activity lead to overactivity of the parathyroid glands as they try to maintain appropriate levels. The relative impacts of calcium, phosphate and PTH are complex and unclear, but, as shown previously, risks of having a fracture, CV event or mortality at least partially depend on patients' PTH level. The PenTAG health economic model rests on the effect of achieving control of patients' PTH level, therefore avoiding fractures, CV events or mortality. Cinacalcet in addition to standard treatment is more effective at meeting target PTH levels than standard treatment plus placebo. Therefore additional benefits are expected that potentially offset extra costs incurred by taking the medicine.

The approach for the model (base case) was to use evidence from the RCTs of cinacalcet about impact on levels of PTH and then use data from large cohort studies about the consequent risk of important outcomes contingent on biochemical levels. A key driver in the model is the use of RCT evidence to track how many patients move from "very uncontrolled" levels of PTH (defined as >800) to either "uncontrolled" (defined as >300 ≤ 800) or "controlled" (defined as >150 ≤ 300) and from "uncontrolled" to "controlled" in the treatment and treatment and placebo arms. The rate of events (mortality, CV events, hospitalisations, fractures) associated with the beginning and end PTH states are then used to estimate the cost-effectiveness of treatment.

This is a sensible approach that we applaud although there remains a problem with this methodology. The trials on which the modelling was based were "treat to target", with the targets being reflective of clinical judgement at the time of the design of the trials i.e. target for a PTH<200pg/mol. The trials were not designed to identify the patients whom it is most cost-effective to treat. Rather, the study designs involved a dose titration phase and an efficacy evaluation phase. During the dose titration phase, dose titration rules were applied where the doses of cinacalcet drug had to be increased until either the target was achieved or a maximum daily dose was achieved, without a stopping rule for patients who failed to respond adequately. Once the target PTH or maximum dose was achieved, patients continued receiving cinacalcet treatment at the dose level achieved at the end of the dose titration phase. These dosing algorithms forced the use of large quantities of costly drug to achieve potentially relatively small changes in PTH which at the margin may not be cost-effective.

We therefore believe there is a need to identify patients in whom treatment is cost-effective and to devise stopping rules for those patients who do not respond adequately after a trial period on

drug. For some "very uncontrolled" patients it may be cost-effective to treat only until they reach an "uncontrolled" state. In the absence of knowledge about this dose response relationship, the PenTAG model assumes patients receive the average dose observed under forced titration rules and receive the same dose of cinacalcet irrespective of the PTH level. They also remain on treatment even if there is no benefit. This average dose is therefore much higher than they would have received if clinically sensible stopping rules were applied for those patients who derive no benefit from the drug or from taking higher doses.

We have set out to use patient level data from the trials in an amended version of the PenTAG model to allow the identification of stopping rules and selection of treatment patterns according to starting PTH levels. These modifications allow the drug to be used at a level of cost-effectiveness usually accepted by NICE. We have constructed a new version of the PenTAG model from a combination of material supplied by PenTAG; rebuilding parts of the model from the Assessment Group's description; addition of a route by which treatment failures could be returned to standard care and utilisation of detailed trial data at patient level to identify how many patients could be expected to move between "very uncontrolled", "uncontrolled" and "controlled" states as a function of the dosage of drug.

We are not sure that our rebuilt model perfectly reproduces all aspects of that used by PenTAG but it does calculate almost exactly the same results to those in the Assessment Report. We therefore feel our reconstructed version produces results that are valid and robust.

We have been provided with a brief description of a reanalysis done by PenTAG, incorporating stopping rules, and we comment on this further in the text of this response. A subgroup analysis we have undertaken, which also incorporates stopping rules, is described below and takes the PenTAG analysis a stage further.

2.0 Analysis

The aim of the analysis reported here was twofold: to discover the impact of setting different dosage regimes of cinacalcet (so that starting PTH level of patients would influence decisions on drug dosage) and to switch those patients to standard care whose response to therapy is less than some preset target.

2.1 Data used

In order to identify the effect of different dosage scenarios, transition matrices were derived from trial data to show how patients move from a baseline to other PTH levels. Patient level trial data for the treatment arm analysis was provided by Amgen trials 172, 183, 188 (phase 3 studies). In these trials subjects who completed studies 172 or 188 could enter a 6 month extension study (240) where they would continue on their treatment (standard care or cinacalcet) for a further 6 months. After this additional 6 months all patients remaining in the extension study would be treated with cinacalcet for long term follow-up. The data for the extension part is not specifically identified in the datasets, it is treated as if the feeder study (172 /183) was of 12 months duration (any data from study 240 beyond 6 months of 240 was excluded). Other studies, 141 (phase 2 study) and 187, 143 (phase 3b studies) were not used in this analysis. The transition matrices gained from the Amgen trial data were subdivided according to dose levels (0-30, 30-60, 60-90, 90-120). Each matrix shows how extra doses of cinacalcet (e.g. from 60 to 90) affect the probability of patients moving from one PTH level to another.

For the standard treatment arm, data from phase 2 and 3 Amgen trials (172, 183, 188 and 141) plus the OPTIMA trial were examined. The phase 2 and 3 trials used placebo whereas the OPTIMA study used standard care rather than placebo. These trial results were merged into one transition matrix for the assessment of the standard treatment arm.

The original PenTAG model used the same trials as we have i.e. trials 172, 183 and 188 to present the distribution of patients according to PTH levels (PenTAG report pg 109) and these studies were regarded as good (best available) quality evidence by the PenTAG reviewers (PenTAG report pg 72).

2.2 Method

The original PenTAG model assumes that patients who did not achieve target PTH with cinacalcet continue on treatment. This is a core assumption that is altered in this analysis: patients who do not respond adequately for cost-effectiveness purposes after a three month trial period will not continue treatment, will not be assigned further drug costs and benefits and will revert to standard care. The second key difference from the PenTAG stopping rule analysis is that patients assigned to different PTH levels will be distinguished according to different dosage scenarios (as opposed to PenTAG which assumed everyone received the average dose of drug). It is important to note that no other assumption was altered in the PenTAG analysis.

The analyses below focus on patients who start either from the very uncontrolled or from the uncontrolled subgroup. This means that the very uncontrolled or the uncontrolled patients are assumed to start from their corresponding subgroup before the titration and move to any of the 3 PTH levels (Tables 1-4). This provides the starting distribution of patients in the model.

Very uncontrolled subgroup (initial PTH >800)
Rules to allow the calculation of cost utility for the very uncontrolled subgroup analysis were the following. If PTH is >800 then titrate with a certain dose level (30mg, 60mg, 90mg or 120mg) up to 120mg. Those who fail to reach targets of PTH >300<=800 or PTH <300 after 3 months of treatment are returned to standard care. Those who reach either of the 2 target levels after 3 months of treatment continue to be treated with the same dose of cinacalcet and are assumed to stay at that level. Also, patients who reached the PTH level <300 *alone* were analysed separately. In all these analyses every patient starts in the very uncontrolled subgroup (PTH> 800).

In the amended model patients who failed to reach the designated PTH level were treated as dropouts, as in the PenTAG model. This resulted in the same treatment/risk pattern as for the standard treatment arm for those patients.

Based on the Amgen trials' evidence, after the initial titration phase the following starting distributions were applied (Table 1).

Table 1 Distribution of patients starting in the very uncontrolled PTH level after using different dosages of cinacalcet

PTH control level	<=150<=300	>300<=800	>800
Titrated to 30mg	3%	30%	68%
Titrated to 60mg	15%	38%	47%
Titrated to 90mg	28%	43%	30%
Titrated to 120mg	32%	46%	22%

The starting distribution in the standard treatments arm was also altered, since in this case all patients start at a very uncontrolled PTH level too (just as in the treatment arm). After the initial standard treatment phase the starting distribution of patients in the standard treatment arm was the following (Table 2).

Table 2 Distribution of patients starting in the very uncontrolled PTH level after having initial standard treatment

PTH control level	<=150<=300	>300<=800	>800
Standard treatment	2%	19%	79%

Uncontrolled subgroup (initial PTH >300 and <=800)
The uncontrolled subgroup analysis was set with the following rules. If PTH is >300 and <=800 then titrate up to 120mg to assess response. If the target of PTH<300 is not reached after 3 months of treatment return patients to standard care. Those who reach the target after 3 months of treatment are continued to be treated with the same dose of cinacalcet and are assumed to stay at the same level. After titration the following distributions were applied (Table 3). In all these analyses every patient starts in the uncontrolled subgroup (PTH>300 and <=800).

Table 3 Distribution of patients starting in the uncontrolled PTH level after using different dosages of cinacalcet

PTH control level	<=150<=300	>300<=800	>800
Titrated to 30mg	34%	62%	3%
Titrated to 60mg	51%	44%	5%
Titrated to 90mg	56%	39%	5%
Titrated to 120mg	53%	42%	5%

After the initial standard treatment phase the starting distribution in the standard treatment arm was the following after the initial treatment phase (Table 4).

Table 4 Distribution of patients starting in the uncontrolled PTH level after having standard treatment

PTH control level	<=150<=300	>300<=800	>800
Standard treatment	16%	69%	16%

3.0 Results

Table 5 below shows the results of the calculation of the cost utility ratios applying the rules set out above. It reflects a simplifying assumption that all patients in a subgroup will receive the stated dose even if they actually responded well enough at a lower one. This assumption increases estimated cost effectiveness ratios and we show the effect of relaxing it later.

Table 5 Incremental cost effectiveness ratios for subgroups of patients with equal dosages assigned to every treated patient

Dosage up to	Patients start with very uncontrolled PTH	Patients start with uncontrolled PTH	Patients start with very uncontrolled PTH (to controlled only)
30mg	£13,493	£13,229	£7,616
60mg	£24,314	£30,623	£12,264
90mg	£35,382	£47,966	£21,214
120mg	£48,254	£66,575	£29,518

The first column of ICERs in Table 5 refers to patients, all of whom are initially in the very uncontrolled state. These patients have a trial period of three months on cinacalcet. If they remain in the very uncontrolled state after that period they are switched to the standard care arm of the model. They accrue costs but no benefits. Those who move to controlled or uncontrolled states are retained on treatment. If the dose provided is no more than 30mg and these rules are applied, Table 1 shows us that 68% of patients would remain very uncontrolled and move to standard care, 30% would move to the uncontrolled state and 3% to the controlled state. The model calculates the cost/QALY for all those patients who start on cinacalcet for the trial period including those who move to standard care and those who remain on cinacalcet. Cost/QALY for this 30mg group is shown as £13,493.

The trial data shows that treatment with 60mg of cinacalcet for all those who do not remain in the very uncontrolled group would yield a cost/QALY of £24,314. In practice we might not expect **all** patients to be given 60mg, as some would reach the best PTH level they could achieve at 30mg and would be maintained at that level. Allowing for this would revise the £24,314 figure downwards to £15,442. This reflects the fact that of the 38% of this subgroup who move to "uncontrolled" at 60 mg, 30% will only need 30 mg (Table 1).

Column 2 of ICERs in Table 5 shows the same analysis applied to patients who start in an uncontrolled state. Patients given 30mg who move to a controlled state are maintained in a controlled state on cinacalcet and the remainder switched to standard care after a three month trial. This gives a cost/QALY for this group of £13,229.

The third column of ICERs in Table 5 shows what happens if the stopping rule for patients who start in the very uncontrolled state is that treatment with cinacalcet is stopped for all patients who do not achieve a controlled state. Table 5 shows that it is cost effective to treat patients up to 120mg if this rule is applied. Table 1 shows that only 32% of patients would reach a controlled state even on 120mg.

These results generate a set of rules which would lead to cost effective use of cinacalcet if applied.

1) For patients who are initially very uncontrolled (initial PTH >800)

    a) If after 3-months of cinacalcet treatment these patients do not remain very uncontrolled with 60mg of cinacalcet (patient is either controlled or uncontrolled), then these patients can be maintained on cinacalcet treatment up to a dose of 60mg
    b) For those who become controlled after 3-months of cinacalcet treatment, these patients can be treated with cinacalcet treatment up to a dose of 120mg

2) For patients who are initially uncontrolled (PTH >300<=800)

    If after 3 months of cinacalcet treatment these patients become controlled with a dose of 30mg, then these patients can be maintained on cinacalcet at the dose of 30mg

In algorithmic form, these rules are shown in Appendix 1.

If all patients in groups 1 (a), 1(b) and 2 were treated with the maximum dose of cinacalcet permitted for that group the cost/QALY ratios would be £24,314, £29,518, and £13,229 respectively.

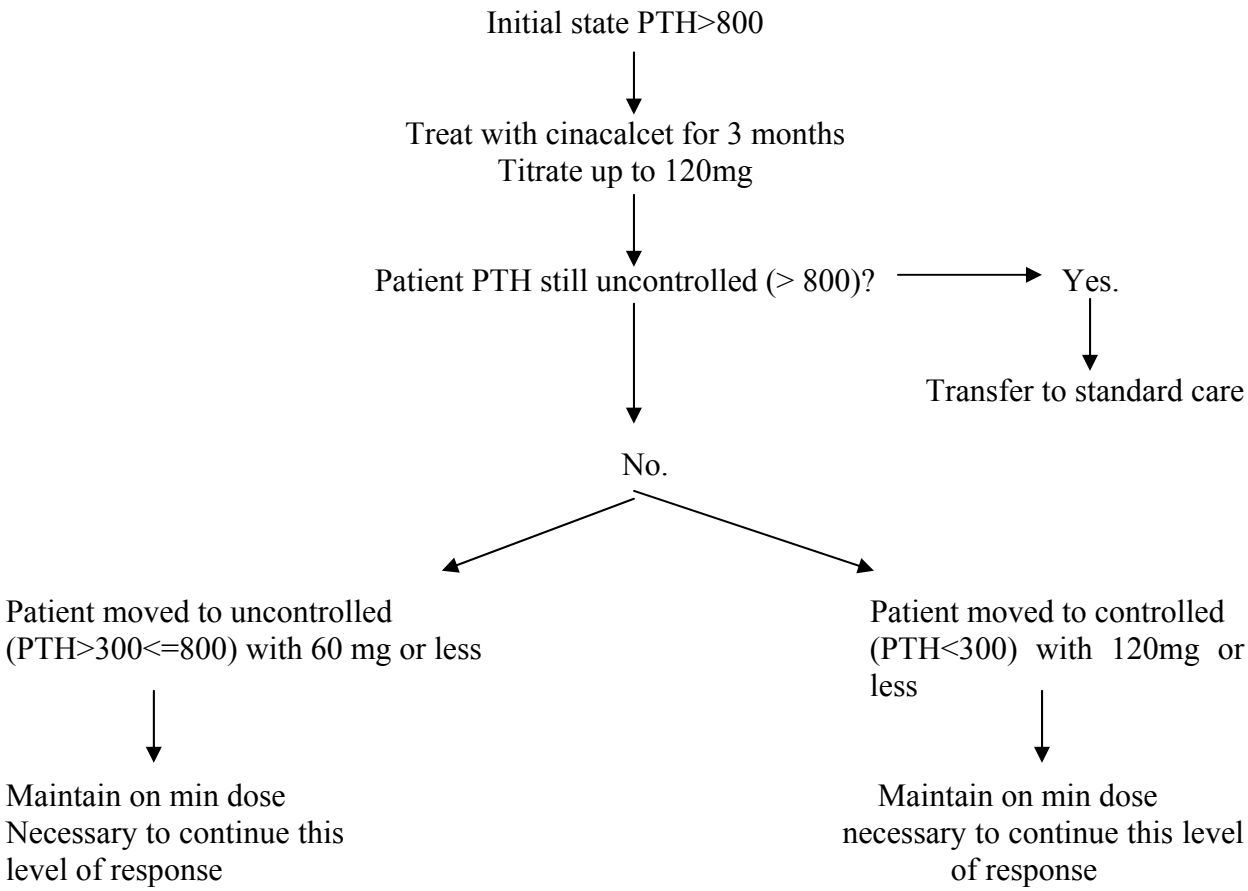
In practice we would expect patients to be only given the minimum dosage necessary to reach targeted levels. Thus, the overall cost/QALY for subgroup 1(a) would be £15,442, as 3% of the controlled patients would require only a 30mg dose and 12% require a 60mg dose, whereas 30% of the uncontrolled patients would require a 30 mg dose and 8% require a 60mg dose. The cost/QALY for 1(b) would be £18,313. This reflects a titration of all patients to 120 mg in the trial period; 3% maintained on 30mg dose; 12% maintained on 60mg dose; 13% maintained on 90mg dose; 4% maintained on 120 mg dose and 68% reverting to standard care. The cost/QALY for (2) remains unchanged, £13, 229.

4.0 Conclusion

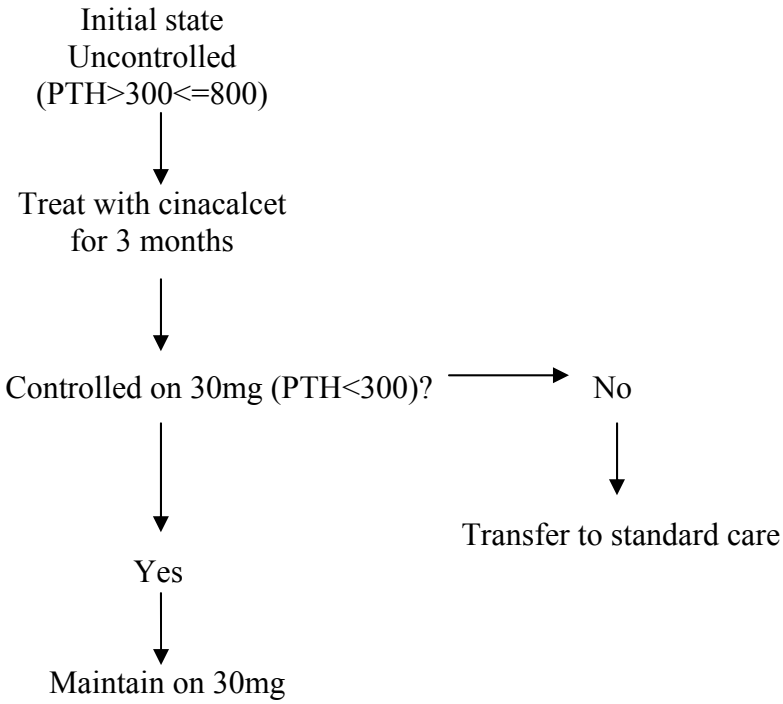
This new HE analysis based upon an amended PenTAG HE model, clearly shows cinacalcet can be used in a cost-effective manner when appropriate stopping and dosing rules are applied. A decision by NICE to support the use of cinacalcet following these rules would ensure that cost-effective, needed care was delivered to the right groups of patients with secondary hyperparathyroidism.

Appendix 1 – stopping rules in algorithmic form

Rule One



Rule 2



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