NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Cinacalcet hydrochloride for the treatment of secondary hyperparathyroidism

Responses to consultee and commentators on the Appraisal Consultation Document

Comments received from:

Patient expert

Clinical expert

North Eastern Derbyshire PCT

Welsh Assembly Government

Quality Improvement Scotland (QIS) – 4 reviewers

Royal College of Pathologists

Renal Association

British Renal Society

Kidney Alliance

Amgen

Patient representatives and clinical experts

Consultee	Comment	Action/response
Patient expert	This is only based on my experience of taking Cinacalcet and the cost savings to the NHS. I was approaching the time when the only treatment for my hyperparathyroidism would be a parathyroidectomy. In common with most long-term kidney patients (I have had chronic renal failure since June 1983) dialysis like old age does not come alone. Our respiration suffers, our hearts get weaker, and strokes become more likely making surgery a risky business. I was prescribed Cinacalcet and within two weeks my phosphate and calcium had dropped to acceptable levels and my PTH was coming down. I was taking 30mg daily. Previously I needed to take large quantities of phosphate binders in a vain attempt to keep my phosphate down. I could only take a limited number of calcium-based binders for fear of hypercalcemia I had been prescribed Renagel (sevelamer) and was taking 9 to 12 tablets a day. Cost of Renagel (sevelamer) £6.80 to £8.16 per day Cost of cinacalcet for me £4.57 per day Now that I am taking cinacalcet I can keep my calcium and phosphate under control with just calcium based phosphate binders For this reason I have stopped researching into expensive non-calcium based phosphate binders such as lanthanum carbonate. Other drugs prescribed to dialysis patients to try to control hyperparathyroidism and hyperphosphataemia must also be taken into account against the cost of cinacalcet. Alfacalcidol for example and I am sure there are many others. Before taking cinacalcet I was having difficulty walking, in fact I was taking the car for a journey of less than ½ mile to the village centre for my daily newspaper, the bone pain was too much. If as seems likely my mobility had got worse, even to the extent of needing a wheelchair, I would have needed hospital transport three times a week for dialysis at huge costs to the NHS. I do not think that the costs to the NHS of not prescribing cinacalcet have been taken into account. I cannot speak for other patients but taking cinacalcet has been a life changing experience for me.	The use of non-calcium-based phosphate binders in very uncontrolled hyperparathyroidism was factored into the model, see new ACD section 4.2.3 Limiting dose escalation to 30 mg was considered to some extent in the algorithm suggested by the manufacturer. The Committee rejected this approach. The Committee heard that cinacalcet would not replace the need for Vit D. Quality of life – comment noted

Consultee	Comment	Action/response
Clinical expert	In the Expert written personal perspectives section, Dr Hutchison and I are affiliated to the NKF. In fact we were representing the RCP: – Dr Neil Gittoes, Consultant Endocrinologist, National Kidney Federation – Dr Alastair Hutchison, Consultant Renal Physician, National Kidney Federation – Christopher Payne, patient expert, National Kidney Federation – Steve Rowe, patient expert, National Kidney Federation I was disappointed to see that the Committee left no leeway for prescribing cinacalcet in the context of the rare dire clinical need context as was described at the meeting. In other respects I acknowledge the proposals set out by the Committee.	Checked – both clinicians nominated by the RCP. See 1.2 in new ACD – allows for prescribing in a subgroup of those with refractory disease in whom parathyroidectomy is contraindicated.
North Eastern Derbyshire PCT	We consider that the content and provisional recommendations of the appraisal document to constitute a suitable basis for the preparation of guidance to the NHS We concur that at this point in time, the use of Cinacalcet for the stated purpose does not appear to be a cost effective use of NHS resources, but that further research to examine the impact of biochemical changes in end-stage renal disease on clinical outcomes would be appropriate	Comments noted.
Welsh Assembly Government	We are content with the technical detail of the evidence supporting the provisional recommendations and have no further comments to make at this stage.	Comments noted.

Consultee	Comment	Action/response
QIS reviewer 1	*i) Whether all the relevant evidence has been taken into account?* Yes. I think the document is wholly encompassing of the relevant information. *ii Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?* I think the summaries very carefully considered the evidence and the interpretation regarding clinical benefit and cost effectiveness most reasonable. *iii) Whether the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?* Yes. The Appraisal Committee have done a very good job and I think their recommendations are extremely sound and relevant to current NHS practice.	Comments noted.
QIS reviewer 2	*i) Whether all the relevant evidence has been taken into account?* Yes *ii) Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?* Yes *iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?* Yes	Comments noted.

Consultee	Comment	Action/response
QIS reviewer 3	*i) Whether all the relevant evidence has been taken into account?* Yes, but have to accept that there is a paucity of relevant evidence and short-term follow up in RCTs; and in certain patient sub-groups there is no evidence (because of lack of appropriate trials rather than trial evidence of lack of benefit). *ii) Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?* Without seeing the original assessment report, it is difficult to answer this question. Conclusions appear to rely on assumption that intermediate end-points (biochemical markers eg PTH) relate to clinical events. *iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?* Committee have accepted that the trials have shown that cinacalcet was effective in reducing levels of PTH, and that there was an observed reduction in adverse clinical outcomes – but state caveat that the trials were not designed to look at clinical outcomes. Committee then use PTH (and make assumptions on clinical benefits) as a marker of risk of adverse clinical events in cost-effectiveness analyses and conclude that Cinacalcet is unlikely to be a cost-effective use of NHS resources. Issues for specific groups eg post-parathyroidectomy hyperparathyroidism, mediastinal parathyroid adenomas etc not addressed. Lack of evidence in these groups might not equate with lack of benefit clinically or on cost-effectiveness. In summary I interpret their conclusions are probably accepting clinical benefit, but are overall not supportive on the basis of cost-effectiveness. These conclusions might be difficult to support on the basis of the available evidence. I think problem sub-groups of patients may need to be addressed separately – prevalence of them is not clear.	Comments noted

Consultee	Comment	Action/response
QIS reviewer 4	This is a complex topic, but the overriding impression is that although Cinacalcet is accepted as doing what it is biochemically designed to do in terms of calcium and phosphate metabolism, the studies have not been designed to determine whether this has any meaningful effect on clinical outcomes. In the absence of such studies, the only conclusion available is the one reached, ie that this agent should not be made available given the high costs. I know of no other evidence that might have been considered, and would consider the conclusion to be soundly based.	Comments noted.
Royal College of Pathologists	Having previously commented on the Health Technology Appraisal report on this topic I am pleased to be able to review the feedback from various sources and the Appraisal Consultation Document (ACD) that has been produced from that feedback. I thank the Appraisal Committee for the detailed and clear content of the ACD. Overall I accept the main recommendation in the ACD that based on current evidence 'Cinacalcet hydrochloride is not recommended for the routine treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy.' The scientific basis for Cinacalcet hydrochloride action is well founded and there is universal agreement that it is an effective drug for reducing plasma PTH in this group of patients, and that it may also have a beneficial effect on other biochemical parameters, including plasma phosphate. It is also clear that the use of Cinacalcet hydrochloride is preferred by patients and that it offers less chance of adverse effects in comparison to some conventional therapy. The 'stumbling block' for Cinacalcet hydrochloride is that at this point in time the strength of evidence to support its introduction into routine practice is very weak. There is currently only poor quality evidence that the undoubted biochemical improvement from use of the drug translates into reduced mortality and morbidity and an improved quality of life. As the ACD makes clear further evidence in these areas is urgently required. I believe that if that evidence is forthcoming then the case for the introduction of Cinacalcet hydrochloride into routine practice will be strong.	Comments noted.

Consultee	Comment	Action/response
Royal College of Pathologists (continued)	The ACD contains a detailed assessment of the cost effectiveness of Cinacalcet hydrochloride and it puts forward data to support a variety of models. In all cases, however, the cost effectiveness looks poor because the data to support the clinical effectiveness is currently missing. It would be misleading if the main message from the ACD is about an 'expensive' drug – the main message is that we have a drug that has yet to be proven to be clinically effective. While waiting for better quality evidence there remains the question about the non-routine use of Cinacalcet hydrochloride in individual patients with severe and/or complex secondary hyperparathyroidism. Although it is not strongly evidence-based I am persuaded by the expert view that a case can be made for short-term use of the drug in individual patients who are awaiting surgical hyperparathyroidism or for longer-term use in individual patients who are considered high risk for surgery for parathyroidectomy. Evidence on the clinical effectiveness of Cinacalet hydrochloride should be kept under regular review.	Analysis of cost effectiveness takes into account both costs and benefits See paragraph 1.2 of new ACD
Renal Association	While it is clear that treatment with cinacalcet hydrochloride leads to significant improvement in the biochemical parameters of secondary hyperparathyroidism I would agree that until additional randomised trials become available the benefits of this drug on patient based end points are uncertain. This concurs with the recently published meta-analysis of biochemical and patient level effects of calcimimetic therapy by the Cochrane Renal Group 1. It is very likely that treatment with cinacalcet hydrochloride will demonstrate clinical benefits in terms of reduction in adverse events but the evidence is not conclusively there yet.	Comments noted

Consultee	Comment	Action/response
Renal Association (continued)	I would be grateful however if the Committee would review their recommendations in 4.3.6 which states:- 4.3.6 The Committee heard from the experts that there may be a very small subgroup of people with refractory or 'tertiary' hyperparathyroidism for whom cinacalcet hydrochloride may be an alternative to surgical parathyroidectomy. This option may be particularly useful where surgical risk is considered to be high. However, there was insufficient clinical evidence on the effectiveness of cinacalcet hydrochloride in this subgroup, and there was no evidence on the clinical effectiveness of cinacalcet hydrochloride compared with surgical parathyroidectomy. In addition, cost-effectiveness analysis suggested that cinacalcet hydrochloride was less cost effective in people with very uncontrolled hyperparathyroidism, although the extent to which this analysis reflected the population with refractory disease was not clear. The Committee therefore concluded that there was insufficient evidence to enable it to recommend cinacalcet hydrochloride in this group. I agree that this small sub-group of patients has not been specifically investigated to assess the benefits of cinacalcet. That cinacalcet significantly improves the biochemical parameters of hyperparathyroidism however is acknowledged by all and while we await out-come data it is clear that some patients that fall into this small sub-group, including those with calciphylaxis will benefit from treatment as shown in case reports 2. The evidence currently is only at case report level and it is unlikely that large trials will be able to show benefit in calciphylaxis as the prevalence of this condition is very low. I do not think that a cost-effective analysis is valid here. I do think that a stopping rule could be included for this sub-group of patients for non-responders after 3 months of treatment. Therefore, while aware that the evidence base is limited as mentioned above, I would urge the Committee to reconsider its recommendation for the use of cinacalcet hydrochloride in this sub-group of patients. Strippoli G.F.M., Palmer S., Tong A., Elder G., Messe P., Craig J.C. Meta-Analysis of Biochemical and Patient-Level Effects of Calcimimetic Therapy. Am J Kidney Dis 2006; 47: 715-726. Nestor Velasco, Mark S. MacGregor, Andrew Innes and Ian G. MacKay. Successful treatment of calciphylaxis with cinacalcet—an alternative to parathyroidectomy? Nephrology Dialysis Transplantation 2006; 21:1999-2004.	The Committee reconsidered the use of cinacalcet hydrochloride in subgroups – see new ACD sections 1.2 and 4.3.6

Consultee	Comment	Action/response
British Renal Society	The council of the British Renal Society has considered the draft NICE appraisal of cinacalcet. We would like to make the following observations. 1. The main conclusion of this appraisal, that the committee does not recommend the use of cinacalcet for the routine treatment of secondary hyperparathyroidism, is reasonable. For routine management of SHPT, alfacalcidol together with calcium carbonate or acetate phosphate binders should provide adequate treatment. 2. For patients with tertiary hyperparathyroidism whose PTH and calcium remain high when all calcium containing phosphate binders have been stopped, there is no treatment available except cinacalcet or parathyroidectomy. The document suggests that parathyroidectomy is 'unsuccessful' in 8% of cases. What little long-term data on parathyroidectomy there is suggests that, in the long term, the success rate may be as low as 20%. These are cases in which the PTH level is in the desired range of 2-5 x normal. There is a high incidence of absent or low PTH levels post-PTX (as high as 65% after total parathyroidectomy) and a high incidence of recurrent severe hyperparathyroidism (15% or so after total parathyroidectomy). The document almost totally ignores problems associated with low PTH levels. The literature suggests that as well as there being an increased mortality at very high PTH levels – there is also a high mortality associated with very low levels. Very low levels are also associated with adynamic bone disease and enhanced vascular calcification. There are similar 'success' rates after subtotal and total with reimplantation, though in both these cases the incidence of chronic hypoparathyroidism is less and the incidence of severe recurrent hyperparathyroidism. There is a high early mortality after parathyroidectomy and a hugely increased complication profile of parathyroidectomy in patients with end-stage renal failure compared to that after primary parathyroidectomy. Cinacalcet is a potential alternative to parathyroidectomy and it will be difficult to recommend parathyroidectomy for a sizeable proportion of patients, especially if the increased risks related to end-stage renal disease are complicated by significant extra-renal co-morbidities.	The Committee reconsidered the use of cinacalcet hydrochloride in subgroups of people with refractory hyperparathyroidism – see new ACD sections 1.2 and 4.3.6

Consultee	Comment	Action/response
British Renal Society (continued)	3. The recommendations are based on the output of a complex modelling process. There are problems with the primary stratification, which is by PTH levels alone. A PTH level, unqualified by a serum calcium or calcium x phosphate product, is almost meaningless. In most individuals with end-stage renal failure and hyperparathyroidism, the PTH level can be manipulated from very low to very high depending on the level of serum calcium one is trying to achieve. A high PTH in the context of a serum calcium of 1.8mmol/l is a world away from the same PTH level with a serum calcium of 2.8mmol/l. It is necessary is to define severe hyperparathyroidism appropriately – that is a high PTH in the context of a serum calcium at the upper levels of normal or even high, after appropriate 'standard therapy'. We suggest that had the modelling been done in this group the outcome may have been different, especially if the points in paragraphs 1, 3 and 4 are also taken into account. . We appreciate that there is limited available evidence to base on which to base such modelling but point out that there are huge numbers of approximations in the model as presented, including the unsustainable assumption that a single PTH reading means very much at all.	The Committee were aware of the complexity of the relationships between biochemical endpoints, but accepted the assessment group approach to the modelling in the light of the current evidence available.
	4. The costs in the appraisal were based on the use of cinacalcet in a manner similar to its use in the clinical trials, in which the drug was essentially continued for the duration of the trial at maximum dose in poor or non-responders. This is not the appropriate basis on which to cost. It would be more appropriate to stop the drug in such cases after a reasonable trial period. We suggest that it would be reasonable to re-analyse the data with this rule.	The Committee considered the use of stopping rules and limitations on dose escalation – see new ACD 4.3.5
	5. There is reasonable evidence of an improvement of haemoglobin levels on resolution of severe hyperparathyroidism. There is reasonable evidence of a reduction in serum phosphate levels with cinacalcet. This may entail savings on EPO and phosphate binders, some of which are very expensive.	Evidence of effect on utilisation of erythropoietin has not been submitted. The use of non-calcium-based phosphate binders in very uncontrolled hyperparathyroidism was factored into the model, see new ACD section 4.2.3

Consultee	Comment	Action/response
British Renal Society (continued)	6. In summary, The British Renal Society maintains the view that Cinacalcet should be available for treatment of severe secondary hyperparathyroidism with hypercalcaemia especially where parathyroidectomy is deemed to have high surgical risk. Moreover, its use can also be justified in patients with calciphylaxis associated with SHPT which has devastating consequences although the evidence so far is anecdotal (Valesco et al, Nephrol Dial Transplant, 2006: 1999-2004).	The Committee reconsidered the use of cinacalcet hydrochloride in subgroups of people with refractory hyperparathyroidism – see new ACD sections 1.2 and 4.3.6
Kidney Alliance	Alongside vascular access, hyperparathyroid renal bone disease ranks equally as the major scourge of the patient surviving with end-stage renal failure. While phosphate binders and vitamin D preparations are employed successfully in early hyperparathyroidism, the treatment of disease when the glands have become autonomous – tertiary hyperparathyroidism- is a very different. The renal community has waited for many years for a new weapon in the armamentarium to combat this destructive disease. The Kidney Alliance think that the NICE appraisal of Cinacalcet is harsh and based on a flawed analysis, which misunderstands the natural history of tertiary parathyroidectomy after surgery. It also fails to address the central issue of patient *choice* i.e. is the avoidance of unnecessary neck surgery in high-risk patients. The Kidney Alliance is concerned about the central assumption that parathyroidectomy (PTx) is a successful procedure which expects to normalise parathyroid hormone (PTH) levels thereby curing the disease. This is probably true for neck surgery in primary hyperparathyroidism but in tertiary hyperparathyroidism, surgery, while it may temporarily relieve bone pain and reduce serum calcium, generally doesn't work. Possibly a majority of patients will end up with too low PTH levels which leads to adynamic bone disease and there is a high incidence of recurrent hyperparathyroidism in about 15% patients. Both these outcomes are associated with continuing destruction of the skeleton. Re-exploration of the neck in recurrent disease is notoriously difficult, carries high risk and is often unproductive.	Comments noted. See 1.3 and 4.3.6 in new ACD Comments noted – the Committee were aware of the consequences of adynamic bone disease.

Consultee	Comment	Action/response
Kidney Alliance (continued)	The nature of PTx itself has not been fully appreciated in this appraisal. Patients undergoing surgery for primary hyperparathyroidism usually have single organ disease and tend to be otherwise well. Not so in ESRF patients. Many being put forward for PTx have had renal failure for a number of years, have multiple co-morbidities, are at hugely increased risk from cardiovascular events and are therefore "high-risk" surgical patients. Indeed there is a sub-group in whom the risks of surgery are too high and desperate measures such as chemical ablation are occasionally attempted. The Informed Kidney Patients of the Kidney Alliance wish to raise the important concept of Choice in a patient centred health service when there is now a potential alternative to neck surgery, the latter often being a last ditch option which has uncertain results. This is particularly the case in recurrent disease. It should be borne in mind that many of these patients will already have had multiple general anaethetic operations along their ESRF pathway and unnecessary surgery is an emotive issue. Extension of life (and hence the QUALY) is not necessarily a meaningful parameter on which to base judgements of benefit in patients with chronic disease for whom relief of suffering (include unnecessary surgery) may be of greater import.	See new ACD sections 1.2 and 4.3.6
	Finally, the analysis assumes that the patients given this drug receive it indefinitely. This does not sit well with clinical reality when using expensive drugs. In practice the drug will be stopped in non-responders and this needs to be taken into account.	The Committee considered the use of stopping rules and limitations on dose escalation – see new ACD 4.3.5
	The Kidney Alliance, while accepting that Cinacalcet should not be used for all cases of hyperparathyroidism, urge NICE to carry out a re-appraisal examining particularly its administration to a subgroup of patients with tertiary (including recurrent tertiary) hyperparathyroidism and those in whom surgery is too risky while taking into account early cessation of the drug in non-responders and the choice which patients could reasonably expect to avoid neck surgery for which the evidence shows, poor outcomes in the majority.	The Committee reconsidered the use of cinacalcet hydrochloride in subgroups of people with refractory hyperparathyroidism – see new ACD sections 1.2 and 4.3.6

Consultee	Comment	Action/response
Amgen	**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** [Figure provided] **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.	4.1.2 has been amended in new ACD 4.1.3 has been amended in new ACD

Consultee	Comment	Action/response
Amgen (continued)	**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 provided] **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). [Figures 1 and 2 provided]	The words “between subgroups” have been added in 4.1.7 to clarify meaning. While acknowledging the uncertainties involved, the Committee accepted the assessment group approach in the light of the availability of evidence.

Consultee	Comment	Action/response
Amgen (continued)	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	this observational study does not appear to investigate any particular intervention to reduce PTH
	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.	While acknowledging the uncertainties involved, the Committee accepted the assessment group approach in the light of the available evidence.

Consultee	Comment	Action/response
Amgen (continued)	**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.	Comments noted

Consultee	Comment	Action/response
Amgen (continued)	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.	Comments noted

Consultee	Comment	Action/response
Amgen (continued)	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.	The Committee carefully considered the analysis presented by the manufacturer (see paragraph 4.3.5 in the new ACD).

Consultee	Comment	Action/response
Amgen (continued)	**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).	

Consultee	Comment	Action/response
Amgen (continued)	**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.	

<table>
<tr><th>Consultee</th><th>Comment</th><th>Action/response</th></tr>
<tr><td>Amgen (continued)</td><td>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
<table>
<tr><th>PTH control level</th><th><=150<=300</th><th>>300<=800</th><th>>800</th></tr>
<tr><td>Titrated to 30mg</td><td>3%</td><td>30%</td><td>68%</td></tr>
<tr><td>Titrated to 60mg</td><td>15%</td><td>38%</td><td>47%</td></tr>
<tr><td>Titrated to 90mg</td><td>28%</td><td>43%</td><td>30%</td></tr>
<tr><td>Titrated to 120mg</td><td>32%</td><td>46%</td><td>22%</td></tr>
</table>
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
<table>
<tr><th>PTH control level</th><th><=150<=300</th><th>>300<=800</th><th>>800</th></tr>
<tr><td>Standard treatment</td><td>2%</td><td>19%</td><td>79%</td></tr>
</table></td><td></td></tr>
</table>

<table>
<tr><th>Consultee</th><th>Comment</th><th>Action/response</th></tr>
<tr><td>Amgen (continued)</td><td>
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
<table>
<tr><th>PTH control level</th><th><=150<=300</th><th>>300<=800</th><th>>800</th></tr>
<tr><td>Titrated to 30mg</td><td>34%</td><td>62%</td><td>3%</td></tr>
<tr><td>Titrated to 60mg</td><td>51%</td><td>44%</td><td>5%</td></tr>
<tr><td>Titrated to 90mg</td><td>56%</td><td>39%</td><td>5%</td></tr>
<tr><td>Titrated to 120mg</td><td>53%</td><td>42%</td><td>5%</td></tr>
</table>
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
<table>
<tr><th>PTH control level</th><th><=150<=300</th><th>>300<=800</th><th>>800</th></tr>
<tr><td>Standard treatment</td><td>16%</td><td>69%</td><td>16%</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Consultee</th><th>Comment</th><th>Action/response</th></tr>
<tr><td>Amgen (continued)</td><td>

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.

</td><td></td></tr>
</table>

Consultee	Comment	Action/response
Amgen (continued)	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. [not reproduced for this table]	

Consultee	Comment	Action/response
Amgen (continued)	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.	