NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Cinacalcet hydrochloride for the treatment of secondary hyperparathyroidism

Responses to consultee and commentators and non-consultee comments on the Appraisal Consultation Document 2

Comments received from:

North Eastern Derbyshire PCT

National Kidney Research Fund

Welsh Assembly Government

Department of Health

Quality Improvement Scotland (QIS) – 3 reviewers

Royal College of Pathologists

Renal Association

British Renal Society

Kidney Alliance

Amgen

National Kidney Federation (responded via web, but included in consultee and commentator table)

NHS professionals (3 responses)

Consultee and commentator comments

Consultee	Comment	Action/response
North Eastern Derbyshire PCT	*i) Whether you consider that all the evidence has been taken into account.* We felt that the first Appraisal Consultation Document (ACD) was very thorough and agreed with the conclusions. It was consistent with work that we had done locally to consider applications for funding of Cinacalcet, which were based on the available evidence and the principles stated in the NICE 'Social Value Judgements' document. It was also consistent with a similar review carried out by NORCOM on behalf of the North Trent PCTs and with the conclusions of the Scottish Medicines Consortium. We do not believe that the preliminary recommendation for the use of Cinacalcet for patients with refractory secondary hyperparathyroidism (1.2) is consistent with the evidence base and NICE Social Value Judgements. These recommendations contradict the findings noted in points 4.3.5, 4.3.6 and 4.3.7 of the original appraisal document. On reviewing the responses to the first consultation, they appear to be strongly influenced by the fact that there is no other specific treatment available to these patients, and therefore the NHS should be required to fund Cinacalcet. The ACD does not show Cinacalcet to be cost effective. Funding Cinacalcet would therefore reduce resources available for cost effective interventions for other patients	Comments noted.

Consultee	Comment	Action/response
North Eastern Derbyshire PCT (continued)	*ii) Whether you consider that 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* We felt the views expressed in the first ACD were reasonable, and disagree with the change to recommend Cinacalcet for the subgroup of patients with refractory disease. We have received a small number of requests to commission Cinacalcet. All requests to date would meet the preliminary recommendations for funding. These are patients with very high PTH, in whom the estimated annual treatment cost would be up to £9 000 per year and the cost per QALY in the region of £48 000. To recommend Cinacalcet in this sub-group of patients may be inconsistent with principle 5 of the NICE's 'Social Value Judgements,' and could require PCTs to direct resources away from other treatments	See FAD 4.3.7 – 4.3.8

Consultee	Comment	Action/response
North Eastern Derbyshire PCT (continued)	*iii) In whom surgical parathyroidectomy is contraindicated* We would expect that patients with renal failure would often have absolute or relative contraindications to surgery. If Cinacalcet is recommended for these patients, it would be appropriate to have clarity on how 'contraindications for surgery' would be interpreted. The prevalence of the sub-group of patients that would meet the criteria for the preliminary recommendation in 1.2 is not stated In our limited experience of applications for Cinacalcet, one patient, appeared to have absolute contraindications to parathyroidectomy, in others, there were relative contraindications to surgery. We consider that there is a potential for significant costs for the NHS if Cinacalcet is recommended by clinicians in preference to surgery, with it's associated increased risks in this 'higher risk' patient group. We agreed with the points discussed in paragraphs 4.3.6 and 4.3.7 from the first ACD, which concluded that there was insufficient clinical evidence for this subgroup and no evidence available on the clinical effectiveness of Cinacalcet compared with surgical parathyroidectomy, and is therefore not consistent with a recommendation for its use.	Wording of 1.2 regarding contraindications for parathyroidectomy were discussed by the Appraisal Committee and modified in the FAD to make it clear that cinacalcet hydrochloride is not recommended as an alternative to surgery where surgery is possible. See FAD 1.2, 4.3.6, 4.3.7 and 4.3.8.

Consultee	Comment	Action/response
North Eastern Derbyshire PCT (continued)	iv) *iv) 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* We are concerned that to proceed with 'Provisional Recommendation 1.2', to recommend Cinacalcet Hydrochloride for patients with refractory secondary hyperparathyroidism, would be inappropriate and would represent divergence from the key principles used in allocating NHS resources. • Cinacalcet has not been demonstrated as cost effective • Clinical effectiveness of Cinacalcet for this patient subgroup is unclear • Contraindications to parathyroidectomy are not made clear and therefore open to interpretation • The recommendation may be inconsistent with NICE Social Value Judgements • Implementation of the recommendation could divert resources away from cost effective interventions for other patients Conclusion The PCT view is that Cinacalcet Hydrochloride should not be recommended for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy	Wording of 1.2 regarding contraindications for parathyroidectomy discussed by Appraisal Committee and modified in FAD. See FAD 1.2 and 4.3.6-4.3.8.
National Kidney Research Fund	I am pleased to see that an indication for the usage of Cinacalcet Hydrochloride has been recognised. I agree that Cinacalcet is not first line or routine treatment for secondary hyperparathyroidism in patients with end stage renal failure. However the wording of section 1.2 is confusing. It implies that Cinacalcet usage should be based purely on the levels of intact parathyroid hormone. However a PTH level can only be interpreted in the context of knowing a patient's serum calcium and I would suggest that this paragraph requires rewording to read "Cinacalcet Hydrochloride is recommending in patients with refractory secondary hyperparathyroidism (typically defined as an intact PTH level >85 pmol/L (or 800pmol/L), with a normal or high serum calcium) and in whom a surgical parathyroidectomy is contra-indicated. "	Wording of 1.2 discussed by Appraisal Committee and has been modified in FAD

Consultee	Comment	Action/response
National Kidney Research Fund (continued)	The final paragraph of section 1.2 is a reasonable overall statement. However I would suggest that 6 months treatment would be required to ascertain response. This reflects the practicality of blood test monitoring in patients on dialytic therapies which generally occur at monthly intervals. Such a pattern would not allow a suitable titration pathway to be achieved in a three month period. I would also draw your attention to an abstract published at the British Renal Society/ Renal Association meeting 2006. This outlines our preliminary experience of this agent in a cohort of patients with refractory hyperparathyroidism. I enclose the abstract and the poster presentation related for information. Not only were PTH target levels achieved in a proportion of this population but target levels of calcium and phosphate were also achieved with greater success. This was achieved at a substantially lower dose of Cinacalcet that has been reported in literature (median daily dose 30mg).	Committee recommended a 4-month titration period.
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. No action required.
Department of Health	The Department of Health has no substantive comments to make on this appraisal.	Comments noted. No action required.

Consultee	Comment	Action/response
QIS reviewer 1	*i) Whether you consider that all the relevant evidence has been taken into account.* Yes *ii) Whether you consider that 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. No action required. Comments noted. No action required. Comments noted. No action required.
QIS reviewer 2	*i) Whether you consider that all the relevant evidence has been taken into account.* This document does take into consideration representation from Health professionals relating to the concerns about a small group of ESRD patients with refractory hyperparathyroidism with relative or absolute contra-indications to surgical parathyroidectomy. I would agree that all relevant evidence has been taken into account but accept the reservations of the Committee that there is a paucity of RCT evidence to support use of cinacalcet in these specific 'problem' groups. *ii) Whether you consider that 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.* They are a significant improvement on the earlier recommendations and address the needs of a group of patients where treatment options are currently limited or ineffective. The 'check' of a 30% improvement at 3 months will prevent inappropriate and costly prolonged use of the drug.	Comments noted. No action required. Comments noted. No action required. Comments noted. No action required

Consultee	Comment	Action/response
QIS reviewer 3	*i) Whether you consider that all the relevant evidence has been taken into account.* Yes *ii) Whether you consider that 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. No action required. Comments noted. No action required. Comments noted. No action required
Royal College of Pathologists	The RCPath welcomes the opportunity to comment on the second consultation. The feedback from the first consultation showed considerable agreement on the need to obtain better clinical outcome studies before being able to take a decision on the routine use of cinacalcet hydrochloride in secondary hyperparathyroidism. However, the feedback also showed strong support for the use of cinacalcet hydrochloride on an exceptional basis in severe and/or complicated cases where conventional therapy may not be indicated. Against this background the RCPath is pleased to see that the second consultation document has now recommended use of cinacalcet hydrochloride in patients with refractory secondary hyperparathyroidism who have very high serum PTH and in whom surgical parathyroidectonmy is not indicated. The College sees this as a sensible step to take while waiting for more definitive clinical outcome studies. The College also supports the recommendation that the exceptional use of cinacalcet hydrochloride should not be allowed to continue if the serum PTH has not fallen by 30% within 3 months.	Comments noted. No action required.

Consultee	Comment	Action/response
Renal Association	We welcome the recommendation on its use in refractory secondary hyperparathyroidism. This may need more accurate definition – PTH concentration is insufficient. The PTH has to be interpreted in relation to the calcium concentration. A patient with a very low Ca++ may have a very high PTH suppressible into an acceptable range if the calcium is increased by calcium containing binders and vitamin D analogues. Does your cost analysis take account of potential savings on the use of expensive phosphate binders such as sevelamer? We have no comments on the remainder of the document and accept its recommendations.	Wording of 1.2 discussed by Appraisal Committee and modified in FAD
British Renal Society	The British Renal Society welcomes the relaxation of the recommendations relating to prescription of cinacalcet. However, we strongly suggest that the condition 'when surgical parathyroidectomy is contraindicated' is inappropriately restrictive. This wording fails to recognise the complexity of such management decisions which are usually a difficult balance of risk versus potential benefit. Nor does it recognise where the responsibility lies for deciding whether or not surgical parathyroidectomy is contraindicated. We should suggest that the condition should more appropriately read 'when in the opinion of the responsible clinician, the risks of surgical parathyroidectomy outweigh the potential benefits'.	Wording of 1.2 regarding contraindications for parathyroidectomy discussed by Appraisal Committee and modified in FAD

Consultee	Comment	Action/response
Kidney Alliance	The Kidney Alliance welcomes the amendments to the recommendations regarding cinacalcet. The Alliance is comfortable with 1.1 which recommends that the routine treatment of secondary hyperparathyroidism should continue as currently with the use of vitamin D preparations and phosphate binders – standard therapy. The Alliance welcomes the recommendation to allow a trial of cinacalcet to those patients whose disease can no longer be controlled by standard therapy and in whom parathyroidectomy is contraindicated. The Alliance believes that the recommendation could be improved if the word contraindicated was replaced by "in those patients in whom attempted parathyroidectomy is considered a last resort by the clinical team". Given the logistics of PTH measurement and the need for incremental dosing the KA would welcome an extension of the "trial period" to 4 months.	Comments noted. No action required. Wording of 1.2 regarding contraindications for parathyroidectomy discussed by Appraisal Committee and modified in FAD. The Committee concluded that cinacalcet hydrochloride should not be recommended as an alternative to surgery where surgery is possible. See FAD 1.2, 4.3.6, 4.3.7 and 4.3.8. Committee recommended a 4-month titration period. See FAD 1.2.
Amgen	Amgen welcomes the recognition by the Appraisal Committee that cinacalcet therapy adds clinical benefit in a defined segment of the dialysis population and the initial recommendation to grant access to this patient segment. However, Amgen is concerned about the validity and appropriateness of the reasons provided by the Appraisal Committee for rejecting the Amgen amended PenTAG health economic modelling. Our comments on this issue are detailed below and we request that the Appraisal Committee gives these points further consideration. Although our main area of concern is the rejection of the amended PenTAG analysis, Amgen also has concerns about the current recommendations contained in the ACD. If the existing recommendations are repeated in the FAD, then we request that the Appraisal Committee considers two specific sub-groups of patients for cinacalcet treatment.	

Consultee	Comment	Action/response
Amgen (continued)	1) Recommending cinacalcet separately in the sub-group of patients for whom the risks of having surgery outweigh the potential benefits. This subgroup of patients should be recommended independently of those with very uncontrolled PTH. 2) Recommending separately the sub-group of patients contraindicated for vitamin D where cinacalcet is their only available treatment option. These points are also detailed below and we would encourage the Appraisal Committee to give them adequate consideration to ensure patients who are most at risk of negative clinical outcomes receive cinacalcet, the only treatment available to them. **Amgen comments on the validity and appropriateness of the reasons provided by the Appraisal Committee for rejecting the amended PenTAG cost-effectiveness modelling** The Amgen response to the first ACD contained a re-working of the PenTAG cost-effectiveness analysis that incorporated a set of dosing and stopping rules (Appendix 1). This work is based entirely on the PenTAG health economic model that was accepted by the Appraisal Committee (4.3.4 2nd ACD). The epidemiological data upon which this work was based is well established and methodologically well respected and has 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 of dialysis patients based on different levels of the mineral metabolism biomarkers. Section 4.3.5 of the second ACD states two reasons for the Appraisal Committee not accepting this new analysis. First, the ACD states '*these treatment strategies were based on the thresholds set by the model and did not reflect clinically appropriate treatment goals consistent with the product's UK marketing authorisation'*. The second reason stated in the ACD for not accepting these algorithms is that '*the biochemical thresholds did not necessarily reflect the clinical effectiveness end points of relevance to patients (for example, the reduction of adverse events)'.*	4.3.5 modified in FAD

Consultee	Comment	Action/response
Amgen (continued)	Why these statements have been made and their mutual consistency is unclear to us. The SmPC for cinacalcet states '*Mimpara should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve a target parathyroid hormone (PTH) in dialysis patients of between **150-300 pg/ml** (15.9-31.8 pmol/l) in the intact PTH (iPTH) assay'* reflecting both the nature of current guidelines for treatment and the design of the pivotal trials. The proposed stopping rules are also based upon achieving a PTH level of less than **300 pg/mol**. Why does the Appraisal Committee conclude the treatment goals are inconsistent with the UK marketing authorisation? The stopping rules were generated using parameters and treatment goals integrated in the PenTAG model that was accepted by the Appraisal Committee. The approach Amgen used in creating these stopping rules was based upon this accepted PenTAG model. In recommending this approach, Amgen are behaving no differently than NICE has itself in the past, for example, in the recent work on osteoporosis to identify interventions which are cost-effective. As to biochemical thresholds not reflecting clinical end points of relevance to patients, the Committee has accepted the links between levels of biochemical markers and clinical outcomes as expressed in the PenTAG health economic model. The fact that PenTAG based its model on the link between these thresholds and the outcomes in itself testifies to the importance and relevance of this link for patient outcomes. These biochemical thresholds are important and relevant end points to patients as indicators of the severity of their disease. The Block et al epidemiological data show the link between PTH and adverse clinical outcomes. In generating the stopping rules, Amgen have merely used the evidence of those relationships, as established in the PenTAG model, in conjunction with sub-group analyses of the clinical trial data to identify patients that it is cost-effective to treat before they experience adverse clinical outcomes, including premature death. What clinical outcomes are more relevant to the concerns of patients? In light of the stopping rules, the proposed receommendations in the 2nd ACD are therefore inappropriate and would deny treatment to groups of patients whom it is clearly cost-effective to treat. In conclusion, Amgen request the Appraisal Committee reconsider the cost-effectiveness approach presented by Amgen in the response to the first ACD.	The FAD has been amended to further clarify the Committee's consideration of the proposed treatment algorithm. See FAD 4.3.5. See FAD 4.3.5. The Committee accepted the link between biochemical endpoints and clinical outcomes, but did not accept the use of a treatment strategy based on *thresholds* used for the purposes of modelling the decision problem.

Consultee	Comment	Action/response
Amgen (continued)	**Separately recommending cinacalcet in patients for whom the risks of having surgery outweigh the potential benefits. This subgroup of patients should be recommended independently of those with very uncontrolled PTH.** Usual indications for parathyroidectomy include the following: 1) therapy-resistant hypercalcaemia or hyperphosphataemia in the presence of very uncontrolled iPTH approximately eight times above the normal range (i.e. approximately > 50 pmol/L) 2) presence of biomechanical problems, e.g. fractures, avulsion of the quadriceps tendon 3) calciphylaxis (Schomig, 2000); however, individual centre practices differ and other poor-performing patient groups can be candidates for surgery. The ACD recommendation (section 1.2) restricts access to dialysis patients in whom parathyroidectomy is contraindicated only if the patient has an iPTH > 85 pmol/L. According to clinicians, the iPTH level is rarely used as a criterion to determine the eligibility of a patient to undergo parathyroidectomy. Amgen believe that the current wording is not practical and more importantly prevents patients who have no alternative treatment options to have access to cinacalcet. Therefore, Amgen suggests that this subgroup of patients is described independently of those with very uncontrolled PTH. This would also be consistent with the issues raised in 4.3.6 of the ACD where the Committee was persuaded that the benefits of cinacalcet were likely to be sufficient to recommend its use in extreme situations (e.g. refractory disease). In conclusion, Amgen request that the Appraisal Committee consider allowing patients access to cinacalcet treatment if the risks of surgery outweigh the potential benefits.	Comments noted. The Committee understood that parathyroidectomy is normally only considered for people with severe hyperparathyroidism. The clinical experts and other consultees have not commented to the effect that the PTH threshold should be lowered.

Consultee	Comment	Action/response
Amgen (continued)	**Separately recommending the sub-group of patients contraindicated for vitamin D where cinacalcet is their only available treatment option.**	
	Vitamin D analogues can be effective for suppressing PTH but it also acts on the intestine to promote intestinal absorption of Ca and P. Hence, persistent hyperphosphataemia or hypercalcaemia is often aggravated by vitamin D therapy. Both the acute clinical sequelae of hypercalcaemia (nausea, vomiting, mental confusion, shortening of the QT interval, and cardiac arrhythmias) and especially the chronic implications of long term hypercalcaemia limit the use of vitamin D in patients with hypercalcaemia. Consequently the prescribing information of all licensed vitamin D sterols (calcitriol, 1-alfacalcidol, and paricalcitriol) contain wording that contraindicates the use of vitamin D in the event of hypercalcaemia. Accordingly, treatment guidelines for the treatment of secondary hyperparathyroidism recommend that the dose of vitamin D is reduced or stopped when serum Ca is above 2.5 mmol/L (REF). In these situations patients and clinicians have no other treatment options to control PTH other than cinacalcet. Cinacalcet is the first treatment that has demonstrated its ability to reduce iPTH, Ca and P.	The comparator for this subgroup would probably be a non-calcium containing phosphate binder such as sevelamer. The cost effectiveness analysis assumed that a proportion of people with 'very uncontrolled' PTH received sevelamer (versus none in the other subgroups), however the proportion receiving vitamin D was assumed to be constant (62.7%) in all subgroups.
	In conclusion, Amgen request the Appraisal Committee consider extending the group of patients recommended for treatment to include those who are contraindicated for vitamin D.	Note that the definition of very uncontrolled hyperparathyroidism in 1.2 of the FAD includes concomitant normal or high levels of Ca^{2+}. The Committee were not persuaded that cinacalcet hydrochloride should be a treatments option in all patients in whom vitamin D was contraindicated.

Consultee	Comment	Action/response
National Kidney Federation (web comment)	The National Kidney Federation is pleased that the second set of recommendations address a number of our original worries, however we still feel that our patients are going to suffer unnecessarily unless further changes are made. Patients are at risk from their calcium and phosphate levels, not just their PTH. We know that these 3 things are the key to measuring if a patient has hyperparathyroidism and if they are likely to have problems with calcium in their arteries and muscles. Controlling calcium and phosphate is difficult, but is essential for the long term health of dialysis patients. We believe that if a patient's calcium remains too high, even after taking all the medication and sticking to diets, then surely they should be eligible for this new drug. Your latest recommendation means that patients will now have access to this new drug but only if they have a very high PTH, you seem to take no account of whether their calcium or phosphate is too high. If a patient's medication is not working and their condition is getting worse, having to wait until their PTH goes through the roof could mean that they are being put at great risk. You also say that the new drug should not be made available unless they cannot have a parathyroidectomy operation. The NKF strongly believes that such an operation is not necessary (or the best treatment) when they now have the option of a single daily tablet to control their PTH level. It should not be assumed that complicated neck surgery is an acceptable option for patients who have to undergo 3 hours of dialysis 3 times a week for the rest of their life, or until they are fortunate enough to get a transplant. If the parathyroid gland is removed and a patient then has a transplant they will face a life of uncontrollable bone disease, whereas if patients can take the new drug when their other medication no longer works (whatever their PTH or fitness for surgery) you have given their doctor the chance to control a patient's bone disease. We would ask you to think again about the restrictions that you are placing on the use of this drug. We feel that our patient members, who have a very poor quality of life on dialysis should not be subjected to extra surgery when an alternative exists. We are also not convinced that a parathyroidectomy is very effective in very many of the cases.	Note that the definition of very uncontrolled hyperparathyroidism now includes concomitant normal or high levels of Ca^{2+}

Non-consultee comments

Status	Section	Comment	Action/response
NHS professional 1	Section 1	I would strongly support your revision of the original consultation document to allow use in this difficult group of patients. I applaud NICE for their response to the initial consultation. I think this is appropriate at this stage until further information is available.	No action required
	Section 2	No further comment.	
	Section 3	No further comment	
	Section 4	I think that this is reasonable, but note if calcium is allowed to plummet on starting the drug, there may be a rebound increase in PTH. If this is unanticipated a longer time frame may be required to correct this.	
	Section 5	No further comment	
	Section 6	Agreed	
	Section 7	No further comment.	
	Section 8	I understand that it may be possible to reappraise the drug if new data become available before Dec 2009, and in this case it may be appropriate.	An early review can be requested if necessary

Status	Section	Comment	Action/response
NHS professional 2	Section 1	May I suggest that cinacalcet be allowed not only where a clear surgical contra-indication exists but also, in the frail elderly, and perhaps others, where they refuse surgery (e.g. for fear of an anaesthetic event)? It also makes no sense to me to deny cinacalcet to those who have accepted the need for parathyroid surgery and who are being worked-up for it, or maybe even on a waiting list, but who could benefit in the interim. 3-4 months treatment during such a time reduces the ravages of severe hyperparathyroidism and probably reduces calcium level instability post-operatively as well.	Comments noted. The Committee concluded that cinacalcet hydrochloride should not be recommended as an alternative to surgery where surgery is possible. See FAD 1.2, 4.3.6, 4.3.7 and 4.3.8.
NHS professional 3	Section 1 Section 4 Section 5 Section 6	A significant improvement A more balanced outcome than before The usual fudge from NICE. You know perfectly well that there will be postcode prescribing here. All true. And who will pay for and conduct these trials, pray, except Amgen ?	Comments noted