Amgen Limited
240 Cambridge Science Park
Milton Road
Cambridge
CB4 0WD
Tel: +44 (0) 1223 420305
Fax: +44 (0) 1223 423049

Alana Miller,
National Institute for Health and Clinical Excellence,
Mid City Place,
71 High Holborn,
London,
WC1V 6NA

September 7th 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 second ACD for this technology appraisal.

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.

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.

Yours sincerely,

Amgen UK

Amgen Response to Issues Raised in the 2nd ACD

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)*'.

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.

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 cinacelet treatment if the risks of surgery outweigh the potential benefits.

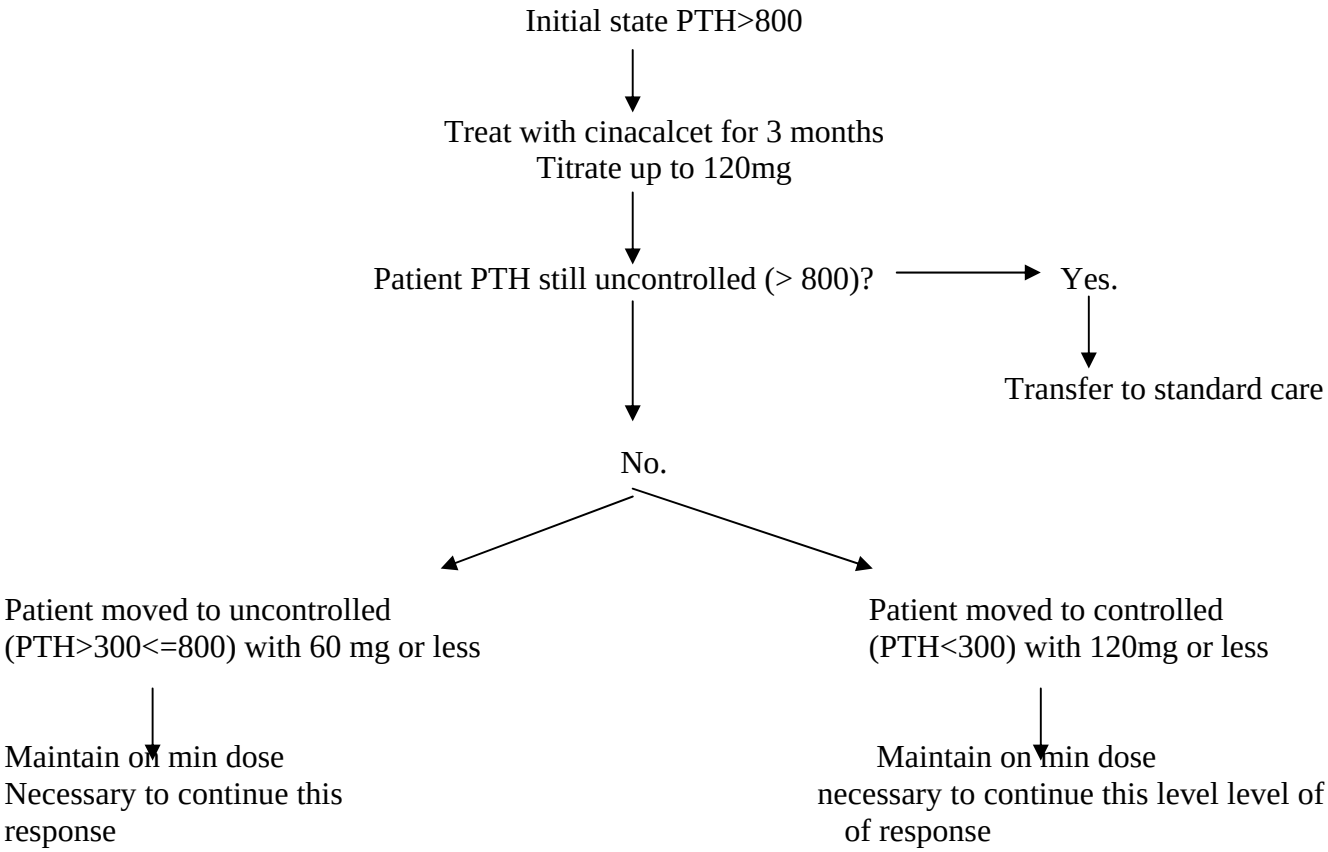
Separately recommending the sub-group of patients contraindicated for vitamin D where cinacalcet is their only available treatment option.

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 sequallae 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.

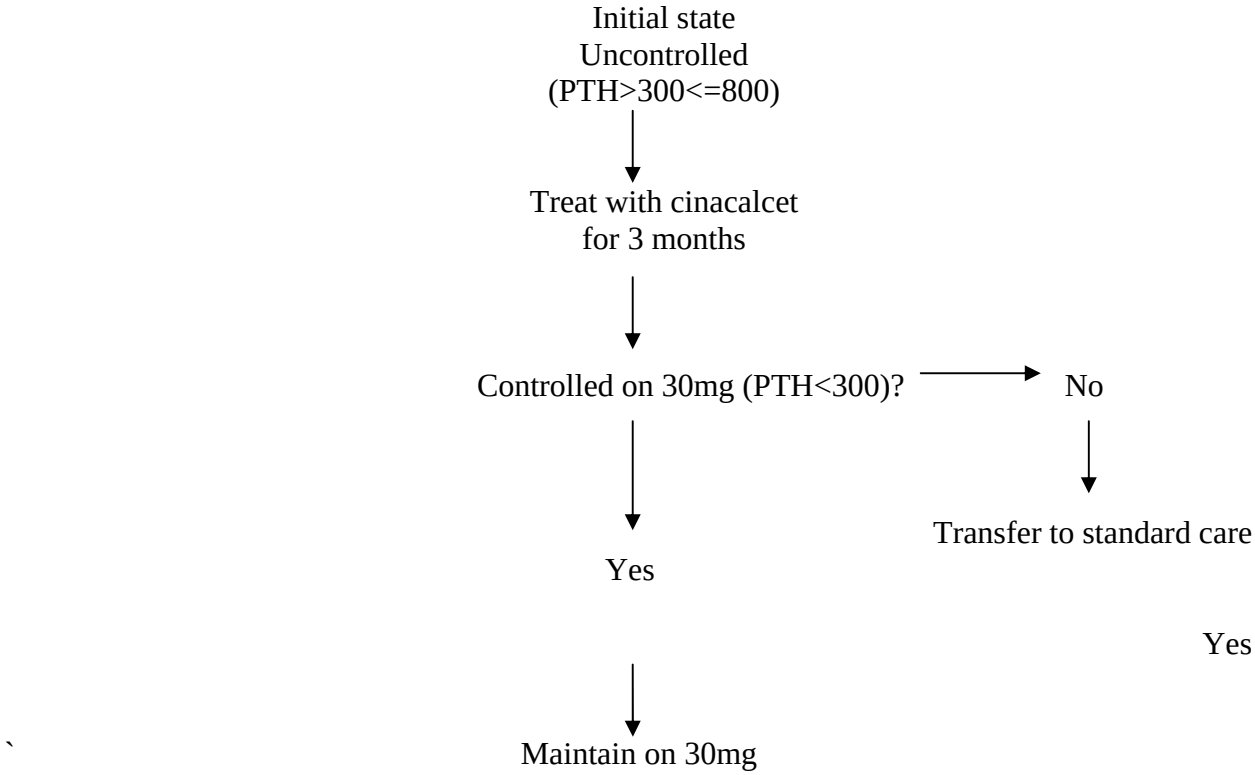
In conclusion, Amgen request the Appraisal Committee consider extending the group of patients recommended for treatment to include those who are contraindicated for vitamin D.

Appendix 1 – stopping rules in algorithmic form

Rule One



Rule 2



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