Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Final Protocol
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1. PROJECT TITLE

The Effectiveness and Cost-Effectiveness of Cinacalcet for the Treatment of Hyperparathyroidism Secondary to Impaired Renal Function

2. PROJECT TEAM

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3. Plain English Summary

This project will review the evidence for the use of cinacalcet, a new treatment for hyperparathyroidism, which is a common complication of renal failure. Hyperparathyroidism disrupts the body's biochemical balance and may result in a range of symptoms; fractures sustained without significant trauma; problems with blood vessels and the heart; and increased risk of death. The assessment report will draw together all relevant evidence on cinacalcet in a systematic review. It will also assess whether the introduction of cinacalcet is likely to represent good value for money to the NHS.

4. Decision problem

Purpose

The purpose of the report is to support the NICE Appraisal Committee in the development of Guidance for the NHS in England and Wales on the use of cinacalcet.

Cinacalcet

Cinacalcet (Mimpara®) is indicated for the treatment of secondary hyperparathyroidism in patients with enstage renal disease on maintenance dialysis therapy. It is the first of a new class of calcimimetic drugs, which acts by increasing parathyroid sensitivity to serum calcium to reduce secretion of parathyroid hormone (PTH). This, in turn, reduces serum calcium. Cinacalcet received marketing approval in October 2004.[1]

Cinacalcet is a first-in-class agent and so has no direct comparator. Vitamin D and phosphate binders are used to ameliorate the effects of increasd PTH secretion in CKD. In some cases of advanced hyperparathyroidism, where parathyroidectomy may be considered, there is interest in whether cinacalcet may obviate or delay the need for surgery. Cinacalcet is an oral preparation, with dosage titrated according to PTH response up to 180mg per day.

Hyperparathyroidism in Chronic Kidney Disease

Secondary hyperparathyroidism is common in chronic kidney disease (CKD).[2] It may develop early in CKD, at glomerular filtration rates (GFR) of less than 60 mL/min, as a response to reduced serum calcium, and progresses as renal function deteriorates. The pathogenesis of hyperparathyroidism in CKD is complex and incompletely understood. A range of factors have been implicated[3]:

- Reduced serum calcium
- Increase in plasma phosphate levels
- Decreased vitamin D activity through a range of possible effects (e.g. reductions in renal calcitriol synthesis and reserve capacity and reduced parathyroid responsiveness to calcitriol)
- Parathyroid tissue hyperplasia in response to uraemia
- Altered parathyroid sensitivity to plasma calcium

Elevated PTH levels from secondary hyperparathyroidism are seen in around 40% of patients on dialysis.[4] Very high levels of PTH may develop in uncontrolled hyperparathyroidism (>800 pg/mL), with nodular hyperplasia of the parathyroid glands. In such cases, parathyroidectomy may be considered. Around 10% of people on dialysis have such increased levels of PTH.[4]

Parathyroid stimulation in CKD has a range of clinical consequences, mediated by increased PTH synthesis and PTH-secreting cell proliferation.[2] PTH increases osteoclast activity and bone resorption, leading to high turnover bone disease, which may include the typical features of osteitis fibrosa. High turnover bone disease may be present in up to 75% of people on dialysis and results in raised serum calcium, phosphorus and calcium-phosphorus product (Ca-PP). Fracture risk may be increased[4]. Treatment with vitamin D and phosphate binding agents may result in over-suppression of PTH so that bone turnover is reduced, resulting in adynamic bone disease. This predisposes to hypercalcaemia and may also be associated with pathological fractures.

Seconday hyperparathyroidism may also be complicated by calcification at a range of sites. Of particular interest is cardiovascular calcification, possibly related to elevated calcium-phosphate product. Direct effects on the heart, resulting in left ventricular hypertrophy and dysfunction may also result from raised PTH levels. These effects account for a proportion of the increased overall and cardiovascular mortality noted in people with CKD.[5]

Symptoms of hyperparathyroidism include tiredness, malaise, muscle weakness, bone and joint pain, abdominal pain, weakness, pruritis.

The Renal Association Register has demonstrated considerable variation in serum phosphate, calcium and PTH control in the UK[6]. In particular, phosphate control is considered to be poor and wide variation in levels of PTH are noted in relation to the Renal Association recommendation that PTH concentration should be three to four times the upper limit of the assay used. The Renal Association Standard does not suggest that there is any clinical risk from over-suppression of PTH.[6]

Current management and place of cinacalcet
Prophylaxis is considered appropriate in asymptomatic patients with hyperparathyroidism as bone changes and parathyroid hyperplasia may be difficult or impossible to reverse.[2;3] National and international guidelines support the attainment of target levels for serum PTH, calcium and phosphate concentrations.[7-9] The main approaches to treatment are:

- Reduction in serum phosphate by the use of phosphate binding agents and, to a lesser extent, dietary restriction
- Reduction in PTH by supplementation of vitamin D

The optimum choice of phosphate binding agent is unclear. Aluminium containing agents (e.g. aluminium hydroxide or aluminium carbonate) may contribute to increased aluminium toxicity and are discouraged.[7] Calcium-containing binders (e.g. calcium carbonate or calcium acetate) were the mainstay of treatment until the development of concerns about associated risk of vascular calcification in people on haemodialysis.[2] Sevelamer hydrochloride is a non-calcium containing phosphate binder which also reduces serum lipid levels. It is licensed for use only in people on haemodialysis and is considerably more expensive than other phosphate binders. The Renal Association recommends that the choice of phospate binding agent should be individualised to each patient.[7]

In cases of uncontrolled secondary hyperparathyroidism, typically with nodular parathyroid hypertrophy and very high levels of PTH, parathyroidectomy may be indicated.

Cinacalcet is an additional therapeutic option in hyperparathyroidism. The extent to which the need for other treatments may be reduced is unclear.

4. Report methods for synthesis of evidence of clinical effectiveness

The assessment report will include a systematic review of the evidence for clinical effectiveness of cinacalcet. The review will be undertaken systematically following the general principles published by the NHS Centre for Reviews and Dissemination.[10] The research protocol will be updated as necessary as the research programme progresses. Any changes to the protocol will be reported to NCCHTA and NICE.

Population

Inclusion criteria:

- People on peritoneal or haemodialysis for end stage renal failure of any underlying cause with hyperparathyroidism.

Exclusion criteria:

- People with CKD not on dialysis.

Interventions

- Cinacalcet HCl in licensed doses

Comparators

- "Standard care", which may include:
  - Phosphate binders
  - Vitamin D
  - Parathyroidectomy

Outcomes

The following outcomes will be included in the systematic review if reported in available primary studies.

- Mortality
- Incidence of cardiovascular events
- Incidence of fractures
- Health related quality of life
- Symptoms related to hyperparathyroidism
- Serum PTH, calcium, phosphate and calcium x phosphate product levels
- Parathyroidectomy
- Hospitalisation

Search Strategy and Inclusion Criteria

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with manufacturers of cinacalcet through the NICE
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

Databases:

Electronic databases: including MEDLINE (Silver Platter); PubMed (previous 6 months for latest publications); EMBASE; The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, NHS EED and HTA databases; NRR (National Research Register); Web of Science Proceedings; Current Controlled Trials; Clinical Trials.gov; FDA website; EMEA website.

Inclusion:
For the review of clinical effectiveness, only RCTs will be included. This criteria will be relaxed for consideration of adverse events, for which observational studies may be included.

Titles and abstracts will be examined for inclusion by two reviewers independently. Disagreement will be resolved by consensus.

Exclusion
- Non-randomised studies (except for adverse events)
- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Non-English language papers
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality

Data extraction strategy
Data will be extracted by one researcher and checked by another.

Quality assessment
Consideration of study quality will include the following factors:

Trial characteristics:
1. Timing, duration and location of the study
2. Method of randomisation
3. Allocation concealment
4. Blinding
5. Numbers of participants randomized, excluded and lost to follow up.
6. Whether intent to treat analysis is performed
7. Methods for handling missing data
8. Appropriateness of statistical analysis

Study participants:
1. Baseline characteristics: age, sex, cause of ESRD, baseline laboratory values, use of phosphate binders and vitamin D
2. Inclusion criteria
3. Exclusion criteria

Methods of analysis/ synthesis
Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses.

Meta-analysis will be carried out using fixed and random effects models, using STATA software. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

5. Report methods for synthesising evidence of cost-effectiveness

The sources detailed in section 4 will be used to identify studies of the cost effectiveness of cinacalcet. Stand alone cost analyses based in the UK NHS will also be sought. We consider it very unlikely that cost effectiveness analyses will have been published in the scientific literature at this early point in the diffusion of cinacalcet. Contact with the manufacturers of cinacalcet, and other agencies (e.g. INAHTA) are more likely to identify relevant evaluations.

Available cost effectiveness analyses will be critically appraised using the frameworks established by the Consensus on Health Economic Criteria[11] and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[12]

In addition, a new economic evaluation will be carried out from the perspective of the UK NHS using a decision analytic modelling approach. Model structure will be determined in consultation with clinical experts and will include the longer term consequences of hyperparathyroidism (fractures, cardiovascular events and mortality), if appropriate data are available. Further literature searches will be carried out to identify studies which relate serum PTH and biochemistry to these longer term outcomes. As the evidence base for long term use of cinacalcet is extremely limited, a range of assumptions will be made regarding sustained effectiveness. If possible, impact on the need for parathyroidectomy will be included.

Resource use will be specified and valued from the perspective of the NHS in 2004. Cost data will be extracted from published work, NHS reference costs and sponsor submissions to NICE as appropriate. If insufficient data are retrieved from published sources, costs may be derived from individual NHS Trusts or groups of Trusts. Costs will be discounted at 3.5%.[13]

Health related quality of life will be incorporated by the application of preference weights (utility) to disease states. Utility values will be sought using the sources detailed in section 4. Outcomes will be discounted at 3.5%.[13]

The evaluation will be constrained by available evidence. If possible, the incremental cost effectiveness of cinacalcet will be estimated in terms of:

- cost to achieve normalisation of PTH
- cost per event avoided (fracture, cardiovascular event)
- cost per life year gained
- cost per QALY.

Analysis of uncertainty will focus on cost utility, assuming cost per QALY can be estimated. Uncertainty will be explored through one way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented using plots on the cost effectiveness plane and cost effectiveness acceptability curves.

6. Handling the company submission(s)

Information provided by sponsors will be included in the report if, in the judgement of the assessment group, it meets relevant inclusion criteria.

A critique of any economic evaluations, including models, submitted by industry will be carried out using the frameworks established by the Consensus on Health Economic Criteria[11] and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[14]

Any data designated as "commercial in confidence" or "academic in confidence" in sponsor submissions and incorporated in the assessment report will be highlighted and the source identified.

7. Competing interests of authors

Dr Richard D'Souza received an honorarium from Amgen in 2004 for making a presentation to clinical nephrology staff in Devon on secondary hyperparathyroidism and its management.

Reference List

(1) UK Medicines Information. New Medicines Profile: Cinacalcet. 05/06. 2005. Liverpool, UK Medicines Information Service.
Ref Type: Report

(2) Joint Specialty Committee on Renal Disease. Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral of Adults. 2005. London, The Renal Association & Royal College of Physicians.
Ref Type: Report

(3) Davison A, Cameron JS, Grunfeld J-P, Ponticelli C, Ritz E, Winearls C et al. The Oxford Textbook of Clinical Nephrology. 3rd ed. Oxford: OUP; 2005.

(4) de Francisco ALM. Secondary hyperparathyroidism: Review of the disease and its treatment. Clinical Therapeutics 2004; 26(12):1976-1993.

(5) Foley.RN, Parfrey P. Cardiovascular disease and mortality in ESRD. Journal of Nephrology 1998; 11(5):239-245.

(6) Ansell D, Feest T, Byrne C, Ahad A. UK Renal Registry: Sixth Annual Report. Bristol: The Renal Association; 2003.

(7) Renal Association. Treatment of Adults and Children with Renal Failure: Standards and Audit Measures. 2002. London, Royal College of Physicians of London and the Renal Association.
Ref Type: Report

(8) European Best Practice Guidelines for Haemodialysis. Nephrol Dial Transpl 2002; 17(supp 7):1-111.

(9) Eknoyan G, Levin A, Levin N. Bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003; 42(4 suppl 3):1-201.

(10) NHS Centre for Reviews and Dissemination. Undertaking Systematic Reviews of Research on Effectiveness. 2nd ed. York: NHS Centre for Reviews and Dissemination; 2001.

(11) Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. International Journal of Technology Assessment in Health Care 2005; 21(2):240-254.

(12) Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. Value Health 2003; 6(1):9-17.

(13) National Institute for Clinical Excellence. Guide to the Methods of Technology Appraisal. 2003. London, National Institute for Clinical Excellence.

(14) Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. Value Health 2003; 6(1):9-17.