The cost-utility of cinacalcet in addition to standard care compared to standard care alone for secondary hyperparathyroidism in end-stage renal disease: a UK perspective


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined the addition of cinacalcet to standard treatment with phosphate binders and vitamin D for the treatment of secondary hyperparathyroidism (SHPT) in patients with end-stage renal disease (ESRD). Cinacalcet was compared to standard treatment with phosphate binders and vitamin D alone. The analysis was based on an average dose of 81.6 mg/day cinacalcet during the titration phase (3 months) and a dose of 94.4 mg/day during the maintenance phase.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis and cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with SHPT, defined as a parathyroid hormone (PTH) level of more than 32 pmol/L (>300 pg/mL).

Setting
The setting was secondary care. The economic study was carried out in the UK.

Dates to which data relate
Most of the clinical estimates came from studies published between 1994 and 2007. Resource use for some items was based on studies published in 2004 and 2005. The costs were estimated using 2004 and 2005 prices.

Source of effectiveness data
The clinical and epidemiological data used in the decision model were:

the effectiveness of cinacalcet (estimated as percentage of patients with "controlled", "uncontrolled" or "very uncontrolled" PHT levels for cinacalcet compared with no cinacalcet),

the mortality rates (from cardiovascular disease, other causes, and perioperative mortality following parathyroidectomy),

the relative risk reduction of mortality associated with cinacalcet, and

the rates of parathyroidectomy, fractures and cardiovascular disease.
Modelling
A Markov model was constructed to simulate the clinical and economic impact of the two strategies under examination in a hypothetical cohort of SHPT patients. The starting age of the typical patient was 55 years. Patients were followed until death, thus simulating a lifetime horizon. Three-month cycles were used. Extensive information on health states and transition patterns was provided. The structure of the model was presented in the appendix. Data and statistical distributions used to populate the Markov model were also reported in the appendix.

Sources searched to identify primary studies
Cinacalcet effectiveness (compared with no cinacalcet) was derived from a published systematic review of cinacalcet trials by the same authors as those of the current study. These estimates were supplemented with data from the UK Renal Registry. Annual mortality rates were also obtained from the UK Renal Registry. Other estimates of event rates for cardiovascular disease, fractures and parathyroidectomy were derived from cohort studies or expert opinion, the details being reported in the appendix.

Methods used to judge relevance and validity, and for extracting data
Clinical data were derived from systematic reviews of published studies, augmented by expert opinion. Little information on the methods and conduct of the review was provided in the paper, although it was stated that more details could be obtained from the authors, if needed.

Measure of benefits used in the economic analysis
The main summary benefit measure used in the economic evaluation was the quality-adjusted life-years (QALYs). These were estimated using the modelling approach. The QALYs were calculated by combining the expected survival and utility weights. The latter estimates were not available from the literature for patients with SHPT, thus the authors used values derived from other populations and estimated utility decrements due to “uncontrolled” PHT (also on the basis of expert opinion). Details on all studies and populations used to associate utility weights with the various health states were given in the appendix. The benefits were discounted at an annual rate of 3.5%. Other model outputs, such as proportions of patients experiencing major fractures, cardiovascular events, parathyroidectomy cases and surgical mortality, were also reported and were combined with the costs.

Direct costs
The analysis of the costs was performed from the perspective of the UK National Health Service. It included the costs of cinacalcet, standard care (vitamin D supplements and phosphate binders), hospital services associated with the treatment of cardiovascular-related adverse events, major and minor fractures, parathyroidectomy and blood tests for biochemical serum levels. Dialysis costs were not included in the base-case analysis. The unit costs and the quantities of resources used were presented separately for some items (data presented in the appendix). Resource use was estimated mainly on the basis of expert opinion and some published studies. The costs were based on national cost data (Reference Costs database and British National Formulary). Since the costs were incurred over a long time, discounting was relevant and an annual rate of 3.5% was applied. With the exception of drug costs, which were priced using 2005 values, the price year was 2004.

Statistical analysis of costs
The costs and quantities were treated deterministically in the base-case analysis.

Indirect Costs
Productivity costs were not included.

Currency
UK pounds sterling (£). Cost-utility ratios were converted into euros (EUR) at the rate of 1.00 = EUR 1.44.
Sensitivity analysis
A deterministic, univariate sensitivity analysis was carried out on all costs, quantities, clinical inputs and utility values in order to assess the robustness of the model results. Alternative values were either based on published data or defined by the authors. Dialysis costs were included in the sensitivity analysis. Sub-group analyses were also conducted. An extensive probabilistic sensitivity analysis was also performed, using a Monte Carlo simulation and attributing probabilistic distributions to all inputs, in order to generate cost-effectiveness acceptability curves. The types of distributions were reported in the appendix.

Estimated benefits used in the economic analysis
The discounted QALYs were 3.04 with standard care alone and 3.39 with cinacalcet added to standard care. The difference was 0.34 in favour of cinacalcet added to standard care.

The addition of cinacalcet reduced the number of major fractures by 0.4%, cardiovascular events by 4.3%, the number of parathyroidectomies by 14.7% and surgical mortality by 0.4%.

The median survival with cinacalcet increased from 4.5 years to 5 years.

Cost results
When dialysis costs were excluded, the total costs per patient were 6,533 with standard care alone and 27,700 with cinacalcet added to standard care (difference 21,167).

When dialysis costs were included, the total costs per patient were 81,523 with standard care alone and 106,946 with cinacalcet added to standard care (difference 25,423).

Synthesis of costs and benefits
Incremental cost-utility ratios and cost-effectiveness ratios were calculated in order to combine the costs and benefits of the two strategies.

The incremental cost per QALY gained with cinacalcet added to standard care over standard care alone was 61,890 when dialysis costs were excluded (approximately EUR 89,000) and 74,334 when they were included.

The incremental cost of treating enough people with cinacalcet added to standard care in order to avoid a cardiovascular event was around 490,000 (EUR 705,600). The incremental cost of avoiding a major fracture was 5,290,000 (EUR 7,617,600), and of avoiding a parathyroidectomy 140,000 (EUR 201,600).

The deterministic sensitivity analysis showed that the model results were sensitive to variations in a number of parameters. However, the incremental cost per QALY gained with cinacalcet was below the commonly cited threshold of 30,000 per QALY (EUR 43,200) in the two scenarios studied: when the cost of cinacalcet was reduced from 0.145/mg to 0.08/mg, or if the relative risk of mortality for patients with "very uncontrolled" PTH levels was more than double that of those with "controlled" PTH levels (2.2 compared with 1.824 in the base-case).

The probabilistic sensitivity analysis suggested that the probability of cinacalcet being cost-effective at a threshold of 30,000 was 0.5%. The cost-effectiveness acceptability curve showed that cinacalcet was unlikely to be the most cost-effective strategy below a threshold of about 62,000 (EUR 89,000).

Further sub-group analyses in patients with different degrees of SHPT, or when stopping rules were employed, did not alter the basic conclusion of the analysis. This suggests that cinacalcet was not cost-effective when using standard cost-effectiveness thresholds.

Authors’ conclusions
Cinacalcet was unlikely to be considered a cost-effective alternative to conventional care with phosphate binders and
vitamin D in patients with secondary hyperparathyroidism (SHTP), unless the costs of cinacalcet were considerably reduced.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparator (i.e. treatment with phosphate binders and vitamin D) was appropriate as it represented the conventional treatment for patients with SHPT in the authors' context. Cinacalcet represents the first of a new class of calcimimetic drugs. You should decide whether this is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
Clinical data were identified through different reviews of the literature, details of which were not presented. The authors stated that more information could be obtained on request. One of the reviews on the clinical effectiveness of cinacalcet included randomised clinical trials, which should ensure the robustness of the clinical estimates. Furthermore, the use of systematic reviews should ensure that all the available evidence was employed in the model. When published estimates were not available, the authors used expert opinion or data from similar populations of patients. Given the uncertainty surrounding some estimates, extensive sensitivity analyses were carried out on all clinical inputs.

**Validity of estimate of measure of benefit**
The primary benefit measure (QALYs) was modelled using the Markov model. Benefits were discounted at the recommended rate. The approach used to estimate the utility weights was fully explained and data were satisfactorily presented in the appendix. Other benefit measures were also used in the cost-effectiveness analysis, although it would be more difficult to compare these results with the benefits of other health care interventions.

**Validity of estimate of costs**
The analysis of the costs appears to have been consistent with the perspective of the analysis. A breakdown of cost items was reported for some items but most costs were presented as macro-categories. The sources of the costs were reported; these represented typical sources for costs in the UK. Statistical analyses were performed and the impact of variations in key cost estimates was fully explored in the sensitivity analysis. The reference prices for costs were reported, which will help when reflating the results of the analysis in other time periods.

**Other issues**
The authors did not make extensive comparisons of their findings with those from other studies. They also did not explicitly address the issue of generalisability of the study results. However, extensive sensitivity analyses were conducted, thus enhancing the external validity of the study. The authors presented their results in full and provided a cost-effectiveness plane and a cost-effectiveness acceptability curve. It was noted that a major limitation of the study was the use of some assumptions, owing to the lack of published data. Furthermore, the model was based on cinacalcet trial populations with an average age of 55 years, while the mean age of patients accepting renal replacement therapy in the UK is usually 65 years. This could have biased the results of the analysis as it was unclear whether the effectiveness of cinacalcet depended on age.

**Implications of the study**
The study results do not support the use of cinacalcet in addition to standard care for the treatment of SHPT.

**Source of funding**
Funded by the UK NHS Health Technology Assessment Programme.

**Bibliographic details**
Other publications of related interest

Because readers are likely to encounter and assess individual publications, NHS EED abstracts reflect the original publication as it is written, as a stand-alone paper. Where NHS EED abstractors are able to identify positively that a publication is significantly linked to or informed by other publications, these will be referenced in the text of the abstract and their bibliographic details recorded here for information.


Indexing Status

Subject indexing assigned by NLM

MeSH

Cinacalcet Hydrochloride; Cost-Benefit Analysis; Diet Therapy /economics /methods; Drug Costs; Great Britain; Humans; Hyperparathyroidism, Secondary /economics /etiology /therapy; Kidney Failure, Chronic /complications; Markov Chains; Middle Aged; Naphthalenes /economics /therapeutic use; Parathyroid Hormone /metabolism; Phosphate-Binding Proteins /economics /therapeutic use; Quality-Adjusted Life Years; Vitamin D /economics /therapeutic use

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