Scottish Medicines Consortium

cinacalcet 30mg, 60mg and 90mg tablets (Mimpara®) No. (169/05)
Amgen Ltd

10 March 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

Cinacalcet (Mimpara®) is not recommended for use within NHS Scotland for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy.

Addition of cinacalcet to standard treatment with phosphate binders and/or vitamin D sterols reduced serum concentrations of parathyroid hormone and was associated with a reduced risk of fractures compared to standard treatment. However, the economic case was not demonstrated.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Treatment of secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy. It may be used as part of a therapeutic regimen including phosphate binders and/or vitamin D sterols, as appropriate.

Dosing information

30mg to 180mg once daily titrated to achieve a parathyroid hormone (PTH) serum concentration of 150 to 300 pg/ml (15.9 to 31.8 pmol/L) in the intact PTH assay.

UK launch date

April 2005

Comparators

Phosphate binders and vitamin D (calcitriol and alfacalcidol) are also used to treat metabolic disturbances associated with secondary hyperparathyroidism in end-stage renal disease. Phosphate binders include calcium- and aluminium-containing compounds and sevelamer. Cinacalcet is indicated in addition to these, not as an alternative. The proportions of patients who decreased (and who increased) their doses of phosphate binders and vitamin D during the trials described below were similar in the cinacalcet- and placebo-treated groups.

Parathyroidectomy is the current treatment for secondary hyperparathyroidism not controlled by phosphate binders and vitamin D. It is estimated that approximately 40 patients with hyperparathyroidism secondary to renal disease undergo parathyroidectomy in Scotland each year.

Cost of relevant comparators

	Daily dose range	Annual cost (£)
Cinacalcet (Mimpara^{O})	**30 - 180mg**	**1646 - 9110**
Sevelamer (Renagel®)	2.4 - 12g	747 - 3734
Calcium carbonate (Calcichew Forte®)	3 tablets	240
Calcium acetate (Phosex®)	3 - 12 tablets	120 - 482
Calcium carbonate (Calcichew®)	3 - 6 tablets	102 - 204
Calcium carbonate (Adcal®)	3 - 6 tablets	79 - 159
Calcitriol (Rocaltrol®)	0.25 - 1mcg	70 - 250
Aluminium hydroxide (Alu-Cap®)	4 - 20 capsules	46 - 228
Alfacalcidol (One Alpha®)	0.25 - 1mcg	41 - 106

Costs from eVadis accessed on 13th December 2005

Summary of evidence on comparative efficacy

Cinacalcet increases the sensitivity of calcium sensing cells in the parathyroid gland, which regulate secretion of parathyroid hormone (PTH), and thereby reduces PTH secretion.

Three double-blind six-month studies recruited 410, 331 and 395 adults who had secondary hyperparathyroidism, intact PTH (iPTH) ≥300 pg/ml and corrected calcium ≥8.4 mg/dL while receiving stable doses of any phosphate binders and/or vitamin D sterols for ≥30days. The first two included patients on haemodialysis for ≥3months, restricting the study population with iPTH >800 pg/ml to ≤20%. The third study recruited 88% and 12% of patients receiving haemodialysis and peritoneal dialysis, respectively. Patients were randomised to placebo or cinacalcet in a 1:1 ratio in the first two studies and in a 1:3 ratio in the third study with stratifications for baseline iPTH level in all studies and for baseline calcium x phosphate (Ca x P) product in the first two studies and type of dialysis in the third study. Cinacalcet was titrated from 30mg to 60mg, 90mg, 120mg then 180mg once daily every 3 weeks in the first two studies and every 4 weeks in the third study if iPTH was >200 pg/ml, calcium was ≥7.8 mg/dL, symptoms of hypocalcaemia were not present and adverse events did not preclude an increase in dose. The remainder of the time comprised the efficacy-assessment period, during which doses could also be adjusted. The primary endpoint, proportion of the intention-to-treat (ITT) population achieving a mean iPTH ≤250pg/ml during the efficacy-assessment phase was significantly greater with cinacalcet compared to placebo in the respective studies: 41% vs. 4%; 46% vs. 7%; and 35% vs. 6%. There were also significant differences between cinacalcet and placebo for the proportion of patients with a reduction in mean iPTH of at least 30% in the respective studies: 61% vs. 11%; 68% vs. 12%; and 59% vs. 10%, and for other secondary outcomes including mean percent reduction from baseline of serum calcium, phosphate and Ca x P product. On completion of the first two trials, 266 patients continued double-blind cinacalcet or placebo in a six-month extension study, with 54% and 13%, respectively, achieving mean iPTH ≤250pg/ml.

Data from 1184 patients treated in a phase 2 study or the three trials described previously, including the extension study, were analysed via Cox proportional hazard models of time to event, with analysis of hospitalisations performed via the Andersen-Gill method, which treats second events as independent of first events. These indicated that relative risks of fracture, parathyroidectomy and hospitalisation due to cardiovascular disease were significantly reduced with cinacalcet compared to placebo, with hazard ratios (95% confidence intervals) of 0.46 (0.22, 0.95; p=0.04), 0.07 (0.01, 0.55; p=0.009) and 0.61 (0.43, 0.86; p=0.005), respectively. The analyses were not powered to demonstrate differences between the groups in mortality or hospitalisation for any cause and none were found, with hazard ratios for cinacalcet to placebo for these outcomes of 0.81 and 1.03, respectively.

In pooled quality of life data from the three trials described previously there were significant improvements with cinacalcet compared to placebo for the short form 36 (SF-36) composite physical score and bodily pain and general health domains, all scored on 100-point scales. There were mean improvements in the respective outcomes of 0.5, 0.6 and 0.2 points from baseline to endpoint with cinacalcet compared to mean deteriorations of 0.8, 1.0 and 1.0 points, respectively, with placebo. There were no significant differences between cinacalcet and placebo for the other SF-36 domains or the kidney disease quality of life instrument cognitive functioning scale (KDQOL-CF).

Summary of evidence on comparative safety

In pooled data from the three studies described previously, adverse effects considered by the investigator to be treatment related that occurred more often with cinacalcet compared with placebo include nausea (31% vs. 19%), vomiting (27% vs. 15%), hypocalcaemia (4.1% vs. 1.3%) and symptoms possibly due to hypocalcaemia: asthenia (6.7% vs. 3.6%), paraesthesia (3.8% vs. 1.1%) and convulsions (1.2% vs. 0.4%). Other adverse events possibly related to cinacalcet include dizziness, myalgia, anorexia and rash.

Summary of clinical effectiveness issues

In the trials described previously, the proportions of cinacalcet-treated patients achieving the primary outcome, mean iPTH <250 pg/ml, were lower in the subgroups with higher baseline iPTH. Pooled data from the two haemodialysis studies indicate that 58%, 42% and 12% of cinacalcet-treated patients with baseline iPTH 300-500pg/ml, 500-800pg/ml and >800pg/ml, respectively, achieved this outcome, with figures for haemodialysis patients in the third study of 65%, 39% and 10%, respectively. Similar pooled data from all three studies indicate that 81%, 60% and 22% of cinacalcet-treated patients in the respective iPTH subgroups achieved the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (NKF-K/DOQI) iPTH target of ≤300 pg/ml, with 59%, 42% and 18% of patients, respectively, achieving K/DOQI targets for both iPTH and Ca x P product. In practice, many patients with higher elevations of iPTH may not expect to achieve target levels of iPTH with cinacalcet, although some could expect to achieve at least a 30% reduction in iPTH. Pooled data from the two haemodialysis trials indicate that 62%, 69% and 63% of cinacalcet-treated patients in the respective iPTH subgroups had reductions in mean iPTH of at least 30%, with corresponding figures for haemodialysis patients in the third study of 65%, 63% and 51%, respectively. The clinical benefits associated with reductions in iPTH of at least 30% are difficult to estimate. In these trials the significant mean placebo-corrected improvements in quality of life outcomes (SF-36 composite physical score, bodily pain and general health) with cinacalcet were less than 2 points on 100-point scales. The clinical significance of these is unknown.

In the trials described previously, there was no requirement for patients to be optimally treated with phosphate binders and vitamin D for inclusion. In each study >90% of patients were taking a phosphate binder at baseline and about two thirds of patients were taking vitamin D. Also, the two trials, which recruited only haemodialysis patients, limited the study population with iPTH >800 pg/ml to less than 20%. It is possible that the study populations may differ from Scottish patients who would receive cinacalcet in practice.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing standard care, (vitamin D and phosphate binders) to standard care plus cinacalcet. The methodology used a Markov model with 31 6-month cycles of over a patient lifetime of 15.5 years. Patients with uncontrolled mineral metabolism start the model without complications; during each 6-month cycle they are exposed to a risk of cardiovascular events, fracture, parathyroidectomy due to refractory secondary hyperparathyroidism and death. Events incur hospitalisation costs and loss in quality of life.

Baseline clinical event rates came from a pooled analysis of cinacalcet trials and registry data (mortality only); effectiveness data came from the same pooled analyses. Costs came from Department of Health reference costs. Of note the estimated cost of a parathyroidectomy was about £2,000. Utility values were obtained from a literature search and were 0.68 for ESRD, with a reduction of 0.09 for a fracture or a cardiovascular event. Such reductions were applied to the patient's lifetime and were additive.

The results were:

- All patients, Incremental cost effectiveness ratio (ICER) of £35,600/QALY
- Mild to moderately elevated iPTH (300-800 pg/ml), ICER of £30,400/ QALY
- Severely elevated iPTH >800 pg/ml, ICER of £48,300/QALY

Considerable sensitivity analysis was performed showing that the result was most sensitive to the assumed drug use during the maintenance phase and the utility of end-stage renal disease.

The strengths of the submission included the complexity of the modelling, good use of costs and utility values that should, in the main, generalise to Scotland and robust statistical analysis and methodology. Shortcomings include:

- no dropouts assumed although a 15% rate was observed in trials in the active group,
- uncertainty as to whether the trial population was representative of the Scottish population with this condition (the trial population seems to have significantly fewer patients under 60 years old compared to Scottish practice):
- Uncertainty about whether the dose used in the model is consistent with the doses in the trials as it could be higher in practice than the model

In conclusion cinacalcet is not judged to be cost effective for the management of patients with severe secondary hyperparathyroidism (cost/QALY of £48,300) or in patients with mild to moderate SHPT.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The manufacturer estimated that in 2005 there were about 1,900 new dialysis patients with secondary hyperparathyroidism and this is forecast to rise to over 2,000 in 2010. Of these, 34% are estimated to fail to reach a target level of 300 pg/ml and would thus be eligible for cinacalcet. The budget impact assumes an uptake of 15% and 30%, equivalent to between 100 and 200 patients per annum.

The estimated drug costs for 2006 vary between an additional £0.3m and £1.0m depending on patient numbers and drug doses. Patient numbers are forecast to rise by about 1% per annum.

Guidelines and protocols

The third edition (August 2002) of the Renal Association's Treatment of adults and children with renal failure standards and audit measures notes that a PTH concentration over four times the upper limit of normal is associated with an increased risk of significant bone disease and that this should therefore be avoided by medical (or if necessary surgical) treatment. It is recommended that PTH levels should be maintained below this for patients who have been on haemodialysis or peritoneal dialysis for more than three months. It is also noted that normal bone turnover is associated with a PTH concentration three times normal in dialysis patients, with some recommending that PTH should be maintained at three to four times the upper limit of the non-renal normal range in order to ensure normal bone turnover. Low bone turnover is associated with hypercalcaemia and, possibly, an increased risk of fracture and vascular calcification. Whereas raised PTH concentration may be responsible for increased cardiac calcium content, vascular calcification and insulin resistance with secondary hyperparathyroidism. The relative importance of hyperparathyroidism as a risk factor for premature vascular disease in renal failure is difficult to determine and in the absence of firm evidence, individual clinicians should decide on the degree to which it should be corrected, and on how this should be achieved.

The NKF-K/DOQI guidelines recommend a target range for iPTH in dialysis patients of 100-300 pg/ml and advise that parathyroidectomy should be recommended for patients with severe hyperparathyroidism (persistent serum levels of iPTH >800 pg/ml) associated with hypercalcaemia and/or hyperphosphataemia that are refractory to medical therapy.

The National Institute of Health and Clinical Excellence (NICE) are conducting a multiple technology appraisal of cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy that is scheduled for publication in December 2006.

Additional information

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 8th April 2005 that cinacalcet (Mimpara®) is not recommended for use within NHS Scotland for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy. Addition of cinacalcet to standard treatment with phosphate binders and/or vitamin D sterols reduced serum concentrations of parathyroid hormone and was associated with a reduced risk of fracture compared to standard treatment. However the economic case was not demonstrated. The licence holder has indicated their decision to resubmit.

In addition to the indication under review, cinacalcet received marketing authorisation on the same date for another indication: reduction of hypercalcaemia in patients with parathyroid carcinoma. SMC has not yet received a submission for this indication.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 21 February 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The under noted references were supplied with the submission.

Block GA, Martin KJ, De Francisco ALM et al. Cinacalcet for secondary hyperparathyroidism in patients receiving haemodialysis. New Eng J Med 2004; 350: 1516-25

Cunningham J, Danese M, Olson K et al. Effects of the calcimimetic cincaclcet HCL on cardiovascular disease, fracture and health-related quality of life in secondary hyperparathyroidism. Kidney International 2005; 68: 1793-1800.

Moe SM, Chertow GM, Coburn JW et al. Achieving NKF-K/DOQI bone metabolism and disease treatment goals with cinacalcet HCL. Kidney International 2005; 67: 760-771