

Cinacalcet

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

- Cinacalcet is an oral calcimimetic indicated for the treatment of secondary hyperparathyroidism (HPT) in patients on dialysis with end-stage renal disease (ESRD), and in patients with parathyroid carcinoma to reduce hypercalcaemia.
- Three key phase III studies have investigated the use of cinacalcet in patients with ESRD on dialysis. A pooled analysis of two of these studies involving 741 patients reported that 43% of patients on cinacalcet achieved the primary endpoint of a mean parathyroid hormone (PTH) level <250pg/ml compared to 5% of those on placebo (p<0.001). The effects of cinacalcet were consistent across a range of subgroups and independent of vitamin D dosage.
- Several unpublished studies have investigated the use of cinacalcet for parathyroid carcinoma. The largest of these, which included 78 patients with primary HPT, reported cinacalcet to be more effective than placebo in reducing serum calcium levels to within the normal range, with concurrent significant reductions in PTH levels.
- The most common adverse effects associated with cinacalcet are nausea and vomiting; these are usually transient and of mild to moderate severity but lead to discontinuation of therapy in some patients.
- The use of cinacalcet represents a potentially important therapeutic development in the treatment of these two groups of patients. However, efficacy has generally been assessed on surrogate markers of disease. A retrospective analysis showed significant reductions in parathyroidectomy and fractures in patients treated with cinacalcet compared to placebo, but these results need to be confirmed in larger, prospective studies.

Introduction

Secondary hyperparathyroidism (HPT) is a common and serious complication of chronic renal disease. The disorder is characterised by persistently elevated levels of parathyroid hormone (PTH), disturbances in calcium and phosphate metabolism and an increase in calcium x phosphorus (Ca x Ph) product. The primary consequence of secondary HPT is the development of renal osteodystrophy; it is also associated with bone pain and fracture, soft tissue and vascular calcification and cardiovascular complications.¹

Current pharmacological therapy for secondary HPT involves the use of phosphate binders (such as aluminium hydroxide, sevelamer or calcium carbonate) and vitamin D or its analogues. These alter levels of PTH, calcium and phosphate without acting directly on the parathyroid gland.¹

Cinacalcet is the first of a new class of drugs, the calcimimetics, which act by increasing the sensitivity of calcium-sensing receptors in the parathyroid gland. In humans this results in a dose-dependent reduction of serum PTH levels and subsequent reduction of serum calcium levels.¹

Cinacalcet has recently been licensed for the treatment of secondary HPT in patients with end-stage renal disease (ESRD) who are on dialysis. It has also gained approval for the reduction of hypercalcaemia in patients with parathyroid carcinoma, a rare cause of primary HPT that causes significant elevations in serum calcium.

Evidence

Secondary HPT:

Three key phase III international, multicentre, randomised, double-blind, placebo-controlled trials of six months' duration have examined the efficacy of cinacalcet in the treatment of patients with secondary HPT on dialysis for ESRD. The protocol for two of these trials was identical and the pooled results have been published and are detailed below.

The two trials enrolled 741 patients receiving haemodialysis three times a week, phosphate binders and/or vitamin D sterols as indicated. The

Brand Name (Manufacturer): Mimpara (Amgen)

BNF Therapeutic Class: 6: Endocrine system

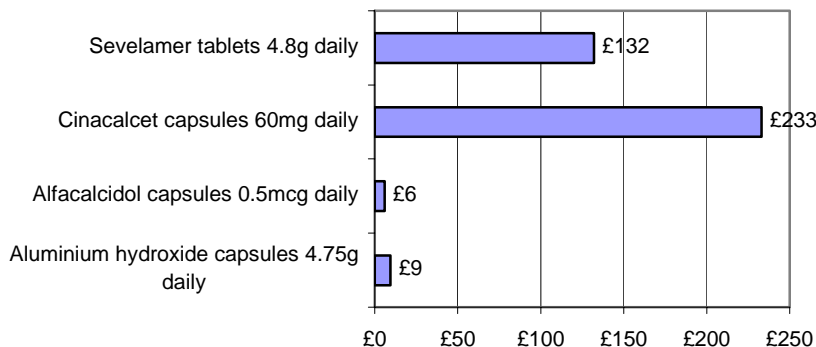
Licensed Indications: The treatment of secondary hyperparathyroidism in patients with end-stage renal failure on maintenance dialysis therapy and for the reduction of hypercalcaemia in patients with parathyroid carcinoma.

Dosage and Administration: For secondary hyperparathyroidism the recommended starting dose is 30mg once daily, titrated every two to four weeks to a maximum of 180mg once daily to achieve a target PTH level of 150-300pg/ml.

For the reduction of hypercalcaemia in patients with parathyroid carcinoma the recommended starting dose is 30mg twice daily, titrated through sequential dose increases to 90mg three or four times daily.

Marketed: January 2005

Cost Comparisons: Cost for 28 days' treatment MIMS February 2005 (Cinacalcet is given with standard therapy resulting in an additional cost)



N.B. Doses shown are for general comparison and do not imply therapeutic equivalence

primary eligibility criterion was a mean plasma PTH level ≥ 300 pg/ml.² Subjects were randomised to daily cinacalcet 30mg or placebo. Over the 12-week titration phase, doses of cinacalcet were increased every three weeks by 30mg to a maximum of 180mg daily. Subjects were followed for a further 14 weeks (efficacy assessment phase). The primary outcome measure was the proportion of patients who had a mean PTH level ≤ 250 pg/ml.

160 patients in the cinacalcet group achieved the primary endpoint compared to 19 in the placebo group (43% vs. 5%, respectively, $p < 0.001$). More patients on cinacalcet had a $\geq 30\%$ reduction in PTH levels from baseline than patients on placebo (64% vs. 11%, $p < 0.001$). During the efficacy assessment phase, mean PTH levels were 43% lower than baseline in the cinacalcet group compared to 9% higher with placebo ($p < 0.001$). Mean serum calcium, phosphorous and Ca x Ph product levels were reduced by 6.8%, 8.4% and 14.6%, respectively, in the cinacalcet group ($p < 0.001$); there was no significant change in levels with placebo.

The third pivotal study, which enrolled 395 patients with secondary HPT (294 randomised to cinacalcet and 101 to placebo) receiving either haemodialysis or peritoneal dialysis for one month or more, achieved similar results.¹

A pooled analysis of all three studies showed the results were consistent across all subgroups, defined by baseline levels of PTH and Ca x Ph product, and by peritoneal and haemodialysis populations. Cinacalcet was also found to reduce PTH and Ca x Ph product levels regardless of whether vitamin D sterol doses were consistent, changed, or not administered during the studies.

A double-blind, placebo-controlled extension study enrolled patients who had completed one of the two identical key studies. Patients continued on their study medication for an additional six months. The results showed that the reduction in levels of PTH and Ca x Ph product were maintained over time.¹

Clinical outcomes were examined in a retrospective analysis in 1184 recipients

(697 cinacalcet, 487 placebo). Patients who took cinacalcet had a lower incidence of parathyroidectomy (hazard ratio 0.07 [95% CI, 0.01 to 0.55]; $p = 0.009$ compared to placebo) and fracture (0.46 [0.22 to 0.95]; $p = 0.04$) than those who took placebo.⁴

Parathyroid carcinoma:

Several studies have evaluated the efficacy of cinacalcet in reducing hypercalcaemia in patients with primary HPT including parathyroid carcinoma, but none have been fully published.

The largest of these studies randomised 78 patients with primary HPT (number with parathyroid carcinoma not stated) to cinacalcet 30mg (titrated to a maximum of 50mg) twice daily or placebo.³ 88% of patients in the cinacalcet group and 5% in the placebo group had a reduction in serum calcium of at least 0.5mg/dL and a mean calcium level of ≤ 10.3 mg/dL during the 12-week maintenance phase.

Additionally, during the maintenance phase, mean PTH levels were significantly reduced in the cinacalcet group compared to an increase in the placebo group (-7.6% vs. +7.7%, respectively; $p = 0.009$).

A pivotal trial for this indication is a single-arm, open-label study which recruited patients with parathyroid cancer ($n = 21$) or intractable primary HPT ($n = 8$) and a serum calcium level > 12.5 mg/dL.¹ After the 16-week dose titration phase (up to 90mg four times a day) 15 patients with parathyroid carcinoma and 6 with primary HPT had reached the primary endpoint of a 1mg/dL reduction in serum calcium level compared to baseline. Mean reductions were 14% and 12%, respectively. The three-year maintenance phase of this study is ongoing.

Safety

Nausea and vomiting appear to be the most common adverse effects associated with cinacalcet therapy.^{1-3,5} These effects are usually transient and of mild to moderate severity but in some patients may necessitate discontinuation of therapy. Other adverse effects commonly (incidence $> 1/100$ and $< 1/10$) associated with cinacalcet include hypocalcaemia, myalgia and rash.

Place in Therapy

There are approximately 15,500 people in England and Wales on dialysis and about 40-50% of these have PTH or phosphate levels outside the recommended range.⁶ For these people, and in those with parathyroid cancer who are not surgical candidates or who have had a recurrence despite surgical intervention, cinacalcet represents a potentially important therapeutic development. However, efficacy data are mainly limited to effects on surrogate markers, such as PTH and Ca x Ph product levels. The retrospective study reporting clinical outcomes (see above) needs to be confirmed by further prospective studies. Data on other mortality and morbidity endpoints such as rupture of tendons and cardiovascular events related to vascular calcification are also required.

Cinacalcet should be initiated and monitored by consultants experienced in the treatment of secondary hyperparathyroidism. Since cinacalcet is given with standard therapy, its cost will be additional to current drug expenditure. If increased monitoring is required, this will also increase potential costs. The Scottish Medicines Consortium have rejected cinacalcet on economic grounds.⁷

Appendix I: Bibliography Appendix II: Table of Clinical Trials

Key Paper

Block GA, Martin KJ, de Francisco ALM et al. N Engl J Med 2004; 350: 1516-25

Risk Management Issues:

Cinacalcet has the potential to interact with other drugs as it is metabolised by multiple enzymes, predominantly CYP3A4 and CYP1A2, and is a potent inhibitor of CYP2D6. See the SPC for possible interactions.⁵

Patients receiving cinacalcet may need additional monitoring for calcium, phosphate and PTH levels compared to those on standard therapy.⁶

Produced for the UK Medicines Information Service
by Pam Buffery, North West Medicines Information Centre, Pharmacy Practice Unit,
70 Pembroke Place, Liverpool, L69 3GF. Tel: 0151 794 8117 Email: druginfo@liv.ac.uk

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Appendix I

Bibliography

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2. Block GA, Martin KJ, de Francisco ALM et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 2004; 350: 1516-25
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<http://www.scottishmedicines.org/press/detail.asp?id=641> (accessed 10/05/05)

Cinacalcet

Appendix II Table of clinical trials: Cinacalcet

Ref No.	Study details	Drug treatment	Outcome measures	Results		
				Cinacalcet	Placebo	P value
2	<p>741 patients with secondary hyperparathyroidism were enrolled in one of two identical multicentre randomised controlled trials in North America, Europe and Australia. All patients had been treated with haemodialysis three times a week for at least three months (mean plasma PTH levels ≥ 300pg/ml).</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - evidence of cancer - active infection - diseases known to cause hypercalcaemia - serum calcium < 8.4mg/dl (2.1mmol/l) 	<ul style="list-style-type: none"> • initially cinacalcet 30mg (n=371) or placebo (n=370) daily • over 12 weeks cinacalcet doses were titrated every 3 weeks up to 60, 90, 120 or 180mg daily, patients were then followed for a further 14 weeks (efficacy assessment phase) • dose increases were permitted if PTH remained > 200pg/ml and if serum calcium ≥ 7.8mg/dl (1.95mmol/l) • dose was not increased if symptoms of hypocalcaemia developed, if serum calcium was < 7.8mg/dl, or because of adverse events • dose reduced if parathyroid levels were < 100pg/ml 	Primary outcome			
			The proportion of patients with a mean PTH level ≤ 250 pg/ml	43%	5%	< 0.001
			Secondary Outcomes			
			The proportion of patients with a reduction from baseline of $\geq 30\%$ in mean PTH levels	64%	11%	< 0.001
			Mean % change (SD) in values from baseline			
			PTH	-43% (± 2)	+9% (± 2)	< 0.001
			calcium	-6.8% (± 0.4)	+0.4% (± 0.3)	< 0.001
			phosphorous	-8.4% (± 1.3)	+0.2% (± 1.3)	< 0.001
			calcium x phosphorus product	-14.6% (± 1.3)	+0.5% (± 1.3)	< 0.001
			Adverse effects			
			Early discontinuation due to adverse effects	15%	7%	Not cited
			Experienced at least one adverse effect	91%	94%	=0.21
			Nausea	32%	19%	< 0.001
Vomiting	30%	16%	< 0.001			
Upper respiratory tract infection	7%	13%	=0.007			
Hypotension	6%	12%	=0.014			
Calcium levels < 7.5 mg/dl (1.9mmol/l) on two consecutive occasions	5%	$< 1\%$	< 0.001			
Ref No.	Study details	Drug treatment	Outcome measures	Results		
3	78 patients with primary HPT and serum calcium levels > 10.3 mg/dL to ≤ 12.5 mg/dL. 23% had recurrent primary HPT after parathyroidectomy.	<ul style="list-style-type: none"> • Cinacalcet 30mg twice daily, titrated to a maximum of 50mg twice daily for 24 weeks • Placebo 	Reduction of pre-dose serum calcium of ≥ 0.5 mg/dl and a mean pre-dose serum calcium of ≤ 10.3 mg/dl over maintenance period	88%	5%	Not cited
			Change in mean 12-hour post-dose PTH levels (SD)	-7.6% ($\pm 22.9\%$)	+7.7% ($\pm 22.6\%$)	=0.009