Emerging Drug List
CINACALCET FOR SECONDARY HYPERPARATHYROIDISM

CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT

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Generic (Trade Name): Cinacalcet hydrochloride (Sensipar™)

Manufacturer: Amgen Inc.

Indication: For the treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD).[1]

Current Regulatory Status: Cinacalcet was approved in Canada in August 2004 for the above indication.[1] It is also approved in the US and EU; and was submitted for review in Australia and New Zealand.[2]

Description: Cinacalcet, which belongs to a new class of medications called calcimimetics, increases the sensitivity of calcium receptors in the parathyroid gland to activation by extracellular calcium. This leads to a decrease in parathyroid hormone levels and a subsequent reduction in serum calcium. When administered orally, cinacalcet reaches maximal plasma concentration in two to six hours; and exhibits a terminal half-life of 30 to 40 hours. Cinacalcet undergoes metabolism via the cytochrome P450 system, which involves the CYP3A4, CYP2D6 and CYP1A2 isoenzymes. In vitro, it is a strong inhibitor of CYP2D6. A discussion of its pharmacodynamic profile has been published.[3] In the US and Canada, Sensipar is supplied as 30 mg, 60 mg and 90 mg tablets.[1]

Current Treatment: In CKD, phosphate excretion is impaired and vitamin D production is decreased, resulting in hypocalcemia. In response, the level of parathyroid hormone (PTH) rises to increase renal calcium reabsorption and transfer calcium from the bone. This may lead to hypercalcemia, bone fragility, fractures and pain, which increase morbidity and mortality.[4] Secondary hyperparathyroidism and its treatments may also contribute to cardiovascular disease in patients with CKD. The goal of treatment is to lower PTH levels and maintain calcium and phosphate homeostasis. This may be done by using phosphate binders (i.e. calcium, aluminum, magnesium salts or sevelamer), vitamin D analogues (i.e. calcitriol or alfacalcidol) or in severe cases, surgical parathyroidectomy.[4,5]

Cost: In Canada, Sensipar™ is priced at C$0.36/mg. A 30 mg tablet would cost C$10.70. Sensipar™ can be titrated every two to four weeks to a maximum of 180 mg daily, which costs C$64.24, to achieve a target PTH level (David Macarios, Amgen Canada, Mississauga, ON: personal communication, 2004 Sept 30).

Evidence:

Secondary Hyperparathyroidism Associated with CKD

Three phase III trials have been conducted comparing cinacalcet to placebo in patients with CKD on dialysis.[1,6] The results of two identically structured trials were published in *The New England Journal of Medicine*.[7] Adults with secondary hyperparathyroidism (n=741) and a mean plasma PTH≥300 pg/mL received placebo or cinacalcet for 26 weeks

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(12 weeks titration plus 14 weeks efficacy phase). Cinacalcet was started at 30 mg daily, then adjusted every three weeks in response to serum calcium and phosphate levels, up to a maximum of 180 mg. Phosphate-binding medications and vitamin D sterols were allowed. Among patients receiving cinacalcet, 68% completed the trial compared with 78% of patients receiving placebo. Significantly more patients receiving cinacalcet achieved the primary end point (serum PTH≤250 pg/mL) compared with those receiving placebo (43% versus 5%, p<0.001). Serum PTH levels decreased by at least 35% in 64% of cinacalcet-treated patients compared with 11% of those in the placebo group (p<0.001). Patients receiving cinacalcet also had significant reductions in calcium and phosphorus levels. The third study, which was described in the product monograph, showed similar results.[1] Among patients who completed the third study, 35% of cinacalcet-treated patients and 6% of placebo-treated patients achieved a serum PTH≤250 pg/mL (p<0.001).[1] A two-year study with cinacalcet has also been reported.[8]

Other diseases

An open-label study was conducted in 10 patients with parathyroid cancer. Titration occurred over two to 16 weeks. The maintenance phase lasted from 16 to 48 weeks (n=3). No patient maintained a normal serum calcium level.

Other off-label indications have also been explored.[9,10] Shobak *et al.* reported the results of a small dose-finding study involving 22 patients with primary hyperparathyroidism.[9] Coburn *et al.* evaluated the efficacy and safety of cinacalcet in 54 patients with CKD not receiving dialysis.[10]

Adverse Effects:

In the two trials reported by Block *et al.*, the incidence of adverse events was similar in the cinacalcet and placebo groups (91% versus 94%, p=0.21). Nausea and vomiting were more frequent among those taking cinacalcet (p<0.001). Hypocalcemia was more frequent with cinacalcet treatment (5% versus 1%, p<0.001), although it was described as transient and amenable to changes in levels of calcium-based phosphate binders or vitamin D sterols.[7]

Commentary:

Cinacalcet will likely be most widely used to treat secondary hyperparathyroidism related to kidney disease. There is evidence to show that cinacalcet improves physiologic outcomes. One abstract describes the effect of cinacalcet on parathyroidectomy, fracture, hospitalization and mortality in a post-hoc analysis involving 1,184 patients.[11] A pharmacoeconomic analysis would further define its role.[12]

References:

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