Formulary Drug Review: Etelcalcetide

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Keywords

formulary management/P&T, nephrology, metabolic/endocrine

Generic Name: Etelcalcetide

Proprietary Name: *Parsabiv* (KAI Pharmaceuticals, Inc)

Approval Rating: 1S

Therapeutic Class: Calcimimetics

Similar Drugs: Cinacalcet

Sound- or Look-Alike Names: Ecallantide

Indications

Etelcalcetide (previously known as velcalcetide and AMG 416) is approved for the treatment of secondary hyperparathyroidism in adults with chronic kidney disease (CKD) on hemodialysis.^{1,2,3}

Etelcalcetide has not been sufficiently evaluated in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or CKD not on hemodialysis, and is not recommended for use in these populations.¹

Clinical Pharmacology

Etelcalcetide is a calcimimetic agent that modulates the calcium-sensing receptor (CaSR).^{1,4,5,6,7} Calcimimetic agents bind to the CaSR and enhance activation of the receptor by extracellular calcium. Activation of the CaSR on parathyroid chief cells decreases parathyroid hormone (PTH) secretion.^{1,4,5,6,7,8} Following intravenous (IV) administration of etelcalcetide, PTH levels decrease within 30 minutes and stay suppressed with continued administration. The reduction in PTH levels results in reductions in

calcium serum levels and attenuation of postdialytic phosphate elevation.¹

Pharmacokinetics

Etelcalcetide has linear pharmacokinetics and exhibits triexponential decay following IV administration. In CKD patients, steady-state concentrations are achieved in 7 to 8 weeks with 3-times-weekly dosing at the end of each 3- to 6-hour hemodialysis session. Etelcalcetide's effective half-life is 3 to 4 days and steady-state volume of distribution is 796 L. Etelcalcetide is predominately bound to plasma albumin by reversible covalent binding and is biotransformed in blood by reversible disulfide exchange with endogenous thiols to form conjugates with serum albumin. Etelcalcetide is not metabolized by cytochrome P450 enzymes. Etelcalcetide is cleared by renal excretion in patients with normal renal function, while hemodialysis is the predominant elimination pathway in CKD patients requiring hemodialysis.^{1,9,10,11,12,13}

Body weight (29-163 kg), gender, race, and age (20-93 years of age) do not influence etelcalcetide pharmacokinetics.¹

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Comparative Efficacy

Indication: Secondary Hyperparathyroidism in Patients With CKD Receiving Hemodialysis

Guidelines

Guideline: Hyperphosphatemia in CKD: Management of hyperphosphatemia in patients with stage 4 or 5 CKD (National Institute for Health and Care Excellence [NICE] clinical guideline 157)

Reference: NICE¹⁴

Comments: NICE guidelines recommend dietary management and phosphate binders (eg, cinacalcet) for management of hyperphosphatemia in patients with CKD to reduce the risk of hyperparathyroidism. Etelcalcetide was not available at the time this guideline was developed. The Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease-Mineral and Bone Disorder Work Group made similar recommendations in 2009.¹⁵

Studies

Drug: Etelcalcetide vs Placebo

Reference: Block GA, et al, 2017 (Food and Drug Administration [FDA] Study 1)^{1,16}

Study Design: Phase 3, randomized, double-blind, placebo-controlled, multicenter, multinational study

Study Funding: Amgen, Inc

Patients: 508 patients with CKD and secondary hyperparathyroidism (PTH greater than 400 pg/mL) receiving hemodialysis 3 times per week. Patients were taking stable doses of calcium supplements or phosphate binders and calcitriol or active vitamin D analogs, and had albumin-corrected serum calcium levels of 8.3 mg/dL or higher. Mean age was 58 years, 57% were men, 69% were white, 28% were black, 2% were Asian, and 13% were Hispanic. Mean baseline PTH level was 834.2 pg/mL, mean baseline corrected serum calcium was 9.6 mg/dL, and average duration of hemodialysis prior to study entry was 5.5 years. Sixty-six percent of patients had a mean screening PTH level greater than or equal to 600 pg/mL, 74% were receiving vitamin D sterols, and 84% were receiving phosphate binders.

Intervention: Patients were randomized 1:1 to treatment with etelcalcetide or placebo for 26 weeks. The starting dose of etelcalcetide was 5 mg 3 times per week administered at the end of hemodialysis. The etelcalcetide dose was titrated every 4 weeks until week 17 to a maximum dose of 15 mg 3 times per week to a target PTH level of less than or equal to 300 pg/mL. Etelcalcetide was held temporarily if 2 consecutive PTH measurements were less than 100 pg/mL. The dose of etelcalcetide was not increased if PTH levels were less than or equal to 300 pg/mL, corrected serum calcium was less than 8.3 mg/dL, symptomatic hypocalcemia occurred, or the investigator judged that no dose increase was needed.

Results:

Primary End Point(s)

- Proportion of patients with a greater than 30% reduction in PTH levels from baseline to the efficacy assessment phase (mean PTH levels for weeks 20 through 27, inclusive) was 77% with etelcalcetide and 11% with placebo ($P < .001$); the number needed to treat (NNT) for this end point is 1.5.

Secondary End Point(s)

- Proportion of patients with a mean PTH of 300 pg/mL or lower was 52% with etelcalcetide and 6% with placebo ($P < .001$).
- Percent change from baseline in PTH was -49.4% with etelcalcetide and 14.9% with placebo ($P < .001$).
- Percent change from baseline in corrected serum calcium was -7% with etelcalcetide and 0.9% with placebo ($P < .001$).
- Percent change from baseline in phosphate levels was -8.8% with etelcalcetide and -3.6% with placebo ($P = .08$).

Comments: This study was conducted in the United States, Canada, Europe, Israel, Russia, and Australia.

Limitations: This study demonstrated biochemical control of secondary hyperparathyroidism compared with placebo but was not designed to assess the effects of etelcalcetide on bone architecture or strength, or the likelihood of fracture. The study was not designed to determine whether etelcalcetide therapy could alter vascular calcification, cardiovascular structure or function, cardiovascular events, or mortality.

Reference: Block GA, et al, 2017 (FDA Study 2)^{1,16}

Study Design: Phase 3, randomized, double-blind, placebo-controlled, multicenter, multinational study

Study Funding: Amgen, Inc

Patients: 515 patients with CKD and secondary hyperparathyroidism (PTH greater than 400 pg/mL) receiving hemodialysis 3 times per week. Patients were taking stable doses of calcium supplements or phosphate binders and calcitriol or active vitamin D analogs, and had albumin-corrected serum calcium levels of 8.3 mg/dL or higher. Mean age was 59 years, 64% were men, 65% were white, 28% were black, 4% were Asian, and 13% were Hispanic. Mean baseline PTH level was 848.4 pg/mL, mean baseline corrected serum calcium was 9.7 mg/dL, and average duration of hemodialysis prior to study entry was 5.4 years. Sixty-seven percent of patients had a mean screening PTH level greater than or equal to 600 pg/mL, 62% were receiving vitamin D sterols, and 81% were receiving phosphate binders.

Intervention: Same as FDA Study 1.

Results:

Primary End Point(s)

- Proportion of patients with a greater than 30% reduction in PTH levels from baseline to the efficacy assessment

phase (mean PTH levels for weeks 20 through 27, inclusive) was 79% with etelcalcetide and 11% with placebo ($P < .001$); the NNT for this end point is 1.5.

Secondary End Point(s)

- Proportion of patients with a mean PTH of 300 pg/mL or lower was 56% with etelcalcetide and 5% with placebo ($P < .001$).
- Percent change from baseline in PTH was -47.8% with etelcalcetide and 18.6% with placebo ($P < .001$).
- Percent change from baseline in corrected serum calcium was -7% with etelcalcetide and -0.8% with placebo ($P < .001$).
- Percent change from baseline in serum phosphate levels was -7.2% with etelcalcetide and -0.3% with placebo ($P < .01$).

Comments: This study was conducted in the United States, Canada, Europe, Israel, Russia, and Australia.

Limitations: This study demonstrated biochemical control of secondary hyperparathyroidism compared with placebo but was not designed to assess the effects of etelcalcetide on bone architecture or strength, or the likelihood of fracture. The study was not designed to determine whether etelcalcetide therapy could alter vascular calcification, cardiovascular structure or function, cardiovascular events, or mortality.

Drug: Etelcalcetide vs Cinacalcet

Reference: Block GA, et al, 2017¹⁷

Study Design: Phase 3, randomized, double-blind, double-dummy, active-control, multicenter, multinational, clinical noninferiority study

Study Funding: Amgen, Inc

Patients: 683 patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism (predialysis PTH level 500 pg/mL or higher). Patients were taking stable doses of calcium supplements or phosphate binders and calcitriol or active vitamin D analogs, and had albumin-corrected serum calcium levels of 8.3 mg/dL or higher. Mean age was 54.7 years, 56.2% were men, 78.7% were white, 15.5% were black, 2.3% were Asian, and 11.5% were Hispanic. Median time since initiation of dialysis was a little over 4 years, and 25% had previous exposure to cinacalcet therapy.

Intervention: Patients were randomized 1:1 to IV etelcalcetide and oral placebo or oral cinacalcet and IV placebo for 26 weeks. The IV study drug was given 3 times weekly after hemodialysis, and the oral study drug was given once daily. The starting dose of IV etelcalcetide was 5 mg, and the starting dose of oral cinacalcet was 30 mg. Etelcalcetide (and corresponding IV placebo) could be titrated in increments of 2.5 mg or 5 mg (dose range, 2.5-15 mg), and cinacalcet (and corresponding oral placebo) could be titrated in increments of 30 mg (dose range, 30-180 mg) at weeks 5, 9, 13, and 17, with target serum PTH levels from 100 to 300 pg/mL. The median average weekly etelcalcetide dose

during the efficacy assessment phase was 15 mg, and the median average daily cinacalcet dose was 51.4 mg. All patients received standard care with phosphate binders and calcitriol or active vitamin D analogs, as prescribed by the individual investigator. Study drug was withheld for 2 consecutive PTH measurements less than 100 pg/mL, serum calcium less than 7.5 mg/dL, symptomatic hypocalcemia, or drug-related adverse events. Serum calcium, albumin, and PTH levels were monitored every 2 weeks.

Results:

Primary End Point(s)

- Proportion of patients with a greater than 30% reduction in mean PTH levels from baseline to the efficacy assessment phase (weeks 20 through 27) was 68.2% with etelcalcetide and 57.7% with cinacalcet; treatment difference was -10.5% (95% confidence interval [CI], -17.5% to -3.5% ; $P < .001$ for noninferiority [primary]; $P = .004$ for superiority [secondary]). NNT to achieve a 30% or more reduction from baseline in mean predialysis PTH concentrations during weeks 20 to 27 was 9.5.

Secondary End Point(s)

- Proportion of patients with a greater than 50% reduction in PTH level was 52.4% with etelcalcetide and 40.2% with cinacalcet; treatment difference was 12.2% (95% CI, 4.7%-19.5%; $P = .001$). NNT to achieve a 50% or greater reduction from baseline in mean predialysis PTH concentrations during weeks 20 to 27 was 8.2.

Comments: This study was conducted in the United States, Canada, Europe, Russia, and New Zealand. The noninferiority margin for the primary end point (proportion of patients achieving a greater than 30% reduction in PTH levels) was 12%. The primary analysis found etelcalcetide was not inferior to cinacalcet and met the superiority criteria for reducing PTH levels from baseline to week 26. All data were analyzed using intention-to-treat principle; missing data were handled by applying a response rate of 60% and 48% to impute response status for patients in the cinacalcet and etelcalcetide groups, respectively. During the efficacy assessment phase, 12.4% of the etelcalcetide group and 9.6% of the cinacalcet group had no PTH data.

Limitations: Additional studies are needed to determine long-term safety and efficacy of etelcalcetide. The focus of this study was change in PTH level, a surrogate end point.

Contraindications, Warnings, and Precautions

Contraindications

Etelcalcetide is contraindicated in patients with known hypersensitivity (eg, pruritic rash, urticaria, face edema) to etelcalcetide or any of its excipients (sodium chloride, succinic acid, sodium hydroxide, and/or hydrochloric acid).¹

Warnings and Precautions

Etelcalcetide lowers serum calcium and can lead to hypocalcemia, including severe hypocalcemia.¹

Etelcalcetide can cause QT interval prolongation and ventricular arrhythmia.¹ Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, or other condition that predisposes to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to etelcalcetide use. Closely monitor corrected serum calcium and QT interval in patients with these risk factors receiving etelcalcetide.¹

Significant reductions in serum calcium levels can lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk of seizures if they develop hypocalcemia during treatment with etelcalcetide.¹ The risk of seizures may be increased in patients switching from cinacalcet therapy. To decrease this risk, cinacalcet should be discontinued for at least 7 days prior to initiating etelcalcetide. All patients receiving etelcalcetide should have their corrected serum calcium monitored within 1 week after initiation or dose adjustment, and every 4 weeks during treatment.¹ If the corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start, or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration), etelcalcetide dose reduction or discontinuation of etelcalcetide may be necessary.¹

Cases of hypotension, congestive heart failure, and decreased myocardial performance were reported in clinical studies. The reduction in serum calcium may be the cause; however, a causal relationship to etelcalcetide therapy could not be excluded. Closely monitor all patients for worsening signs and symptoms of heart failure during etelcalcetide treatment.¹

Patients with risk factors for upper gastrointestinal (GI) bleeding (eg, gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding during etelcalcetide treatment. Monitor patients for worsening of common GI adverse reactions (ie, nausea and vomiting) associated with etelcalcetide.¹

Adynamic bone may occur if PTH levels are chronically lowered. PTH levels should be monitored, and if they drop below the recommended target range, the dose of vitamin D sterols and/or etelcalcetide should be reduced or therapy discontinued. If therapy is restarted after discontinuation, reinitiate at a lower dose to maintain PTH levels within the target range.¹

There are no available data on the use or safety of etelcalcetide in pregnant women.¹

Safety during breastfeeding is unknown; there are no data regarding the presence of etelcalcetide in human milk

Table 1. Adverse Reactions in Etelcalcetide Studies of Patients With CKD and Secondary Hyperparathyroidism on Hemodialysis (Occurring in $\geq 5\%$ of Etelcalcetide Patients and at $\geq 1\%$ Greater Incidence Than Placebo).¹

Adverse reaction	Etelcalcetide (n = 503)	Placebo (n = 513)
Blood calcium decreased	64%	10%
Muscle spasms	12%	7%
Diarrhea	11%	9%
Nausea	11%	6%
Vomiting	9%	5%
Headache	8%	6%
Hypocalcemia	7%	0.2%
Paresthesia	6%	1%

Note. CKD = chronic kidney disease.

or its effects on the breastfed infant or milk production. Use of etelcalcetide is not recommended while breast feeding.¹

The safety and efficacy of etelcalcetide have not been established in pediatric patients.¹

Adverse Reactions

The most common adverse reactions reported in clinical trials were blood calcium decreases, muscle spasms, diarrhea, nausea, vomiting, headache, hypocalcemia, and paresthesia (see Table 1).^{1,5,16,17,18}

Other important adverse reactions included hyperkalemia, hospitalization for heart failure, myalgia, hypophosphatemia, QTc interval prolongation secondary to hypocalcemia, and hypersensitivity reactions.^{1,18}

Immunogenicity is a potential risk with all peptide therapeutics. If formation of anti-etelcalcetide binding antibodies with clinically significant effect is suspected, contact the manufacturer.¹

Drug Interactions

Drugs related to enzyme induction/inhibition or changes in various transport systems are unlikely to cause drug-drug interactions with this agent. In *in vitro* assessments, etelcalcetide did not inhibit or induce cytochrome P450 enzymes, and was not a substrate of cytochrome P450 enzymes. Etelcalcetide also was not an inhibitor of common transporter proteins (P-glycoprotein, breast cancer resistant protein [BCRP], organic anion transporter [OAT] 1, OAT3, organic anion polypeptide transporter [OATP] 1B1, OATP1B3, organic cation transporter [OCT] 2, or bile salt export pump [BSEP]). Etelcalcetide was not a substrate of efflux and uptake transporter proteins (P-glycoprotein, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, and peptide transporter [PEPT] 1 and PEPT2).^{1,12}

Recommended Monitoring

Monitor corrected serum calcium and PTH levels during dose initiation, dose adjustment, and dose maintenance. Corrected serum calcium levels should be obtained 1 week after starting therapy or a dose adjustment, then rechecked every 4 weeks throughout therapy. The PTH level should be obtained 4 weeks after starting therapy or a dose adjustment, then rechecked throughout therapy based on clinical needs.¹

Electrocardiograms should be monitored periodically throughout therapy in patients at risk of increased QT interval changes.¹

Patients should be monitored for signs and symptoms of heart failure and upper GI bleeding during etelcalcetide therapy.¹

Dosing

Corrected serum calcium must be at or above the lower limit of normal prior to etelcalcetide initiation, a dose increase, or reinitiation of etelcalcetide therapy following dosing interruption.¹

The recommended starting dose of etelcalcetide is 5 mg administered by IV bolus injection 3 times per week at the end of hemodialysis treatment. The maintenance dose of etelcalcetide is individualized and determined by the patient's PTH and corrected serum calcium response. The target effects are maintenance of PTH levels within the recommended target range and corrected serum calcium within the normal range. The lowest recommended maintenance dose is etelcalcetide 2.5 mg 3 times per week; the highest recommended maintenance dose is etelcalcetide 15 mg 3 times per week.¹

Do not mix or dilute etelcalcetide prior to administration. Etelcalcetide is administered by IV bolus injection into the venous line of the dialysis circuit at the end of the hemodialysis treatment during rinse back, or IV after rinse back.¹

If a regularly scheduled hemodialysis treatment is missed, resume etelcalcetide therapy at the end of the next hemodialysis treatment at the prescribed dose. If doses of etelcalcetide are missed for more than 2 weeks, reinitiate etelcalcetide at the recommended starting dose of 5 mg (or 2.5 mg if that was the patient's last dose).¹

A reduction in dose or temporary discontinuation of etelcalcetide may be necessary if PTH levels are below the target range. In individuals with corrected serum calcium below the lower limit of normal but at or above 7.5 mg/dL without symptoms of hypocalcemia, consider decreasing or temporarily discontinuing etelcalcetide, or use concomitant therapies to increase corrected serum. If etelcalcetide is stopped and then restarted, dosing should be reinitiated at a lower dose after PTH is within the target range and hypocalcemia has been corrected.¹

Stop etelcalcetide therapy and treat hypocalcemia if corrected serum calcium falls below 7.5 mg/dL or patient

reports symptoms of hypocalcemia. When corrected serum calcium is within normal limits, symptoms of hypocalcemia have resolved, and predisposing factors for hypocalcemia have been addressed, reinitiate etelcalcetide at a dose 5 mg lower than the last administered dose. If the last administered dose of etelcalcetide was 2.5 mg or 5 mg, reinitiate at a dose of 2.5 mg.¹

If the patient is switched from cinacalcet to etelcalcetide, cinacalcet should be discontinued at least 7 days prior to starting etelcalcetide and etelcalcetide should be initiated at 5 mg 3 times per week. Ensure corrected serum calcium is at or above the lower limit of normal prior to starting etelcalcetide.¹

Product Availability

Etelcalcetide is available in single-dose vials as a 2.5 mg per 0.5 mL, 5 mg/mL, or 10 mg per 2 mL solution. Each dosage strength is available in a carton containing 10 single-dose vials.¹

Store refrigerated in the original carton at 2°C to 8°C (36°F-46°F) and protect from light. Once removed from the refrigerator, do not expose to temperatures above 25°C (77°F) and use within 7 days if stored in the original carton. If removed from the original carton, use within 4 hours and do not expose to direct sunlight.¹

Drug Safety/Risk Evaluation and Mitigation Strategy (REMS)

No REMS is required for etelcalcetide.

Conclusion

Etelcalcetide is approved for secondary hyperparathyroidism in adults with CKD receiving hemodialysis. The IV formulation is given during the patient's visit to the dialysis center, which allows the dose to be adjusted based on laboratory values and helps ensure adherence to therapy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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