Brand Name[2,4]: Parsabiv

Generic Name[2,4]: Etelcalcetide

Manufacturer[4]: Amgen, Inc.

Drug Class[1,2,3,4]: Calcimimetic: Calcium-sensing receptor (CaSR) agonist

Uses[1,2,3,4]:

Labeled Uses:
Secondary hyperparathyroidism in adults with chronic kidney disease on hemodialysis
Unlabeled Uses:
None

Mechanism of Action[1,2,3,4]:

Etelcalcetide works by allosterically binding to the calcium-sensing receptor (CaSR) and enhancing activation of the receptor through mimicking of extracellular calcium. CaSR is then activated on parathyroid chief cells and this decreases parathyroid hormone (PTH) synthesis and secretion. As PTH decreases so does serum calcium and phosphorous.

Pharmacokinetics[1,2,3,4]:

Absorption:

T_{max}	0
V_d[1]	796 L
$t_{½}$ [2]	3-4 days
Clearance[1]	7.66 L/hr
Protein binding	Not reported
Bioavailability	100%

Metabolism[1,2,3,4]:

Etelcalcetide undergoes biotransformation in the blood by a reversible disulfide exchange with endogenous thiols to predominantly form conjugates with serum albumin that exist mainly as serum albumin peptide conjugates (SAPC). Etelcalcetide is not metabolized by CYP450 enzymes.

Elimination[1,2,3,4]:

Etelcalcitide is excreted by the kidneys through urine in those with normal renal function, and is eliminated during hemodialysis in those undergoing hemodialysis. During clinical trials, it was observed that 60% of the drug was

recovered in dialysate in those undergoing hemodialysis. An additional 7% of the drug was recovered in the urine and feces combined over 175 days of collection.

Efficacy:

Block, G. A., Bushinsky, D. A., Cunningham, J., et al. Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism. *JAMA.* 2017; 317(2): 146-155. doi:10.1001/jama.2016.19456

Study Design: Multicenter, parallel, randomized, placebo-controlled study

Description of Study: This study consisted of two separate phase 3 studies of a combined 1023 patients (508 etelcalcetide; 515 placebo) evaluating the safety and efficacy of etelcalcetide compared with placebo in patients with secondary hyperparathyroidism receiving dialysis. Patients in both groups were given either intravenous etelcalcetide or placebo following each hemodialysis session for 26 weeks. The primary endpoint was the number of patients achieving reduction of parathyroid hormone by greater than 30% from baseline during weeks 20-26. The secondary endpoint was patients achieving a mean parathyroid hormone concentration of 300 pg/mL or less. The primary endpoint was reached in 74% of patients receiving etelcalcetide vs. 8.3% in the placebo group ($p<0.001$) for trial A and 75.3% vs. 9.6% ($p<0.001$) for trial B. Patients randomized to etelcalcetide were significantly more likely to achieve a parathyroid level of 300 pg/mL or lower.

Limitations: The length of the study is a limitation that needs to be addressed. While 26 weeks is long enough to evaluate short-term safety and efficacy of etelcalcetide, it is not long enough to determine long-term safety and efficacy. Patients on hemodialysis might be on it for many years, so a longer-term study is needed to address these issues. In addition, while having a large sample size is good, the amount of variability among the hundreds of study sites could be a limitation of the study. While the administration instructions for etelcalcetide and placebo are the same for all sites, there is no guarantee that each site is administering the medication in the instructed manner.

Conclusion: Etelcalcetide more effectively lowered parathyroid hormone levels in patients with secondary hyperparathyroidism receiving hemodialysis when compared with placebo. Patients in the etelcalcetide treatment group were much more likely to have a 30% or greater reduction in mean parathyroid hormones than patients in the placebo group (74.0% vs 8.3% and 75.3% vs 9.6%).

Block, G. A., Bushinsky, D. A., Cheng, S., et al. Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism. *JAMA.* 2017; 317(2): 156-164. doi:10.1001/jama.2016.19468

Study Design: Multicenter, randomized, active-controlled, double blind, double-dummy study

Description of Study: This study was a randomized clinical trial of 683 patients from 164 sites around the globe evaluating the safety and efficacy of etelcalcetide compared with cinacalcet in patients with secondary hyperparathyroidism receiving hemodialysis with parathyroid hormone concentrations higher than 500 pg/mL. 340 patients were given IV etelcalcetide (2.5-15mg/day, titrated in 2.5 or 5mg increments) and oral placebo, while 344 patients were given oral cinacalcet (30-180mg/day, titrated in 30mg increments) and IV placebo. The IV study drug was administered 3 times weekly with hemodialysis and the oral study drug was administered daily for 27 weeks. The primary endpoint was non-inferiority of etelcalcetide at achieving more than a 30% reduction from baseline in mean predialysis parathyroid hormone concentrations during weeks 20-27 (non-inferiority margin, 12.0%). Secondary end points included superiority in achieving biochemical end points (>50% and >30% reduction in parathyroid hormone) and self-reported nausea or vomiting. Etelcalcetide was non-inferior to cinacalcet regarding the primary end point. The estimated difference in the number of patients achieving reduction in parathyroid hormone concentrations of more than 30% between the 198 of 343 patients (57.7%) randomized to receive cinacalcet and the 232 of 340 patients (68.2%) randomized to receive etelcalcetide was −10.5% (95% CI, −17.5% to −3.5%, *P* for non-inferiority=<0.001; *P* for superiority=0.004). 178 patients (52.4%) randomized to etelcalcetide achieved more than 50% reduction in parathyroid hormone concentrations compared with 138 patients (40.2%) randomized to cinacalcet (*P* = .001; difference in proportions, 12.2%; 95% CI, 4.7% to 19.5%). Adverse event rates were similar between the two groups. Death occurred in 15 patients (9 etelecalcetide; 6 cinacalcet). Other adverse events reported in participants in both groups included nausea (62 etelcalcetide; 77 cinacalcet), vomiting (45; 47), heart failure (10; 2), and hypocalcemia (233; 204).

Limitations: The length of the study is a limitation that needs to be addressed. While 27 weeks is long enough to evaluate short-term safety and efficacy of etelcalcetide, it is not long enough to determine long-term safety and efficacy. Patients on hemodialysis might be on it for many years, so a longer-term study is needed to address these issues. In addition, while having a large sample size is good, the amount of variability among the many study sites could be a limitation of the study. While the administration instructions for etelcalcetide and placebo are the same for all sites, there is no guarantee that each site is administering the medication at the exact same time and in the proper manner. Another limitation is that Amgen, the maker of both drugs, funded the study and had employees as non-voting members on the trial steering committee. This could mean bias is present since they were also responsible for analyzing the data.

Conclusion: Etelcalcetide more effectively lowered parathyroid hormone levels in patients with secondary hyperparathyroidism receiving hemodialysis when compared with cinacalcet. Patients in the etelcalcetide treatment group were more likely to have a 30% or greater reduction in mean parathyroid hormones than patients in the cinacalcet group (68.2% vs 57.7%).

Martin, K. J., Pickthorn, K., Huang, S., et al. AMG 416 (velcalcetide) is a novel peptide for the treatment of secondary hyperparathyroidism in a single-dose study in hemodialysis patients. *Kidney International*. 2014; 85(1): 191-197. doi:10.1038/ki.2013.289

Study Design: Single center, cohort, crossover, randomized, placebo-controlled study

Description of Study: AMG 416 (formerly velcalcetide, now etelcalcetide) was studied to determine safety and efficacy in hemodialysis patients suffering from secondary hyperparathyroidism. Major inclusion criteria were hemodialysis for at least 3 months, serum parathyroid hormone over 300pg/ml, corrected serum calcium of 9.0mg/dl or more, and stable doses of vitamin D analogs for at least 3 weeks prior to screening. Twenty-eight patients were enrolled in one of five cohorts (5, 10, 20, 40, 60mg). Cohorts 1–3 (four patients each) were treated in a two-period crossover design, while cohorts 4 and 5 (eight patients each) were randomized 1:1 to AMG 416 or placebo. Patients were admitted to a clinical research unit following hemodialysis and studied for 3 days prior to discharge for hemodialysis. Single intravenous doses of AMG 416 from 5 to 60mg were well tolerated, and plasma levels increased in a dose-related manner. AMG 416 treatment was associated with significant reductions in serum parathyroid hormone and fibroblast growth factor 23. Decreases in parathyroid hormone values occurred within 30 minutes of dosing and were dose dependent (-64% for 5mg; -86% for 60mg). Fibroblast growth factor reductions were also dose dependent but only associated with doses >10mg.

Limitations: The number of patients enrolled in the study is a major limitation. With only twenty-eight patients participating, it can be very difficult to determine if the results are statistically significant with such a low sample size.

Conclusion: Dose-dependent reductions in parathyroid hormone and serum calcium were observed and were well tolerated. All treatment dose groups of 10mg or more compared with placebo were associated with a rise in serum potassium during the hemodialysis period. AMG 416 (etelcalcetide) could be a good potential option for the treatment of secondary hyperparathyroidism in hemodialysis patients due to its effectiveness in reducing parathyroid hormone.

Contraindications[1,2,3,4]:

Hypersensitivity: Hypersensitivity reactions have been associated with the use of etelcalcetide. Etelcalcetide is contraindicated in patients with a known hypersensitivity to etelcalcitide or any of its excipients.

Pre-existing Hypocalcemia: Etelcalcetide is contraindicated in patients who have pre-existing hypocalcemia. Ventricular arrhythmias and QT prolongation may occur secondary to hypocalcemia. Before initiating etelcalcetide, verify that corrected serum calcium is at or above lower limit of normal.

Precautions[1,2,3,4]:

Seizure Disorder: Seizure threshold can be lowered following a decrease in serum calcium. Use cautiously in patients with a known seizure disorder.

Ventricular Arrhythmias/QT Interval Prolongation: Ventricular arrhythmias and QT prolongation may occur secondary to hypocalcemia.

Heart Failure: Worsening congestive heart failure has been reported. In addition, decreased myocardial functioning and hypotension have been observed.

GI Bleed Risk: Increased risk in those who already have risk factors for an upper GI bleed, such as known gastritis, ulcers, or severe vomiting.

Adynamic Bone: Can occur if parathyroid hormone levels are suppressed for a long period of time. Discontinuation or dose reduction may be necessary if this occurs.

Adverse Effects[1,2,3,4]:

Occurring in >10% of patients:

- Endocrine & Metabolic:
  - Decreased serum calcium (≤79%)
  - Hypophosphatemia (1-18%)
- Gastrointestinal:
  - Diarrhea (11%)
  - Nausea (11%)
- Neuromuscular & Skeletal:
  - Muscle Cramps/Spasms (12%)

Occurring in >1% to <10% of patients:

- Cardiovascular:
  - QT prolongation (1-5%)
  - Cardiac failure (2%)
- Central Nervous System:
  - Headache (8%)
  - Hypoesthesia (6%)
  - Paresthesia (6%)
- Dermatologic:
  - Pruritus (4%)
  - Rash (unspecified) (4%)
  - Urticaria (4%)
- Endocrine & Metabolic:
  - Facial Edema (4%)
  - Hyperkalemia (4%)
  - Hypocalcemia (8%)
- Gastrointestinal:
  - Vomiting (9%)
- Immunologic:
  - Antibody Formation (7%)

Neuromuscular & Skeletal:
Myalgia (2%)

Drug Interactions[3]:

Cinacalcet: avoid combination due to potential for enhanced hypocalcemia

Dosing/Administration[1,2,3,4]:

Adult Dosing

Initial Dosing: 5mg IV bolus three times weekly at the end of hemodialysis
Maintenance Dose: Minimum dose of 2.5mg IV three times weekly; maximum dose of 15mg IV three times weekly
Dosage Adjustments: Titrate dose in 2.5mg or 5mg increments every 4 weeks as needed to a dose that maintains PTH levels within target range and corrected serum calcium within the normal range

Pediatrics

Drug has not yet been studied in the pediatric population. Safety and efficacy have not been established.

Elderly

Refer to adult dosing

Renal impairment

No dosage adjustments provided

Hepatic impairment

No dosage adjustments provided

Use in special circumstances[1,2,3,4]**:**

Pregnancy:

Use of etelcalcetide should be avoided in pregnant patients. Although no data is available in humans, use of etelcalcetide in rats at 1.8 times the human exposure of 15mg three times weekly, resulted in a slight increase in mortality, delay in parturition, and transient effects on pup growth. In addition, use of etelcalcetide in rats at 2.7 times the human dose and rabbits at 7 times the human dose, resulted in reduced fetal growth due to hypocalcemia, tremors, and reductions in body weight and food consumption.

Lactation:

Although there is no human data available, breast-feeding should be avoided when taking etelcalcetide. In trials of rats, etelcalcetide was present in milk at concentrations similar to plasma.

Underweight/Obesity:

Body weight of 29-163kg does not affect pharmacokinetics of etelcalcetide.

Missed Dose:

Skip missed dose and restart drug at next normal dosing time

Conclusion[1,2,3,4,5,6,7]**:**

Etelcalcetide has been proven to be an effective calcimimetic agent that significantly reduces parathyroid hormone concentrations in patients who have secondary

hyperparathyroidism and are undergoing hemodialysis. It appears to be an acceptable alternative that can be used in place of cinacalcet, as it has shown non-inferiority and superiority in comparison trials. However, further studies are still needed to determine the long-term safety and efficacy of etelcalcetide in patients who are undergoing hemodialysis.

Recommended References:

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3. Etelcalcetide. Lexi-Drugs [database online]. Lexi-Comp, Inc; May 26, 2017.
4. Parsabiv (etelcalcetide) [prescribing information]. Thousand Oaks, CA: Amgen, Inc.; February 2017.
5. Block, G. A., Bushinsky, D. A., Cunningham, J., et al. Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism. *JAMA.* 2017; 317(2): 146-155. doi:10.1001/jama.2016.19456
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7. Martin, K. J., Pickthorn, K., Huang, S., et al. AMG 416 (velcalcetide) is a novel peptide for the treatment of secondary hyperparathyroidism in a single-dose study in hemodialysis patients. *Kidney International*. 2014; 85(1): 191-197. doi:10.1038/ki.2013.289

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