Etelcalcetide (Parsabiv) for Secondary Hyperparathyroidism in Adults With Chronic Kidney Disease on Hemodialysis

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INTRODUCTION
Chronic kidney disease (CKD), a condition characterized by an irreversible reduction in the number of functioning nephrons, results in progressive and permanent deterioration in kidney function. CKD is a prevalent disorder throughout the world. In the United States, it is estimated that more than 30 million individuals (15% of the population) may have CKD, with nearly 662,000 living with end-stage kidney disease requiring dialysis (468,000) or with a functional renal transplant (193,000).

The complications associated with CKD are numerous and costly: Medicare spending for patients with CKD 65 years of age or older was greater than $50 billion in 2013 and accounted for approximately 20% of all Medicare spending for this age group. In addition, patients with CKD have a risk of experiencing complications related to this condition, including anemia, electrolyte disturbances (e.g., hyperkalemia, hyperphosphatemia), and CKD–mineral and bone disorder (MBD), including secondary hyperparathyroidism, alterations in vitamin D activation, and renal osteodystrophy. In regard to bone disease, in particular, there is interest in maintaining biochemical markers, including corrected calcium, phosphorus, and measures of the intact parathyroid hormone (PTH), within normal values in order to suppress parathyroid hormone secretion and restore normal skeletal development. Controlling elevated serum phosphorus levels, restoring vitamin D levels, and directly targeting suppression of PTH production remain targets for effective treatment of this condition. National and international organizations and working groups, including the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative and Kidney Disease, Improving Global Outcomes, have published clinical guidance documents to encourage best practices in managing CKD–MBD.

A multitude of drug classes, including phosphate binders, vitamin D analogues, and calcimimetics, have been developed for directly or indirectly influencing markers of CKD–MBD. Notably, within the calcimimetic class of agents, cinacalcet (Sensipar, Amgen, Inc.) and etelcalcetide (Parsabiv, Amgen, Inc.) are two medications available in the U.S. Cinacalcet, an oral tablet, was approved by the Food and Drug Administration (FDA) in March 2004. This drug was the first calcimimetic indicated for patients with CKD on dialysis with secondary hyperparathyroidism and patients with hypercalcemia due to parathyroid carcinoma or patients who are unable to undergo parathyroidectomy. Etelcalcetide, an intravenous (IV) calcimimetic agent, received FDA approval in 2017 for treatment of secondary hyperparathyroidism in adult patients with CKD on hemodialysis. This article focuses on etelcalcetide.

PHARMACOLOGY
Although cinacalcet and etelcalcetide are both calcimimetic drugs, these agents differ in their mechanism of reducing PTH production. Etelcalcetide is a synthetic peptide that allosterically activates the calcium sensing-receptor (CaSR) in the extracellular domain of the receptor, located on the parathyroid chief cells. By binding to the CaSR, it enhances the activation of the receptor by extracellular calcium, which results in decreased PTH secretion. Cinacalcet, in contrast, directly lowers PTH by increasing the sensitivity of the CaSR to extracellular calcium. While etelcalcetide binds in the extracellular N-terminal domain of the CaSR, cinacalcet binds within the seven-transmembrane domain of the CaSR, indicating these agents have different receptor sites where they exert their pharmacological effects.

PHARMACOKINETICS
In patients with CKD receiving hemodialysis, etelcalcetide has demonstrated linear pharmacokinetics. The pharmacokinetics do not change over time with single or multiple IV doses, and etelcalcetide has demonstrated triexponential decay.

In a single-dose and multiple-dose study that evaluated the pharmacokinetics, pharmacodynamics, and safety and tolerability of etelcalcetide in Japanese hemodialysis patients, etelcalcetide exhibited a dose-dependent reduction in serum PTH and serum calcium. Etelcalcetide plasma concentration predialysis reaches steady state around week 4. Plasma concentration decreases rapidly after IV administration, but remains stable after 24 hours and up to the time of the next dialysis session, and then decreases during dialysis.

Distribution
Etelcalcetide has an onset of action within 30 minutes of administration and a peak time to effect in seven to eight weeks. The effective half-life of etelcalcetide is three to four days, and the volume of distribution at steady state is approximately 796 L. The majority of etelcalcetide in vivo is bound to albumin via reversible covalent binding, and its unbound ratio is 0.53.
Metabolism

Etelcalcetide is not metabolized by hepatic cytochrome P450 (CYP) isoenzymes. Rather, it is biotransformed in the blood via reversible disulfide exchange with endogenous thiols, which forms conjugates with serum albumin. After administration of a single, radiolabeled dose of etelcalcetide, approximately five times the biotransformed product is found in the plasma compared with the concentration of etelcalcetide itself.

Excretion

In patients with normal renal function, etelcalcetide is eliminated by the kidneys. In patients with CKD requiring hemodialysis, however, etelcalcetide is eliminated by hemodialysis and has a clearance value of 7.66 L/hour. While most of the drug is eliminated through hemodialysis, 7% of etelcalcetide can be found in the urine and feces in combination during a 175-day collection period. According to population pharmacokinetic analyses, body weight (29–163 kg), gender, race, and age (20–93 years) do not alter the pharmacokinetics of etelcalcetide. Dose adjustment in patients with hepatic impairment is not required.

PHASE 3 CLINICAL TRIALS

Block et al. conducted two phase 3, parallel, randomized, placebo-controlled, double-blind, 26-week trials to evaluate the efficacy and safety of etelcalcetide in 1,023 patients with CKD and secondary hyperparathyroidism on hemodialysis. Baseline characteristics in both trials were balanced. The primary efficacy endpoint was the proportion of patients achieving a greater than 30% reduction from baseline mean PTH concentrations during the assessment phase (week 20 to week 27). The secondary efficacy endpoint was the proportion of patients achieving a mean PTH of 300 pg/mL or less. Patients were administered etelcalcetide or placebo three times a week following hemodialysis.

The mean age of the patients was 58.2 years with a standard deviation of 14.4, and 60.4% of patients were men. A notable difference between the two trials is that predialysis and postdialysis laboratory data and electrocardiograms were obtained in Trial 2 while only predialysis measurements were taken in Trial 1. In addition, Trial 1 had more patients who were using hemodialfiltration rather than hemodialysis (16.1% versus 12.8%) and fewer patients using low baseline dialysate calcium concentrations (6.1% versus 10.1%).

The starting dose for the trials was 5.0 mg, which could be increased in increments of 2.5 mg or 5.0 mg during weeks 5, 9, 13, and 17 (maximum dose, 15 mg). The study drug was temporarily withheld if a patient’s level of PTH was less than 100 pg/mL. The dose was not increased if the patient’s PTH concentration was 300 pg/mL or less, serum calcium was less than 8.3 mg/dL, the patient had symptomatic hypocalcemia, or according to investigator judgment.

In Trial 1, 254 patients were randomized to the etelcalcetide arm, and 254 patients were given placebo. Seventy-four percent of patients who were randomized to etelcalcetide achieved the primary endpoint versus 8.3% of placebo-treated patients (P < 0.001). Patients randomized to etelcalcetide were also more likely to achieve a PTH level of 300 pg/mL or less (49.6% for etelcalcetide versus 5.1% for placebo; P < 0.001). The difference between patients achieving the secondary efficacy endpoint was significant (P < 0.001).

In Trial 2, 255 patients were randomized to etelcalcetide, and 260 were randomized to receive placebo. Of the patients who were randomized to etelcalcetide, 75.3% met the primary endpoint while 9.6% met the primary endpoint in the placebo arm (P < 0.001). Patients randomized to etelcalcetide achieved a PTH level of 300 pg/mL 53.3% of the time versus 4.6% of patients on placebo.

More than 50% of patients on etelcalcetide achieved a greater than 30% reduction in PTH in less than six weeks. Patients treated with etelcalcetide also exhibited a decrease in serum intact fibroblast growth factor 23, bone-specific alkaline phosphatase, and collagen type-1 cross-linked C-telopeptide. However, etelcalcetide-treated patients were more likely to experience muscle spasms, nausea, and vomiting than placebo-treated patients.

Based on the findings of these two trials, etelcalcetide demonstrated a favorable effect compared with placebo on achieving a statistically significant reduction in PTH of greater than 30% in less than six weeks along with a reduction in markers of bone function. Etelcalcetide use was generally safe and well tolerated.

An additional phase 3 trial conducted by Block et al. was unique in that it was a head-to-head comparison of the relative efficacy and safety of the IV calcimimetic etelcalcetide and the oral calcimimetic cinacalcet. This study was a double-blind, randomized, double-dummy, active clinical trial that was conducted in 164 sites in the United States, Canada, Europe, Russia, and New Zealand for 26 weeks. Patients were randomized to IV etelcalcetide and oral placebo (n = 340) or IV placebo and oral cinacalcet (n = 343). The mean age of patients enrolled was 54.7 years old, and 56.2% were men. While the oral drug was administered daily, the IV drug was administered three times a week with hemodialysis. The primary efficacy endpoint was the noninferiority of etelcalcetide in achieving a more than 30% reduction from baseline in mean predialysis PTH concentrations during week 20 to week 27, with a noninferiority margin of 12%. The secondary endpoints of this study were superiority in achieving biochemical endpoints, a greater than 50% and a greater than 30% reduction in PTH, and self-reported nausea and vomiting.

The results of this study concluded that etelcalcetide was noninferior and superior to cinacalcet in achieving the primary endpoint. The difference in the proportion of etelcalcetide-treated patients achieving a more than 30% reduction in PTH concentrations compared with patients receiving cinacalcet was −10.5% (95% confidence interval, −17.5% to −3.5%; P for noninferiority, < 0.001; P for superiority, 0.004). Of the 178 patients randomized to etelcalcetide, 52.4% achieved a more than 50% reduction in PTH concentrations (versus 40.2% with cinacalcet; P < 0.001). The most common adverse effect was decreased blood calcium, which occurred in 68.9% of patients given etelcalcetide and 59.8% of patients taking cinacalcet. Overall, etelcalcetide had minimal side effects, and the adverse effects profile consisted of decreased blood calcium, nausea, and vomiting.

SAFETY AND TOLERABILITY

A summary of the reported adverse effects of etelcalcetide can be found in Table 1. Monitor patients’ corrected serum calcium and PTH levels during dose initia-
tions, dose adjustment, and dose maintenance according to the schedule provided in the full prescribing information. Patients should not start etelcalcetide if their corrected serum calcium levels are less than the lower limit of normal; therefore, corrected serum calcium levels should be measured prior to initiation. After initiation, corrected serum calcium levels should be measured within one week after initiation or following a dose adjustment and every four weeks during treatment. The dose of etelcalcetide should be increased in increments of 2.5 mg or 5 mg if the patient’s correct serum calcium is within the normal range and PTH levels are above the recommended target range. The maximum recommended dose is 15 mg administered at each hemodialysis treatment three times a week. In the case of patients with corrected serum calcium levels falling below the lower limit of normal or exhibiting signs of hypocalcemia, patients should start or increase calcium supplementation and may have to reduce the dose of etelcalcetide or discontinue the medication.

**CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS**

Etelcalcetide is contraindicated in patients with known hypersensitivity to etelcalcetide or its excipients. One precaution associated with etelcalcetide is hypocalcemia, which can lead to QT interval prolongation and ventricular arrhythmia or seizures. Hypocalcemia can also occur with coadministration of etelcalcetide with other oral calcium-sensing receptor agonists. When switching from cinacalcet to etelcalcetide, patients should discontinue cinacalcet for at least seven days prior to initiating etelcalcetide. No studies have been done in patients switching from etelcalcetide to cinacalcet. In addition, ensuring the corrected serum calcium level is at or above the lower limit of normal prior to initiation, an increase in dose, or re-initiation of therapy after a dosing interruption is imperative.

Worsening heart failure was noted in 2% of patients treated with etelcalcetide versus 1% in the placebo group. Cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Two patients taking etelcalcetide had upper gastrointestinal bleeding at the time of death, but the cause of death is unknown. Adynamic bone may also develop if PTH levels are chronically suppressed. If PTH levels fall below the recommended target range, doses of vitamin D and/or etelcalcetide should be reduced or discontinued. It is also not recommended for use when breastfeeding.

Because etelcalcetide is a peptide, there is risk for immunogenicity. In the clinical trial participants treated with etelcalcetide for up to six months, 71 of 995 (7.1%) tested positive for binding antietelcalcetide antibodies (57 patients have pre-existing antietelcalcetide antibodies). There was no evidence of altered pharmacokinetics, clinical response, or safety associated with pre-existing or developing antibodies.

**DRUG FORECAST**

**Table 1 Percentage of Adverse Effects in Individuals Receiving Etelcalcetide Compared With Placebo**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Etelcalcetide (n = 503)</th>
<th>Placebo (n = 513)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood calcium decreased</td>
<td>64</td>
<td>10</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*a* Asymptomatic reduction in calcium (below 7.5 mg/dL) or clinically significant asymptomatic reductions in corrected serum calcium.

*b* Symptomatic reductions in corrected serum calcium < 8.3 mg/dL.

**Drug Interactions**

During *in vitro* assessment, etelcalcetide did not inhibit or induce CYP enzymes, and it is not a substrate of CYP enzymes. Etelcalcetide was not a substrate of efflux and uptake transporter proteins and was also not an inhibitor of common transporter proteins.

**STORAGE, DOSAGE, AND ADMINISTRATION**

Etelcalcetide vials must be stored in the original carton in the refrigerator at 2° to 8° C (36° to 46° F) away from light. After removal from refrigeration, the vials should not be exposed to temperatures greater than 25° C (77° F) and should be used within seven days if stored in the original carton or within four hours if removed from the carton. Etelcalcetide should not be mixed or diluted prior to administration and should be inspected for particulate matter or discoloration. Etelcalcetide is administered via IV bolus injection into the venous line of the dialysis circuit at the end of hemodialysis during the rinse back. It can also be administered IV after the rinse back.

**P&T COMMITTEE CONSIDERATIONS**

The cost of treatment with either cinacalcet or etelcalcetide is dose dependent because each drug is titrated according to patient response. Cinacalcet is initiated at a dose of one 30-mg oral tablet once daily. If a patient continues this initial treatment for one month, the average wholesale price (AWP) is $968 for a 30-count package of 30-mg tablets. A patient’s maintenance dose is determined by PTH response and can range from 30 mg once daily to 180 mg once daily. The AWP for a one-month supply of cinacalcet at the maximum dose is $5,808. Etelcalcetide is administered IV by a health care provider following hemodialysis at a starting dose of 5 mg three times a week. A one-week course at the starting dose has an AWP.
of approximately $589. A patient’s maintenance dose, based on PTH and serum calcium response, can be as little as 2.5 mg three times per week (AWP for one week, $294) or as high as 15 mg three times per week (AWP for one week, $1,765). Starting on January 1, 2018, both cinacalcet and etelcalcetide began to be paid for by Medicare through an add-on adjustment to the end-stage renal disease (ESRD) prospective payment system (PPS) base rate. The ESRD PPS includes all renal dialysis services, drugs, and biologics. Specifically, they are paid for using a transitional drug add-on payment adjustment (TDAPA), which is covered by Medicare Part B. For patients that have commercial insurance, copay card programs are available, and for uninsured or underinsured patients, Amgen Safety Net may be able to assist with the cost of both products.

Etelcalcetide represents another option for controlling elevated parathyroid hormone levels in the treatment of CKD–MBD in patients with ESRD on maintenance hemodialysis and could be considered as an alternative therapeutic option when treatment with a calcimimetic is indicated, but cinacalcet is not suitable or cost-effective. The availability of a parenteral formulation offsets the need to administer yet another oral medication for these patients, and administration on dialysis treatment ensures compliance. It has demonstrated comparable efficacy to cinacalcet in clinical trials, with reduced potential for drug interactions and a favorable safety profile.

CONCLUSION

The approval and availability of etelcalcetide represents another treatment option for managing the mineral and bone disorder associated with CKD. The availability of an IV formulation that allows the consolidation of a patient’s medication regimen and permits one more drug to be administered while on dialysis represents a shifting of responsibility and potential opportunity to improve compliance in patients with already complex medication administration regimens who frequently suffer from nausea and vomiting due to their underlying medical condition. Questions remain regarding the clinical use of etelcalcetide in patients receiving home hemodialysis or nocturnal hemodialysis or peritoneal dialysis because this agent was only studied with in-center hemodialysis. There is a lack of data, at present, regarding the safety and efficacy of etelcalcetide in children (unlike cinacalcet) and regarding use in peritoneal dialysis, where cinacalcet and use of an orally administered therapy by the patient is reasonable. Ongoing studies evaluating the effects of etelcalcetide on left ventricular remodeling when used in the management of mineral and bone disorder in patients with CKD requiring chronic dialysis are under way. Recruitment for a study designed to evaluate the use of etelcalcetide in pediatric patients 2 years to less than 18 years of age is in progress.

REFERENCES


