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*APPLICATION NUMBER:*

**208325Orig1s000**

**SUMMARY REVIEW**

## Summary Review of Class 2 Resubmission

<b>Date</b>	2/2/2017
<b>From</b>	Marina Zemskova, MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	208325
<b>Supplement#</b>	
<b>Applicant</b>	Amgen
<b>Date of Submission</b>	12/13/2016
<b>PDUFA Goal Date</b>	2/9/2017
<b>Proprietary Name / Established (USAN) names</b>	Parsabiv/etelcalcetide
<b>Dosage forms / Strength</b>	Solution for injection/ 5 mg, 10 mg, (b) (4)
<b>Proposed Indication(s)</b>	Secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis
<b>Recommended:</b>	Approval

### Memorandum

On December 13, 2016 Amgen resubmitted a New Drug Application (NDA) for Parsabiv (etelcalcetide) under Section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act in support of the following indication:

*Treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis.*

This NDA was originally submitted to the Agency on 8/24/2015. Data to support the application were reviewed and summarized during the previous cycle. Refer to these previous memoranda for details.

The Division issued a Complete Response (CR) because agreement between the Applicant and the Division on the proposed labeling could not be reached. During the previous cycle, the Agency requested that the Applicant (b) (4)

(b) (4) in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis. (b) (4)

(b) (4)  
 (b) (4)  
 (refer to CDTL review from 8/ 24/2016 and CR Letter from 8/24/2016 in DARRTS).

In the current submission, the Applicant provided a complete response to the deficiencies outlined in the Division’s CR Letter on 12/9/2016 and accepted changes to Prescribing Information proposed by the FDA. Specifically, Amgen agreed to (b) (4) in the treatment

of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis from the label [REDACTED] (b) (4).

### **Proprietary Name**

The proposed proprietary name for etelcalcetide, Parsabiv, was reassessed and deemed acceptable by the Office of Medication Error Prevention and Risk Management (refer to the review from 1/3/2017). A letter stating this was issued to the Applicant on 1/3/2017.

### **Safety Update**

Updated safety data on 884 patients with CKD on hemodialysis participating in an, ongoing, long-term, open-label, extension study (i.e., Study 20130213 or Study 213 for short) was included in the current submission and reviewed by Dr. Sullivan. The new data covers the period from July 18, 2015 (the date of the last 120-day safety update included in the original application and reviewed by the Division) to October 6, 2016 (database lock for re-submission). Dr. Sullivan concludes that the reported causes of death and SAEs in this interim analysis are not unexpected in a population of patients with CKD requiring hemodialysis and who are at high risk for cardiovascular disease and infection. She assessed the rates of adverse events as comparable to those observed in the original submission and did not identify new adverse events current submission.

In the current submission, the Applicant provided updated information and analyses related to events of fatal gastro-intestinal bleeds based on re-review of the data in Amgen's Global Safety Database (AGSD). Three additional cases of fatal GIB were identified by the Applicant since the last review cycle for a total of 10 fatal GI bleed in patients treated with etelcalcetide in the etelcalcetide clinical program to date. Dr. Sullivan reviewed the three new cases and concluded that no new cases of upper GI bleed were reported in this submission. Of the three new cases with fatal GI bleed, 2 patients had lower GI bleed and one patient had bleeding from a preexisting duodenal ulcer.

In addition, the Applicant also re-assessed three cases with fatal upper GI that were included in the original submission and USPI and concluded that only two of three patients had upper GI bleed and should be included in the label. These changes are based on the updated information for patient 0517-1547: this patient had a lower, and not an upper, GI bleeding at the time of death. Dr. Sullivan reviewed the narrative and the full autopsy report of this patient and agreed with the Applicant's conclusion that the new information excludes an upper GI bleed.

In conclusion, I agree with Dr. Sullivan that no new safety signals is identified in the extension study in patients with CKD on hemodialysis and secondary hyperparathyroidism were identified in the current submission.

### **Labeling**

1. The Applicant's proposed changes to the label are:

- [REDACTED] (b) (4)  
in the treatment of secondary hyperparathyroidism in patients with chronic kidney

- disease on hemodialysis (b) (4)  
outlined in CR letter from 8/24/2016..
- The Applicant also proposed the numerical change in Section 5.3, i.e. *“In clinical studies, ~~three~~ two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death...”*. These changes are acceptable as discussed above.
  - The Applicant also removed the adverse reaction of vomiting Adverse Reactions section in Highlights because the incidence of vomiting was 9%, and Adverse Reactions section in Highlights listed only adverse reactions seen in (b) (4) % of patients. Since vomiting is a known common adverse event associated with etelcalcetide (and with calcimimetics as a drug class), the Division recommended to include adverse reactions that occurred in > 5% of subjects in order to capture the adverse event of vomiting. The Applicant accepted the proposed modifications (refer to the clinical review in DARRTS from 1/30/2017).
2. The statistical reviewer revised the label and recommended to modify table 3 in Section 14 of the label in order to include analyses results that provide the most reliable estimate of the treatment difference after appropriately address missing data (refer to the review in DARRTS from 1/26/2017). The Applicant modified the table accordingly.

The revised label was reviewed by associate director for labeling, by DMEPA reviewer (refer to the review in DARRTS from 1/5/2017), by OPDP reviewer (refer to the review in DARRTS from 1/13/2017) and was found to be acceptable.

### **Conclusion:**

The applicant has adequately addressed all deficiencies listed in the Division’s CR letter issued on 28 March 2016.

A review of the data submitted in the original NDA concluded that the Applicant provided substantial evidence to support the safety and effectiveness of Parsabiv in patients with CKD on hemodialysis (refer to the CDTL review from 8/24/2016).

No new information or data was included in the re-submission of the NDA that would change risk/benefit assessment of Parsabiv in the intended population.

Numerical change in Section 5.3 of the label that only two patients (not three patients as stated in the original label) had upper GI bleeding at the time of death is acceptable.

### **Recommended Regulatory Action**

I recommend approval of Parsabiv for the following indication:

*Treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis.*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARINA ZEMSKOVA

02/03/2017

JEAN-MARC P GUETTIER

02/03/2017

Dr. Zemskova has summarized the issues and new data in this complete response. The applicant has adequately responded to the deficiency in the Complete Response Letter and new safety data do not alter the original benefit risk assessment (see original CDTL memorandum). The applicant has agreed to the label and I concur with Dr. Zemskova's assessment and recommend approval.

## Summary Basis for Regulatory Action

<b>Date</b>	August 24, 2016
<b>From</b>	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
<b>Subject</b>	Summary Review
<b>NDA/BLA #</b>	208325
<b>Supp #</b>	
<b>Applicant Name</b>	Amgen
<b>Proprietary / Established (USAN) Names</b>	Parsabiv etelcalcetide
<b>Dosage Forms / Strength</b>	Single-use vials of solution for intravenous (IV) administration 5 mg/ mL Proposed starting dose: 5 mg injection three times a week to a maximum dose of 15 mg three times a week.
<b>Proposed Indication(s)</b>	Secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis
<b>Action:</b>	<i>Complete Response</i>

### Benefit-Risk Summary and Assessment

The applicant has proposed marketing Parsabiv, an allosteric activator of the calcium-sensing receptor (CaSR)<sup>1</sup>, for the treatment of secondary hyperparathyroidism (SHPT) in adults with chronic kidney disease on hemodialysis.

Secondary hyperparathyroidism (SHPT) refers to parathyroid gland hyper-function caused by an underlying disease that affects phosphorus, calcium or vitamin D metabolism (e.g., chronic kidney disease, Gastrointestinal, primary vitamin D metabolism disease etc.). Loss of kidney function perturbs vitamin D metabolism and mineral homeostasis and advanced chronic kidney disease (CKD) is the most common cause of secondary hyperparathyroidism.

Chronically elevated levels of circulating parathyroid hormone (PTH<sup>2</sup>), the biochemical hallmark of hyperparathyroidism, leads to increased bone turnover and bone resorption and in the absence of normal functioning kidneys to elevated circulating levels of calcium and phosphorus. The changes in PTH regulation that accompany progression of renal disease, along with changes in the regulation of Vitamin D and Fibroblast Growth Factor-23, contribute to the mineral and bone disorders associated with CKD (i.e., CKD-Mineral and Bone Disorders). These disorders have been associated with vascular calcification (media of vessel walls and heart valves) and with defects in bone turnover and mineralization and are believed to contribute to both the cardiovascular (i.e., hypertension, left ventricular hypertrophy, calcific uremic arteriopathy) and skeletal (i.e., fracture, bone pain) complications of chronic kidney disease. Therapies to treat CKD-Mineral and Bone Disorders, including those indicated for the treatment of secondary hyperparathyroidism in adults with chronic kidney disease on hemodialysis, aim to prevent skeletal and cardiovascular complications of CKD.

<sup>1</sup> The term “calcimimetic” will be used to refer to allosteric activators of the calcium-sensing receptor for simplicity

<sup>2</sup> PTH in this review refers to intact PTH or the full length, 84 amino acid, protein.

Documentation of a drug-induced decrease in serum PTH has been used as a surrogate to establish the efficacy, and support the full approval, of several marketed therapies indicated for the treatment of secondary hyperparathyroidism in adult patients with CKD on hemodialysis (i.e., vitamin D analogs and an oral allosteric activator of calcium sensing receptors). In the regulatory context, we have allowed that a significant reduction in levels of PTH from baseline (i.e., at least 30%) correlates with a reduction in adverse skeletal outcomes (e.g., fracture, bone pain) and establishes the benefit of these drugs for that indication. However, there is some uncertainty around the validity of this assumption because of an absence of prospective, controlled, data establishing that interventions that reduce PTH levels reduce the risk of skeletal complications in this population. Absent these data, it is not possible to verify whether the assumption is valid or to determine the exact relationship between drug induced PTH changes and risk of skeletal complication.

The most recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines recognize this uncertainty and state that the optimal PTH in adult dialysis patients with secondary hyperparathyroidism is not known but recommend maintaining PTH levels in the range of 2 to 9 times the upper limit of normal (e.g., 130-600 pg/mL). While some observational data suggest an association between very highly elevated PTH levels (>600 pg/mL) and the risk of death and cardiovascular event in this population, the only prospectively planned, randomized, controlled trial designed to examine the relationship between PTH lowering and CV-risk reduction (i.e., the EVOLVE trial<sup>3</sup>) did not clearly and definitively establish that PTH lowering with an oral allosteric activator of calcium sensing receptors co-administered with standard of care therapies for CKD-Mineral and Bone Disorders reduces the risk of death or major cardiovascular events in patients with moderate-to-severe secondary hyperparathyroidism on dialysis.

### Benefits

The applicant demonstrated, in two adequate and well-controlled trials carried out in adults with secondary hyperparathyroidism due to CKD on hemodialysis, that Parsabiv significantly reduced baseline PTH levels compared to placebo at the end of 6 months. In these two trials a greater proportion of individuals randomized to Parsabiv experienced a 30% reduction in PTH levels from baseline compared to placebo (i.e., 75% versus 9% respectively). PTH levels decreased, on average, by 56% from baseline in the Parsabiv group and rose by 13% from baseline in the placebo group [PBO-adjusted difference (95% CI); -71.3% (-75.8, 66.8)]. Directional changes in mineral (calcium, phosphorus) and bone-turnover biomarkers (CTX and BASP) were consistent with expectations and suggest that Parsabiv use is associated with a net decrease in bone resorption. The overall data in these two trials establish the benefit of Parsabiv. Notwithstanding the uncertainty noted above, it is expected that Parsabiv will have salutary effects on bone disease associated with CKD and will reduce the risk of skeletal complications (i.e., fracture, bone pain) in these patients.

Vitamin D analogs are considered first line therapy in the treatment of SHPT in patients with CKD on hemodialysis but these drugs can cause hypercalcemia and hyperphosphatemia which can limit their usefulness. Treatment with a calcium sensing receptor (CaSR) agonist is recommended when adequate control of PTH cannot be achieved with a vitamin D analog as these drugs lower PTH without raising circulating levels of calcium and phosphorus. The only calcimimetic approved for the treatment of SHPT in patients on dialysis is the oral tablet Sensipar (cinacalcet). Parsabiv would be the second calcimimetic to be marketed and would be administered intravenously at the end of the dialysis. Compared to a once daily oral drug, Parsabiv would reduce the high daily pill burden in this population and may facilitate management of SHPT.

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<sup>3</sup> N Engl J Med 2012; 367:2482-2494

The applicant submitted a comparative efficacy study which compares PTH lowering achieved at the end of 6 months between Parsabiv and Sensipar and seeks to show data that would suggest Parsabiv has superior efficacy than Sensipar. The superiority claim was not found to be substantiated because it is derived from a single trial and because the drugs were not compared at each of their maximally effective doses. Although a slightly higher proportion of patients on etelcalcetide were observed to have a greater than 30% and greater than 50% decrease in PTH by trial end, review of these data suggest that this was, at least in part, attributable to suboptimal dosing of Sensipar in the trial. Even without the fairness of comparison issue, the absolute numerical difference in PTH lowering was small between the two groups and ultimately of unknown clinical relevance. Finally, no clear differences in tolerability were observed between the two drugs to suggest one is superior to the other.

### Risks

The risks associated with the use of Parsabiv are generally consistent with risks expected for the calcimimetic class of drugs. Gastrointestinal adverse reactions (i.e., nausea, vomiting), hypocalcemia, hypophosphatemia and oversuppression of PTH (that increase the risk for adynamic bone disease) are adverse reactions associated with this class and Parsabiv. Overall, incident nausea and vomiting was one of the most common reaction associated with Parsabiv use and occurred at a rate similar to that reported for Sensipar. The incidence of mineral abnormalities (hypocalcemia and hypophosphatemia) was slightly higher with Parsabiv compared to Sensipar. This may have been due to dose differences between the two groups (see above). These mineral abnormalities improved in the majority of patients with changes to concomitant therapies or with Parsabiv dose adjustment. These risks will be mitigated through product labeling which will include recommendations on the appropriate patient selection, on monitoring for occurrence of these reactions and on interventions to address these reactions including but not limited to Parsabiv dose adjustment.

Congestive heart failure (CHF) is an adverse reaction associated with the use of calcimimetics. The exact mechanism for this adverse reaction is not known but may be due to changes in circulating calcium levels caused by the drug or to a direct drug effect involving calcium-sensing receptors in cardiac tissue. A Warning and Precaution section discussing this safety concern will be included in labeling to ensure prescribers recognize Parsabiv may be associated with this risk and can take appropriate precautions in patients with this condition.

A small imbalance in fatalities due to upper gastrointestinal (GI) bleeding the Parsabiv clinical program. Three patients died due to an upper GI bleed versus zero across all comparators while on-treatment. Although this may represent a chance finding in a population known to be at high baseline risk, we could not completely exclude the possibility that the drug may have contributed to increasing this risk. Several factors were considered in recommending that this risk be labeled as a Warning and Precautions. First the risk was interpreted in the light of the fact that efficacy was based on a surrogate measure and some uncertainty around the exact benefit(s) of these drugs remain. Second, all cases resulted in death (arguably the most serious outcome), third a relationship between Parsabiv and gastrointestinal toxicity was found to be biologically plausible and fourth it was felt to be important to mitigate this potential risk by including instructions on patient selection, monitoring and interventions in labeling. With regard to biological plausibility the CaSR is known to be expressed in the gastric mucosa and to play a role in nutrient sensing and gastric secretion. Furthermore, data from non-clinical studies in rodents appeared to demonstrate a Parsabiv-related toxic effect on the gastro-intestinal mucosa. Finally, gastro-intestinal reactions are common Parsabiv-related reactions suggesting the drug may have an effect in the GI tract in humans.

The clinical trial data show that anti-drug antibody (ADA) formation is low with Parsabiv. The clinical data did not suggest an effect of ADA on safety or efficacy. There are no data on neutralizing

antibodies. Hypersensitivity reactions are a concern with all peptide products including Parsabiv. Incident allergic reactions were rare and all allergic reactions were mild and no events of anaphylaxis were reported in the clinical development program.

Overall, the benefits of using Parsabiv for the treatment of SHPT in patients with CKD on hemodialysis outweigh the identified risks. Parsabiv resulted in a large and significant decrease in PTH levels in most patients. These changes should improve bone health and decrease bone-related morbidities (bone pain and fractures). The safety profile was found to be generally consistent with the safety profile of the other approved calcimimetic. In the data, a 3 to 0 imbalance in fatal events of upper GI bleed was observed. It is unclear whether this is real or due to chance. However, in light of the seriousness of the event this will be reported in labeling to ensure prescribers consider this a potential risk in their therapeutic decision making. To gain additional insights on the potential association between Parsabiv and events of upper GI bleeding, the applicant will be required to carry out an observational study as a post-marketing requirement. All other safety concerns will be mitigated by communicating risks in the product label and recommending appropriate patient selection, monitoring and dose adjustment if required.

I have discussed the details of my review and recommendation at length with Dr. Jean-Marc Guettier, Division Director for the Division of Metabolism and Endocrinology products, and he concurs with my assessment of the benefits and risks for Parsabiv and with my decision to recommend approval of this product for the treatment of secondary hyperparathyroidism (SHPT) in adults with chronic kidney disease on hemodialysis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#">Analysis of Condition</a></p>	<ol style="list-style-type: none"> <li>1. Chronically high levels of PTH in patients with CKD on dialysis increase bone turnover and cause excessive loss of calcium and phosphorus from bone contributing to metabolic bone disease (i.e., renal osteodystrophy) and calcification of extra-osseous tissues (e.g., cardiovascular tissues).</li> <li>2. Prospective, controlled, data establishing that interventions that reduce PTH levels reduce the risk of skeletal or cardiovascular complications in this population are not available.</li> <li>3. The 2009 KDIGO guidelines, recommend treating elevated PTH levels in subjects with CKD on dialysis as a means to prevent bone and CV-risk complications. The PTH level associated with a reduced risk of bone and CV complications in these patients is not known. The current recommendations is to maintain PTH levels between two and nine times the</li> </ol>	<ol style="list-style-type: none"> <li>1. Chronically high levels of PTH could lead to bone pain, fractures, arrhythmias, coronary artery disease or other CV complications (i.e., hypertension).</li> <li>2. Treatments to lower chronically high PTH levels in this population aim to prevent the skeletal and cardiovascular complications. Establishing that a drug reduces PTH by a large amount has been used as a surrogate to support full approval of drugs to treat secondary hyperparathyroidism (SHPT) in the setting of renal disease.</li> <li>3. The optimal PTH level to prevent skeletal and cardiovascular complications is not known.</li> </ol>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>upper limit of normal (UNL) for the assay.</p>	
<p><a href="#">Current Treatment Options</a></p>	<ol style="list-style-type: none"> <li>1. Oral and injectable active vitamin D analogs (e.g., calcitriol, doxercalciferol and paricalcitol)</li> <li>2. Oral calcimimetic (e.g., cinacalcet)</li> <li>3. Treatment of SHPT occurs in parallel with correction of mineral abnormalities (hyperphosphatemia and hypocalcemia) which are also implicated in the bone disease and mineral metabolism disorders associated with chronic kidney disease.</li> </ol>	<ol style="list-style-type: none"> <li>1. Vitamin D analogs are first line in the treatment of SHPT in patients with CKD on hemodialysis but this class of drugs can be associated with hyperphosphatemia and hypercalcemia.</li> <li>2. Calcimimetics can lower PTH levels without increasing calcium and phosphorus levels which may be desirable for some patients. There is no intravenous (IV) calcimimetic and Parsabiv would be the first IV CaSR to be approved.</li> <li>3. Parsabiv will used with standard of care drugs to treat CKD-Mineral and Bone disorders.</li> </ol>
<p><a href="#">Benefit</a></p>	<ol style="list-style-type: none"> <li>1. Parsabiv reduced PTH levels by &gt; 30% in the majority (75%) of patients with SHPT and CKD on hemodialysis compared to placebo (9%) in two adequate and well controlled studies.</li> <li>2. The mean placebo-adjusted percent change from baseline to final visit in serum PTH levels was a decrease of 69% across the two placebo controlled trial. Bone turnover marker revealed a trend towards decrease bone resorption. Calcium and phosphorus levels decreased with use of Parsabiv.</li> <li>3. An active comparator trial against cinacalcet reported slightly greater PTH lowering efficacy of Parsabiv over cinacalcet. However, in this study dosing of cinacalcet was not optimal and the comparison was biased in favor of Parsabiv.</li> <li>4. The magnitude of the observed difference in PTH between the two arms is small and of unknown clinical significance.</li> </ol>	<ol style="list-style-type: none"> <li>1. Treatment with Parsabiv should reduce the risk of skeletal complications in CKD patients with SHPT receiving hemodialysis.</li> <li>2. Treatment with parsabiv should reduce the risk of skeletal complications in CKD patients with SHPT receiving hemodialysis and help in the management of mineral metabolism in these patients.</li> <li>3. The claim that Parsabiv has a superior PTH lowering effect than cinacalcet is not substantiated because it is derived from a single trial and the trial dosing design between groups favored Parsabiv. The comparative PTH lowering efficacy of the two drugs when both are used at maximally effective doses remains unknown.</li> <li>4. Even if the comparison had been fair, it is unclear that observed between group differences are large enough to have a clinically meaningful effect on outcomes (bone pain, fractures, end-organ damage, etc.).</li> </ol>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk</u>	<ol style="list-style-type: none"> <li>1. The safety profile of Parsabiv has been generally well characterized and is generally consistent with the class.</li> <li>2. The incidence of mineral abnormalities observed (hypocalcemia and hypophosphatemia) was slightly higher with Parsabiv compared to cinacalcet.</li> <li>3. Over-suppression of PTH levels may predispose patients to adynamic bone disease. Incidence of PTH suppression to &lt; 100 pg/ml observed with Parsabiv was slightly higher compared to cinacalcet; however, no other clinical evidence of adynamic bone disease was seen.</li> <li>4. Congestive heart failure is a known adverse reaction that has been associated with use of calcimimetic drugs, including Parsabiv. The mechanism is unclear.</li> <li>5. More fatal GI bleeding events (3 versus 0) were seen in the Parsabiv clinical program. While the exact etiology for these events is not clear, the clinical and nonclinical data raise the possibility that these events could potentially be drug-related.</li> <li>6. The ADA data did not raise any particular immunogenicity concerns. The pre-marketing clinical safety data did not raise concerns related to severe allergic reactions with this peptide.</li> </ol>	<ol style="list-style-type: none"> <li>1. Treatment with Parsabiv is associated with nausea/vomiting. Risks of hypocalcemia and hypophosphatemia are monitorable risks.</li> <li>2. Differential use of maximally effective doses between groups may account for this difference. Monitoring and dose adjustment will be recommended to mitigate these risks.</li> <li>3. Over-suppression of PTH is a monitorable risk. The risk of adynamic bone disease will be mitigated through labeling.</li> <li>4. The risk of CHF will be mitigated by proper patient selection, monitoring and dose adjustment if required.</li> <li>5. The potential risk for fatal upper GI bleeds will be communicated through labeling and mitigated through proper patient selection and monitoring. The signal will be further characterized and followed in a post-marketing requirement (i.e., an observational study).</li> </ol>
<u>Risk Management</u>	<ol style="list-style-type: none"> <li>1. A post-marketing requirement for an observational study to further characterize the potential relationship between Parsabiv use and upper GI bleeding will be issued.</li> <li>2. Labeling will be used to mitigate against the real or potential serious risks of hypocalcemia, CHF, and</li> </ol>	<ol style="list-style-type: none"> <li>1. There are insufficient data to conclude whether an association between Parsabiv and GI bleeding is real or the product of chance. More data are needed to reduce the uncertainty around this risk. Several study options (i.e., spontaneous reports, Sentinel)</li> </ol>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>upper GI bleeding.</p> <p>3. No risks identified require risk management beyond labeling to warrant consideration of a Risk Evaluation and Mitigation Strategy (REMS).</p>	<p>were considered and an observational study was determined to be best suited to address the question.</p> <p>2. Patient selection, monitoring and interventions will be recommended in labeling to address these risks.</p> <p>3. No REMS will be issued.</p>

## 1. Introduction

This review will be a brief summary of the basis for the regulatory action regarding etelcalcetide and I refer the reader to the other reviews in the action package for a more detailed discussion. Etelcalcetide is a synthetic peptide allosteric activator of the calcium-sensing receptor (calcimimetic) with the proposed use for secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis. Patients with worsening chronic kidney disease (CKD) are unable to excrete phosphorus or convert vitamin D to its active form which may result in low serum calcium. In response to these changes, parathyroid hormone (PTH) levels increase leading to excessive bone turnover, excessive calcium and phosphorus release from bone that can result in renal osteodystrophy and cause bone pain and increase the risk for fractures. Etelcalcetide enhances the activation of the calcium sensing receptor by extracellular calcium and in the parathyroid gland this leads to a reduction in PTH secretion and to lowering of serum PTH levels.

The information contained within this application demonstrates substantial evidence of efficacy of etelcalcetide in significantly (> 30%) decreasing elevated PTH levels in adult hemodialysis patients with secondary hyperparathyroidism and also demonstrates acceptable safety. The review team is recommending approval with appropriate labeling and I agree with this assessment.

Product quality, nonclinical pharmacology and toxicology, clinical pharmacology and clinical microbiology have been adequately reviewed and summarized in Dr. Zemskova's review. All of these disciplines are recommending approval with appropriate labeling. I will review pertinent aspects of efficacy and safety below.

**Addendum 8/24/2016:** We are not able to come to agreement with the sponsor regarding labeling, so this application will receive a CR. This will be explained further below in the addendum at the end of the review.

## Efficacy

This has been thoroughly covered in reviews authored by Drs. Lubas, Zemskova, and Cambon. The primary endpoint in two six month, randomized placebo-controlled trials for clinical efficacy studies was the proportion of individuals who by study end experienced an at least 30% reduction in intact parathyroid hormone (iPTH) from baseline. One randomized active-controlled non-inferiority trial (compared to cinacalcet) was also performed. Primary analysis results are demonstrated in the table below from Dr. Zemskovas' review.

**Table 1: Number and percentage of patients with PTH reduction > 30% at EAP in the Full Analysis Set (FAS) population in Study 229 and Study 230<sup>b</sup>.**

	<b>Etelcalcetide</b>	<b>Placebo</b>	<b>p value<sup>a</sup></b>
<b>Study 229</b>	N=254	N=254	
Responders, n (%)	<b>188 (74)</b>	<b>21 (8)</b>	<0.001
<b>Study 230</b>	N=255	N=260	
Responders, n (%)	<b>192 (75)</b>	<b>25 (10)</b>	<0.001
<b>Combined</b>	N=509	N=514	
Responders, n (%)	<b>380 (74.7)</b>	<b>46 (8.9)</b>	<0.001

<sup>a</sup>Based on the Cochran-Mantel-Haenszel test,

<sup>b</sup> Subjects with missing data during EAP are counted as non-responders

FAS defined as all randomized subjects. Source: Adapted from Dr. Cambon's review.

Secondary endpoints and exploratory endpoints are thoroughly covered in Dr. Zemskova's review. In summary, secondary endpoints related to bone and mineral biomarkers were directionally consistent with expected favorable effects from etelcalcetide.

Overall etelcalcetide demonstrated adequate efficacy in lowering PTH in patients receiving hemodialysis for chronic kidney disease. Changes in secondary endpoint were supportive of a salutary effect. The Agency accepts lowering of PTH as a surrogate of clinical benefit in patients with secondary hyperparathyroidism.

The primary objective of the active-controlled trial was to demonstrate non-inferiority of etelcalcetide to cinacalcet on achieving a > 30% reduction from baseline in serum iPTH. Non-inferiority was declared if the upper bound of the two-sided 95% CI of the treatment difference did not exceed 12%. The results are demonstrated below in a table taken from Dr. Lubas' review.

Table 1 Primary Endpoint for the Active Controlled Study 20120360

	Cinacalcet (N = 343)	AMG 416 (N = 340)	Treatment Difference
<b>Subject Status</b>			
Number of subjects	310	298	
Yes - n (%) <sup>a</sup>	198 (63.9)	232 (77.9)	
Screening iPTH < 900 pg/mL	112 (36.1)	120 (40.3)	
Screening iPTH ≥ 900 pg/mL	86 (27.7)	112 (37.6)	
North America	54 (17.4)	67 (22.5)	
Non-North America	144 (46.5)	165 (55.4)	
No - n (%) <sup>a</sup>	112 (36.1)	66 (22.1)	
Screening iPTH < 900 pg/mL	46 (14.8)	23 (7.7)	
Screening iPTH ≥ 900 pg/mL	66 (21.3)	43 (14.4)	
North America	43 (13.9)	20 (6.7)	
Non-North America	69 (22.3)	46 (15.4)	
Stratified <sup>b</sup> treatment difference of proportion <sup>c</sup> for subjects who achieve iPTH reduction > 30% during EAP (%)			-10.48
95% CI(%) <sup>d</sup>			(-17.45, -3.51)

Full analysis set: all randomized subjects

n=Number of subjects with observed data before imputation. CI=Confidence Interval.

<sup>a</sup>Subject has iPTH reduction > 30% (yes) or ≤ 30 % (no) during the EAP (study visits during week 20 to week 27, inclusive).

<sup>b</sup>Stratification factors based on mean screening iPTH level (<900 pg/mL, ≥ 900 pg/mL), and region (North America and Non-North America) from IXRS

<sup>c</sup>Mantel-Haenszel (M-H) estimator of the proportion difference of cinacalcet minus AMG 416

<sup>d</sup>If the upper bound of 95% CI is smaller than 12% (the non-inferiority margin), then AMG 416 is considered non-inferior to cinacalcet.

Pre-specified multiple testing procedures included tests for superiority to cinacalcet (key secondary endpoints); however, it is important to note that the primary endpoint was evaluated at Week 26 but no dose titration was allowed after 17 weeks. As pointed out by Dr. Zemskova, the demonstration of a greater effect with etelcalcetide is most likely just a function of a trial design which allowed for a higher starting percentage of the maximal dose for etelcalcetide (30% vs 17% of maximum dose), greater percentage of maximal dose for each dose escalation (again 30% vs 17%) and some other study design factors resulting in quicker titration for etelcalcetide than overall effect as the maximal dose of each drug was not compared in a comparable percentage of the population (14.3% for etelcalcetide vs 5% for cinacalcet). Additionally, there did not seem to be tolerability issues that would have warranted such a dose differential, indeed the data demonstrated that etelcalcetide actually had more hypocalcemia than the comparator. As such, the trial was not conducted under ‘level playing field’ conditions and etelcalcetide has not demonstrated ‘superiority’ but rather that a dose titration up to 16 weeks (with favorable dose escalation criteria) resulted in slightly lower PTH levels when monitored without dosage change for an additional 10 weeks for those receiving etelcalcetide.

The results of all three trials are summarized here in a table from Dr. Cambon’s review.

**Table 7: Primary and Secondary Analysis Results - Sponsor**

Study	Non-Responder Imputation			Response Rates Excluding Missing data	
	Response Rate Etelcalcetide	(> 30% Red. PTH) Cinacalcet	P-value	Response Rate Etelcalcetide	(> 30% PTH) Cinacalcet
229	74%	8%	<0.0001	-	-
230	75%	10%	<0.0001	-	-
360	68%	58%	0.004	80%	64%
360	Response Rate	(> 50% PTH)			
	52%	40%	0.0015	-	-

Results using sponsor's analysis method – FAS, CMH, non-responder imputation. Results using stratified logistic regression are almost identical. Unstratified chi-squared analysis for the active-control study 360: p-value =0.004.

### *Safety*

Safety findings have been thoroughly reviewed by Drs. Lubas and Zemskova. Please refer to their reviews for a detailed analysis. Adverse events were similar to those seen with the other approved calcimimetic agent and consisted mainly of hypocalcemia, hypophosphatemia and low serum PTH which may predispose to adynamic bone disease. There seemed to be an association of etelcalcetide use with nausea and vomiting, which also is not unusual for calcimimetic agents. There were a few cases of GI hemorrhage in the database, some associated with severe outcomes, and some types of events (ulcerations) more common in the etelcalcetide group. There was an imbalance in GI bleeding events associated with a fatal outcome with three in the etelcalcetide group and none in the placebo treatment group. Of the three deaths, the first occurred during the first two weeks of study and the other two patients died one and two weeks after drug discontinuation. The overall incidence of GI bleeding (upper and lower and regardless of severity) between subjects receiving etelcalcetide [2% (10/503)] and placebo [2.1% (11/513)] was similar. It is not clear, due to the limited number of events and serious concurrent diseases if there is a causal association with severe outcomes with GI hemorrhage and etelcalcetide or if the imbalance in fatal events is a chance finding. Dr. Zemskova also reviewed some animal data that may explain a possible mechanistic ground for the concern (perhaps for the class). The review team is recommending that a warning be included in the drug label for this potential risk and that a post-marketing requirement to further evaluate the signal be carried out. The team will also review possible further evaluation/actions for the class.

### *Advisory Committee Meeting*

An Advisory Committee meeting was not held as the drug is not the first in its class and the application did not raise significant safety or efficacy issues that were unexpected for this class in the intended population.

## **2. Conclusions and Recommendations**

This application contains data that support the efficacy of etelcalcetide in adult hemodialysis patients with secondary hyperparathyroidism. The intravenous dosage form and administration during the dialysis may result in greater compliance than the oral form of the medication. Etelcalcetide is not metabolized through the cytochrome P450 system as with the

other calcimimetic and therefore may have less of a concern for drug-drug interactions. The safety profile appears comparable to the other product. There was a concern regarding GI bleeding, but the number of cases is too small to establish with any degree of certainty the existence of a causal link.

I agree that etelcalcetide can be approved with appropriate labeling.

**Addendum (8/24/2016):**

(b) (4)  
(b) (4)  
(b) (4) I do not agree with this and will therefore take a CR action. As nicely summarized in Dr. Zemskova's review (b) (4)  
(b) (4)

Design issues were identified that placed the cinacalcet arm at a dosing disadvantage in the trial. These were summarized in details in Dr. Lubas and Zemskova's review and are briefly highlighted here.

1. The starting dose favored etelcalcetide. The starting dose for etelcalcetide represented 30% of the maximal dose compared to 17% of the maximal dose for cinacalcet (see #2).
2. The dose escalation instructions favored etelcalcetide. Etelcalcetide's doses are 5 to 15 mg. Dose increments could be 2.5 or 5 mg on a 4 week basis. Cinacalcet has doses of 30, 60, 90, 120, 180. Therefore, there could be 2 dose-steps of 5 mg (30% of the recommended maximal dose) to attain the maximum dose with etelcalcetide, compared to 4 dose-steps of 30 mg of cinacalcet (17% of the maximally recommended dose) to attain the maximum dose of cinacalcet. This in and of itself would not be a problem, if adequate time were allowed for patients to reach the appropriate dose, however this was not the case.
3. Time allowed for titration favored etelcalcetide. 17 weeks was the time for dose titration without adjustment afterwards. As we can see from the table below (Dr. Lubas, page 88), there was an imbalance of patients still requiring a dose increase by week 17 with over 3x more in the cinacalcet group.

Titration Visit	Number of Patients Requiring a Dose Increase		
	Cinacalcet	AMG 416	Difference
Week 5	140	94	46
Week 9	96	30	66
Week 13	68	17	51

Week 17	63	20	43
Source SDN 018 (8/15/16) Response to 25 July 2016 IR			

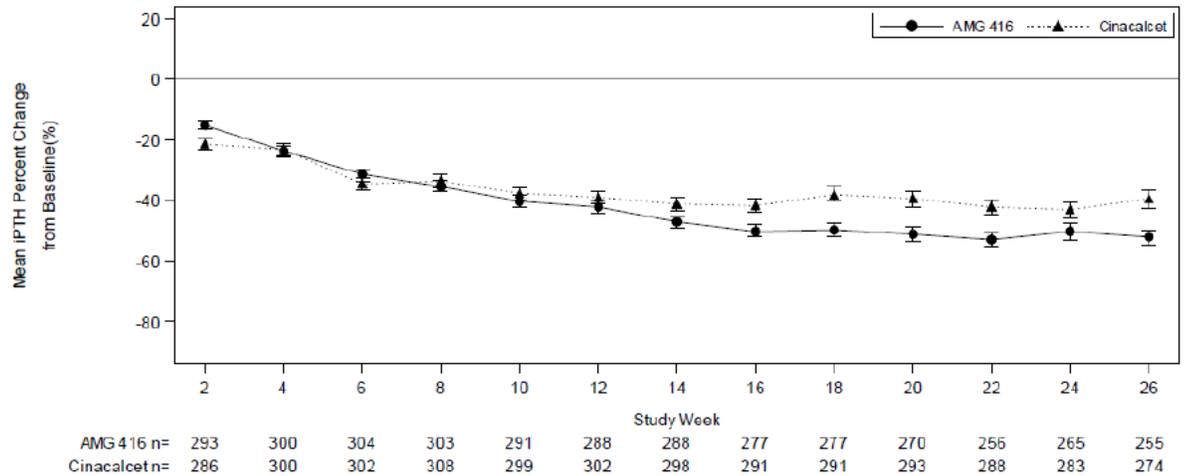
Dr. Lubas also relayed, in the same e-mail, that the sponsor's own calculations were that 29 subjects on the cinacalcet arm and 7 subjects on the etelcalcetide arm (AMG 416) needed a dose increase on week 21. At the end of the study, 14.3% of patient on etelcalcetide and 5% of patients on cinacalcet had attained the highest dosage level (while 17% of the etelcalcetide group and 29% of the cinacalcet group received the lowest dose). This imbalance would certainly impact any assessment of true efficacy and illuminates that any demonstration of superior efficacy by etelcalcetide may be more a function of trial design than true increased efficacy as there was room for more advancement of patients receiving cinacalcet. That more subjects receiving AMG 416 experienced hypocalcemia (a tolerability issue) while there was still room to advance patients receiving cinacalcet also demonstrates that dose titration in the AMG group was more aggressive than in the cinacalcet group.

Therefore, it is clear that dosing for the cinacalcet group was suboptimal and this trial should not be used for superiority claims of etelcalcetide compared to cinacalcet.

One other issue that we did not explore fully [REDACTED] (b) (4)

[REDACTED] was differential discontinuation and missing data. This can be seen in the table below obtained from Dr. Lubas.

**Figure 10-1. Mean (Standard Error) Percent Change From Baseline in Parathyroid Hormone Over Time by Treatment Group (Safety Analysis Set With On-treatment Approach)**



iPTH = parathyroid hormone

On-treatment approach: data collected on or before the last nonmissing dose of investigational product were summarized by visit.

Vertical lines represent the standard error.

Source: [Figure 14-7.3](#)

As can be seen from this graph, there appears to be less PTH data (i.e., more missing data) in the AMG 416 group starting at about week 8, which also seems to temporally coincide with larger reductions in mean iPTH in that group. This could suggest that a differential amount of missing data could account for some of the differences seen. There seems to be a different amount of missing data, depending upon what population is looked at (on-treatment vs mITT) or what analyses are considered (mean vs responder). However, due to all the other design flaws mentioned above, we did not pursue this further, but if patients with lower efficacy had selectively discontinued, this could have affected the results of the trial.

In summary, this single, relatively short term trial, comparing sub optimally dosed cinacalcet to etelcalcetide on a surrogate measure does not provide the necessary substantial evidence (b) (4)

(b) (4) The applicant will have to either agree to (b) (4) or conduct another trial addressing the dosing issues above in order to obtain approval for marketing.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CURTIS J ROSEBRAUGH  
08/24/2016