APPLICATION NUMBER:

208325Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<tr>
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<td><strong>Review Completion Date</strong></td>
<td>May 5, 2016</td>
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<td><strong>Subject</strong></td>
<td>Evaluation to determine if a REMS is necessary</td>
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<td><strong>Established Name</strong></td>
<td>etelcalcetide</td>
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<td><strong>(Proposed) Trade Name</strong></td>
<td>Parasabiv</td>
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<td><strong>Applicant</strong></td>
<td>Kai Pharmaceuticals</td>
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<td><strong>Therapeutic Class</strong></td>
<td>calcium-sensing receptor agonist</td>
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<td><strong>Formulation(s)</strong></td>
<td>Injection</td>
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<tr>
<td><strong>Dosing Regimen</strong></td>
<td>5 mg administered 3 times weekly</td>
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<tr>
<td><strong>Proposed Indication(s)</strong></td>
<td>secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis</td>
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Parasabiv® (etelcalcetide) is necessary to ensure the benefit of this product outweighs its risk. Kai Pharmaceuticals Incorporated submitted a New Drug Application (NDA) 208325 for Parasabiv (etelcalcetide) for the treatment of patients with secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis. The risks associated with the use of etelcalcetide are hypocalcemia, worsening heart failure, and adynamic bone disease. The applicant did not submit a proposed REMS or risk management plan with this application. DRISK is not recommending a REMS is to ensure that the benefits of etelcalcetide outweigh its risks. This recommendation was discussed with the Division of Metabolism & Endocrinology Products (DMEP) and they agreed with this recommendation. The risks seen with this drug will be communicated through labeling.

1 Introduction

Kai Pharmaceuticals submitted a New Drug Application (NDA 208325) for etelcalcetide with the proposed indication for the treatment of patients with secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis. This application is under review in the DMEP. The applicant did not submit a REMS or risk management plan with this application but proposed risk minimization measures through product labeling.

2 Background

2.1 PRODUCT INFORMATION
Parasabiv (etelcalcetide) is a new molecular entity, calcium-sensing receptor agonist. The sponsor proposed the following indication: treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis. The proposed dosing schedule for patients with secondary hyperparathyroidism is 5 mg administered by bolus injection three times per week at the end of hemodialysis. The dose could be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks to a maximum dose of 15 mg three times per week to achieve the target parathyroid hormone (PTH).

The dose of etelcalcetide could be reduced or administration stopped if the parathyroid hormone is below the target range and/or serum calcium level is below the lower limit of normal. If the dose is stopped, then etelcalcetide could be reinitiated at a lower dose to achieve the desired PTH target and normal limits for the serum calcium.

1 Clinical Overview (section 2.5), etelcalcetide

Reference ID: 3927471
Etelcalcetide is to be administered no more frequently than 3 times per week. Missed doses for etelcalcetide should not be administered. If doses of etelcalcetide are missed for more than 2 weeks, then etelcalcetide should be administered at 5 mg or 2.5 mg, depending on patient’s last administered dose, and titrated to achieve the desired parathyroid hormone target level.

Etelcalcetide is supplied in a single-use vial (type I glass) with stopper (fluoropolymer laminated elastomeric) and aluminium seal with flip-off dust cover containing 5 mg/mL of etelcalcetide as a sterile, preservative-free, ready-to-use solution in 2.5 mg/0.5 mL, 5mg/1 mL, and 10 mg/2 mL strengths. This is a NME 505 (b)(1) application. The evidence of clinical benefit for etelcalcetide in the treatment of secondary hyperparathyroidism is based upon two pivotal, placebo-controlled 26-week studies, Study 20120229 and Study 20120230, and an active-controlled, double-blind study, Study 20120360, comparing etelcalcetide with cinacalcet. The application is under Standard review with a Prescription Drug User Fee Act (PDUFA) date of August 24, 2016.

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for NDA 208325 relevant to this review:

- 8/19/2010: IND 109773 submitted
- 7/9/12: Type B EOP2 Meeting
- 5/13/2015: Type B Pre-NDA Meeting
- 8/24/2015: New Drug Application 208325 submitted
- 1/29/2016: Midcycle Meeting
- 2/8/2016: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data a REMS was not needed for etelcalcetide
- 6/1/16: Late Cycle Meeting

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION
Secondary hyperparathyroidism is a chronic, progressive disease that develops early during the course of chronic kidney disease, worsens as kidney function decreases over time, and affects patients with advanced kidney disease. According to the United States Renal Data System 2014 Annual Data Report, close to 449,000 patients with end-stage renal disease (ESRD) require treatment with dialysis in the United States (US).²

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS
Sensipar (cinacalcet) is the only calcimimetic, approved in 2004, for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease undergoing dialysis. The drug does not contain a Boxed Warning. Hypocalcemia, adynamic bone disease, and hepatic impairment are listed as Warnings & Precautions for this drug. In the primary efficacy analysis, 40% of the patients on the cinacalcet arm and 5% of placebo-treated patients achieved an iPTH≤250 pg/mL.³

Even though cinacalcet is effective in reducing elevated PTH levels among patients with CKD receiving dialysis, it is only available in a tablet to be administered orally. There is a medical need for a calcimimetic that can be administered by the intravenous route of administration as the only calcimimetic available, Sensipar (cinacalcet), is susceptible to suboptimal medication adherence which is a common problem in chronic kidney disease patients who already have a high daily pill burden.

4 Benefit Assessment

Based upon FDA analysis, the evidence of clinical benefit for etelcalcetide in the treatment of secondary hyperparathyroidism is based upon two pivotal, placebo-controlled 26-week studies, Study 20120229 and Study 20120230.

Both placebo-controlled studies were identical in design and included a 26-week treatment period. Patients were randomized to either AMG 416 or placebo in a 1:1 ratio, double-blind, placebo-controlled trial. Patients were administered at a starting dose of 5 mg three times per week at the end of hemodialysis and titrated every 4 weeks through week 17 to a maximum dose of 15 mg three times per week to achieve target parathyroid hormone level ≤ 300 pg/mL.⁴

The outcome measures were identical for both studies. The main outcome measure was the proportion of patients who achieved a >30% reduction from baseline in mean predialysis parathyroid hormone during the efficacy assessment period (EAP). The proportion of patients with pre-dialysis parathyroid hormone ≤ 300 pg/mL during the EAP, percent change from baseline during the EAP for PTH, serum corrected calcium, and phosphate were the other outcome measures.

Based upon the discussion during labeling meetings for the two placebo-controlled studies, Study 20120229 enrolled 508 patients (254 on etelcalcetide & 254 on placebo).⁴ The mean age of the patients was 57.7 years; 57.3% were male and 68.5% were white. The mean baseline parathyroid hormone level was 834.2 pg/mL, the mean baseline corrected serum calcium was 9.63 mg/dL, and the average duration of hemodialysis prior to study entry was 5.5 years. Three hundred thirty-seven (66.3%) patients had mean screening parathyroid hormone level ≥ 600 pg/mL, 376 (74.0%) patients were receiving vitamin D sterols, and 429 (84.4%) patients were receiving phosphate binders. One hundred eighty-eight (74%) patients experienced a reduction >30% in parathyroid hormone during the EAP versus 21 in the placebo group.

³ Sensipar (cinacalcet) US Prescribing Information, dated 11/2014

⁴ Parasabiv (etelcalcetide) proposed draft label with FDA edits, April 27, 2016
Study 20120230 enrolled 515 patients. The mean age of the patients was 58.7 years; 63.5% were male and 64.5% were Caucasians. The mean baseline parathyroid hormone level was 848.4 pg/mL, the mean baseline corrected serum calcium was 9.66 mg/dL, and the average duration of hemodialysis prior to study entry (minimum to maximum) was 5.4 (0.3 to 32.1) years. Three hundred forty-seven (67.4%) patients had mean screening PTH level ≥ 600 pg/mL, 320 (62.1%) patients were receiving vitamin D sterols, and 422 (81.9%) patients were receiving phosphate binders. One hundred ninety-two (75.3%) patients experienced a reduction >30% in parathyroid hormone during the EAP versus 25 in the placebo group. The results were considered by FDA to be statistically significant.5

Etelcalcetide was also evaluated in Study 20120360, a 6-month, randomized, active-controlled, double-blind study in patients with secondary hyperparathyroidism and chronic kidney disease receiving hemodialysis that compared the efficacy and safety of etelcalcetide with cinacalcet. Patients were randomized to receive either etelcalcetide IV and daily oral placebo tablets or oral cinacalcet tablets and placebo IV. The dosing regimen of etelcalcetide was similar to Studies 20120229 and 20120230 and for cinacalcet followed the US Prescribing Information. The proportion of patients who achieved >50% and >30% reductions from baseline in mean parathyroid hormone during the EAP were other outcome measures.

5 April 28, 2016 Statistical Review by Dr. Alexander Cambon

5 Risk Assessment & Safe Use Conditions

The safety of etelcalcetide was evaluated in 1016 patients with chronic kidney disease on hemodialysis. Adverse event data was summarized by system organ classes (SOCs) and preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Based upon FDA analysis, serious adverse reactions were reported in 25.8% of patients treated with etelcalcetide versus 29% in the placebo controlled clinical studies.

Adverse reactions reported in ≥ 5% of patients in the etelcalcetide group in the placebo-controlled clinical studies were blood calcium decreased, muscle spasms, diarrhea, nausea, vomiting, headache, hypocalcemia, and paresthesia.
Hypocalcemia, ventricular arrhythmia & QT prolongation secondary to hypocalcemia, convulsions, worsening heart failure, and adynamic bone disease was included under the Warnings & Precautions section of the labeling. Appropriate monitoring parameters were proposed in the labeling by the applicant for the adverse reactions.

6 Expected Postmarket Use
Etelcalcetide will be administered in the inpatient and outpatient setting and the likely prescribers will be endocrinologists and nephrologists. Treatment will likely be provided in hemodialysis centers and supported by healthcare providers who are familiar with the risks and management of adverse events with calcimimetics.

7 Evaluating the Need for a REMS
There is a medical need for a calcimimetic that can be administered by the intravenous route of administration as the only calcimimetic available, Sensipar (cinacalcet), is susceptible to suboptimal medication adherence which is a common problem in chronic kidney disease patients who already have a high daily pill burden. Kai Pharmaceuticals proposed as the indication for etelcalcetide, the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis.

The anticipated duration of use for etelcalcetide is a starting dose of 5 mg administered by bolus injection three times per week at the end of hemodialysis and titrated every 4 weeks through week 17 to a maximum dose of 15 mg three times per week until the desired parathyroid hormone level is reached.

The efficacy of etelcalcetide for treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis was considered by FDA to be statistically significant. It is another treatment option for secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis. In the placebo-controlled trials, close to 75% of the patients experienced a reduction >30% in parathyroid hormone during the EAP and results of the active-controlled study showed that etelcalcetide was non-inferior to cinacalcet in the proportion of patients achieving >30% reduction from baseline in mean parathyroid during the EAP.

Hypocalcemia, ventricular arrhythmia & QT prolongation secondary to hypocalcemia, convulsions, worsening heart failure, and adynamic bone disease will be included in the Warnings & Precautions section of the label. The risk mitigation strategy for the current therapy, cinacalcet, used for this patient population, included hypocalcemia, QT prolongation, seizures, hypotension and/or worsening heart failure, adynamic bone disease, and hepatic impairment in labeling, is does not have a REMS.

In comparison with cinacalcet recommended for the treatment of secondary hyperparathyroidism, etelcalcetide had similar side effects.
The Division determined that the adverse events for etelcalcetide will be addressed under the Warnings & Precautions section of the label.

The likely prescribing population for etelcalcetide will be endocrinologists and nephrologists who are familiar with the disease and adverse events seen with this drug.

8 Risk Management Activities Proposed by the Applicant

Kai Pharmaceuticals Incorporated did not submit a REMS or propose any other risk management activities for etelcalcetide beyond routine pharmacovigilance and labeling.

9 Conclusion & Recommendations

At the time of this review, evaluation of safety information and labeling was ongoing, therefore based on the data available at the time of this review, anticipated prescribing population, and patient population for use of this drug, DRISK is not recommending a REMS for etelcalcetide. Please notify DRISK if new safety information becomes available; this recommendation can be reevaluated.

10 Appendices

10.1 Materials Reviewed

The following is a list of materials informing this review:

1. Clinical Overview (section 2.5), etelcalcetide
3. January 29, 2016 Midcycle Slides by Dr. William Lubas
4. April 28, 2016 Statistical Review by Dr. Alexander Cambon
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONA G PATEL
05/05/2016

CYNTHIA L LACIVITA
05/05/2016
Concur