Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	July 27, 2020
Safety Evaluator:	Debra Ryan, PharmD, MBA Division of Pharmacovigilance I (DPV-I)
Medical Officer:	Ivone Kim, MD DPV-I
Team Leader:	Carmen Cheng, PharmD DPV-I
Division Director:	Cindy Kortepeter, PharmD DPV-I
Product Name:	Sensipar (cinacalcet)
Pediatric Labeling Approval Date:	May 23, 2017
Application Type/Number:	NDA 021-688
Applicant/Sponsor:	Amgen
OSE RCM #:	2019-2110

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Sensipar (cinacalcet) in pediatric patients through age 16 years. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Best Pharmaceuticals for Children Act (BPCA). This BPCA review was triggered by the pediatric labeling change approved on May 23, 2017 that described failed safety and efficacy pediatric studies. This review focuses on unlabeled serious adverse events reported to the FAERS database associated with cinacalcet in pediatric patients.

Cinacalcet is an oral calcimimetic agent, approved on March 8, 2004 for the treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on dialysis, and the treatment of hypercalcemia in adult patients with parathyroid carcinoma; and approved on February 25, 2011 for the treatment of severe hypercalcemia in adult patients with primary hyperparathyroidism (HPT) who are unable to undergo parathyroidectomy. Based on three trials in pediatric patients, a safe and effective dosing regimen could not be established for the pediatric population; therefore, the labeling for cinacalcet states that the safety and efficacy of cinacalcet has not been established in pediatric patients.

In our case series, there were no U.S. cases identified in FAERS and two pediatric cases with an unlabeled adverse event are from foreign sources. One case described a patient that experienced increased liver function tests (LFTs) after initiating therapy with cinacalcet. However, the patient received multiple medications and had underlying comorbidities that may have contributed to the elevations in LFTs. The second case described a patient with precocious puberty. This case described hormonal abnormalities prior to cinacalcet exposure, lacked complete diagnostic data and history, and described negative dechallenge with cinacalcet.

Cinacalcet is not indicated for use in pediatric patients. DPV-I did not identify any new pediatric safety concerns for cinacalcet at this time. DPV-I recommends no regulatory action specific to pediatric patients at this time and will continue to monitor all adverse events associated with the use of cinacalcet.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Sensipar (cinacalcet) in pediatric patients through age 16 years. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Best Pharmaceuticals for Children Act (BPCA). This BPCA review was initiated by the pediatric labeling on May 23, 2017 that described failed safety and efficacy pediatric studies. This review focuses on unlabeled serious adverse events reported to the FAERS database associated with cinacalcet in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Cinacalcet is an oral calcimimetic agent, approved on March 8, 2004 for the treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on dialysis, and the treatment of hypercalcemia in adult patients with parathyroid carcinoma; and approved on February 25, 2011 for the treatment of severe hypercalcemia in adult patients with primary hyperparathyroidism (HPT) who are unable to undergo parathyroidectomy. The safety and efficacy of cinacalcet has not been established in pediatric patients.

The FDA issued a Written Request (WR) on May 5, 2010 requesting the applicant evaluate the safety and efficacy of long-term use of cinacalcet in the treatment of SHPT in pediatric patients 28 days to 18 years of age with CKD receiving dialysis in whom SHPT is not adequately controlled with standard of care (SOC) therapy. Efficacy in pediatric patients was to be established in the same manner as in the adult with a focus on hypocalcemia and bone health (growth velocity, bone density, and bone turnover) as drug-specific safety concerns.

Three pediatric studies (20070208, 20130356, and 20110100) submitted to evaluate the efficacy and/or safety of cinacalcet for the treatment of SHPT in pediatric patients with CKD receiving dialysis failed to establish a clinical benefit for cinacalcet.[1]

Study 20070208[2] was a multicenter, randomized, double-blind, placebo-controlled, and dose titration study in participants between the ages of 6 to <18 years old who had CKD and SHPT treated with either hemodialysis or peritoneal dialysis for ≥ 2 months. The study consisted of 2 periods: a 30-week randomized, double-blind, placebo-control period followed by a 30-week open-label period. All participants received cinacalcet and SOC therapy, which could include vitamin D sterols, calcium supplements, and phosphate binders, regardless of treatment assignment. The primary outcome measure of the study was to show the percentage of participants achieving ≥ 30% reduction in mean intact parathyroid hormone (iPTH) from baseline. This study was terminated due to a fatality associated with severe hypocalcemia.

Study 20130356[3] was a multicenter, 24-week, randomized, open-label, active control study evaluating safety and efficacy of cinacalcet in participants between the ages of 6-18 years old with CKD and SHPT on dialysis. Participants were randomized into one of two treatment arms; oral administration of cinacalcet daily in addition to SOC, or SOC alone. Randomization was stratified by age group (6 to < 12 and 12 to < 18 years of age). The primary outcome measure of

the study was the same as in Study 200702208, i.e., the number of participants who experienced a mean decrease of ≥ 30% in plasma iPTH from baseline during the efficacy assessment period. Study 20110100[4] was a multicenter, 26-week, single-arm, open-label, safety study in children 28 days to < 6 years of age with CKD and SHPT receiving dialysis. Participants were to remain on the study for 26 weeks or until time of kidney transplantation, whichever came first. The primary outcome measure was the percentage of participants with hypocalcemia defined as corrected serum calcium levels <9.0 mg/dL (2.25 mmol/L) for participants aged 28 days to < 2 years, and <8.4 mg/dL (2.1 mmol/L) for participants aged ≥ 2 years to < 6 years at any time during the study. The applicant terminated the study early in order to meet regulatory timelines for filing.

The FDA determined that there was inadequate data to support efficacy or safety in pediatric children age 28 days to < 18 years from the clinical studies submitted due to the large amount of missing data and patient drop outs that occurred in these inconclusive studies. As substantial evidence does not exist to support a pediatric indication, the relevant pediatric information related to the pediatric studies was added to the Pediatric Use subsection 8.4 of the product labeling as required by 21 CFR 201.57(c)(9)(iv) on May 23, 2017.[5,6]

Cinacalcet has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION[7]

The following provides safety information and information on use in pediatrics excerpted from the pertinent sections of the cinacalcet labeling.

----------CONTRAINDICATIONS----------

- Sensipar treatment initiation is contraindicated if serum calcium is less than the lower limit of the normal range.

----------WARNINGS AND PRECAUTIONS----------

- *Hypocalcemia:* Life threatening events and fatal outcomes were reported. Hypocalcemia can prolong QT interval, lower the threshold for seizures, and cause hypotension, worsening heart failure, and/or arrhythmia. Monitor serum calcium carefully for the occurrence of hypocalcemia during treatment.

- *Upper Gastrointestinal (GI) Bleeding:* Patients with risk factors for upper GI bleeding may be at increased risk. Monitor patients and promptly evaluate and treat any suspected GI bleeding.

- *Hypotension, Worsening Heart Failure and/or Arrhythmias*: In postmarketing safety surveillance, isolated, idiosyncratic cases of hypotension, worsening heart failure, and/or arrhythmia have been reported in patients with impaired cardiac function.

- *Adynamic Bone Disease*: May develop if iPTH levels are suppressed below 100 pg/mL.

----------ADVERSE REACTIONS----------

- The most common adverse reactions (i.e., ≥ 25%) associated with Sensipar were nausea and vomiting.

----------USE IN SPECIAL POPULATIONS----------

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

The use of Sensipar for the treatment of secondary HPT in pediatric patients with CKD on dialysis was evaluated in two randomized, controlled studies (Pediatric Study 1 and Study 2) where 47 pediatric patients aged 6 years to less than 18 years received at least one dose of Sensipar and in one single-arm study (Pediatric Study 3) where 17 pediatric patients aged 28 days to less than 6 years received at least one dose of Sensipar. Dosing with Sensipar in Pediatric Study 1 was stopped because of a fatality in a Sensipar-treated individual. The individual was noted to be severely hypocalcemic at the time of death. The cause of death was multifactorial and a contribution of Sensipar to the death could not be excluded. Study 1 was terminated and changes to Sensipar dosing after the fatality were implemented in Pediatric Study 2 and Study 3 to minimize the risk of severe hypocalcemia. The data in Pediatric Studies 2 and 3 were insufficient to establish the safety and efficacy of Sensipar for the treatment of secondary HPT in pediatric patients with CKD on dialysis. In aggregate, the pediatric studies did not establish a safe and effective Sensipar dosing regimen for the pediatric population.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of Search	January 29, 2020
Time Period of Search	March 8, 2004† - January 28, 2020
Search Type	FDA Business Intelligence System (FBIS) Quick Query
Product Terms	Product Active Ingredient: cinacalcet; cinacalcet hydrochloride; cinacalcet\cinacalcet hydrochloride
MedDRA Search Terms (Version 22.0)	All Preferred Terms (PTs)
* See Appendix A for a description of the FAERS database. † U.S. Approval date for Sensipar (cinacalcet).	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from March 8, 2004 through January 28, 2020 with cinacalcet.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From March 8, 2004 - January 28, 2020 With Cinacalcet

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	43,462 (40,374)	15,153 (12,108)	1,967 (1,389)
Pediatrics (0 - <17 years)	91‡ (63)	60‡ (32)	8‡ (7)

* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
‡ Two reports of pediatric deaths were identified among reports not reporting an age and were added to the pediatric report count

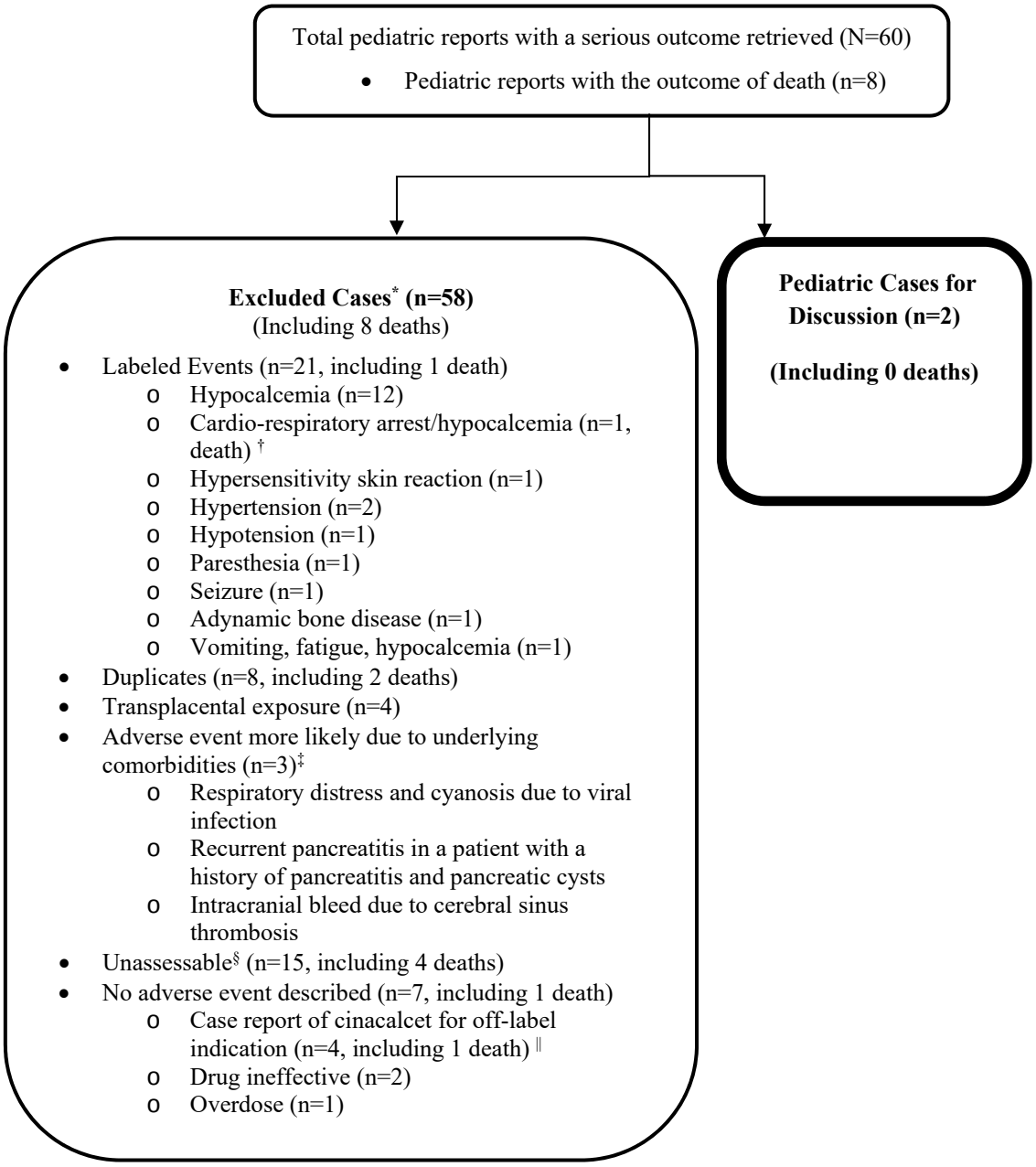
3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 60 serious pediatric reports from March 8, 2004 through January 28, 2020.

We reviewed all 60 FAERS pediatric reports, foreign and domestic, coded with a serious outcome.

Reports were excluded from our case series if the adverse event reported was an event addressed in the current label (n=21), a duplicate report (n=8), described transplacental exposure (n=4), underlying comorbidities provide a more likely explanation for the reported adverse event (n=3), did not provide sufficient information to assess causality (i.e., reports that cannot be clinically assessed because information is insufficient, lacking, or contradictory) (n=15), or did not describe an adverse event (n=7). See Figure 1 for selection of cases included in our case series and a description of reasons for excluded reports.

Figure 1. Selection of Serious Pediatric Cases with Cinacalcet



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above

† Death in an adolescent with a history of prolonged QT interval at baseline, CKD, SHPT receiving peritoneal dialysis, cinacalcet, and multiple unreported concomitant medications. Patient developed hypocalcemia. Death was determined to be multifactorial; a causal role for hypocalcemia with cinacalcet could not be excluded.

‡ These three reports described alternative causes for the reported adverse event: 1) Cyanosis and Respiratory distress due to a respiratory viral infection; 2) Pancreatitis in a child with significant unspecified comorbidities including a history of pancreatic cysts and pancreatitis; 3) Intracranial hemorrhage, Blood pressure increased, in a child with end-stage renal disease and acute respiratory infection.

§Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory or information provided in the case cannot be supplemented or verified.

|| Cinacalcet used as rescue therapy for refractory hyperparathyroidism in a pediatric patient. Patient death was due to complications from peritonitis six months after cinacalcet was discontinued.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event reports where the cause of death was likely related to the use of cinacalcet.

3.1.4 Summary of Non-Fatal Pediatric Serious Cases (N=2)

DPV-I identified no U.S. FAERS cases and two foreign FAERS cases for cinacalcet in the pediatric population that reported an unlabeled, non-fatal, serious outcome. The cases are summarized below.

Case#7945511 (Foreign): This report describes a 2.5-year-old male enrolled in an open-label, active treatment study to evaluate the efficacy, safety, tolerability and pharmacokinetics of cinacalcet for the treatment of SHPT in pediatric patients with CKD on dialysis. The patient experienced elevated liver function tests (LFTs) within 10 days of receiving cinacalcet. Concomitant medications included amoxicillin, ranitidine, oxybutynin, calcium carbonate, calcitriol, clavulanic acid, ferrous sulfate, levoleucovorin calcium, and erythropoietin. Medical history included end stage renal failure due to bilateral cystic dysplasia and complex malformation of urinary tract, resection of urethral valves, urinary tract infection, SHPT resistant to standard therapy with Vitamin D analogues and phosphate binders, LFT abnormalities when recently treated with cefaclor, malnutrition and tube feeding.

Upon pre-study screening, the patient's LFT values were within normal ranges: serum glutamic-oxaloacetic transaminase (SGOT)=25 U/L (normal values 0-40); serum glutamic-oxaloacetic transaminase (SGPT)=17 U/L (normal values 0-40); gamma-glutamyl transpeptidase (GGT)=22 U/L (normal values 11-50). The patient's SGOT, SGPT, and GGT began increasing 10 days after initiating treatment with cinacalcet and within six weeks had increased to five times the upper limit of normal (ULN) for SGOT, ten times ULN for SGPT, and eight times ULN for GGT. There were no significant hemodynamic changes, sepsis, respiratory insufficiency, thrombosis or other vascular insufficiency experienced by the patient prior to cinacalcet administration or around the time of the event. An ultrasound scan was performed and showed hepatomegaly. Tests for hepatitis (A, B and C), human immunodeficiency virus (HIV), cytomegalovirus (CMV) and Epstein Barr virus (EBV) showed negative results. Treatment with cinacalcet was discontinued and within four weeks SGOT, SGPT, and GGT had returned to normal values. One month later treatment with cinacalcet was resumed and within four weeks SGOT, SGPT, and GGT were again elevated (7.6 times ULN for SGOT, 5.8 times ULN for SGPT, and 2.6 times ULN for GGT). Cinacalcet was permanently discontinued and SGOT, SGPT, and GGT levels decreased.

Reviewer's Comments: Cinacalcet is not approved for pediatric patients and elevated LFTs are not a labeled event for adults in the prescribing information for cinacalcet. This case describes a temporal relationship and positive dechallenge and rechallenge between initiation of cinacalcet, increased LFTs, and resolution upon discontinuation of cinacalcet. This patient received multiple medications, including amoxicillin, clavulanic acid, and calcitriol which are labeled for increasing liver enzymes, and the patient has a history of developing increased liver enzymes with cefaclor prior to treatment with cinacalcet. The temporal association and positive

dechallenge and rechallenge support cinacalcet having a causal role in contributing to the elevated LFTs in this patient; therefore, we conducted an expanded search of the FAERS database for all cinacalcet reports received by the FDA from March 8, 2004 through January 28, 2020 with the PTs: Hepatic enzyme increased; Transaminases increased; Alanine aminotransferase increased; Gamma-glutamyltransferase increased; Aspartate aminotransferase increased; Liver function test abnormal; Alanine aminotransferase abnormal; Aspartate aminotransferase abnormal; Gamma-glutamyltransferase abnormal in the adult population. A high-level review of the 39 unique reports retrieved was performed and the majority of the reports described patients on multiple medications, many labeled for increasing LFTs or did not contain sufficient information to attribute causality to cinacalcet. In the absence of more clinical data, this single report does not represent a new safety signal for cinacalcet at this time.

Case#7015009 (Foreign): This is a literature report[8] describing a 5-year-old boy with severe CKD secondary to renal hypodysplasia, renal cysts, and diabetes syndrome. The patient had hyperparathyroidism that progressed "despite conventional conservative measures." The patient started on alphacalcidol (active metabolite of Vitamin D), calcium carbonate, and sevelamer but developed increased serum calcium levels without parathyroid hormone (PTH) level change, so calcium carbonate and sevelamer were discontinued. He started lanthanum carbonate but PTH remained at 500-800 pg/mL despite good therapeutic and dietary compliance, so cinacalcet was started and lanthanum was discontinued. Cinacalcet dose was increased 4 weeks after initiation and then again 1 week later due to stable but elevated PTH levels ~500 pg/mL. Serum calcium and phosphate levels remained stable, so cinacalcet was discontinued due to digestive intolerance symptoms of nausea, vomiting, and weight loss, 50 days after its introduction and lanthanum was restarted to be discontinued sometime later at an unreported date. PTH levels increased again and cinacalcet was reintroduced 3 weeks after discontinuation. Concomitant medications included alphacalcidol, iron supplementation, and sodium bicarbonate. The patient was noted to be at prepubertal Tanner stage G1P1 prior to cinacalcet initiation. Mother noted progressive pubarche with recurrent erections 2 weeks after cinacalcet initiation and the family presented to care 45 days after start of symptoms (1 week after cinacalcet reinitiation). Physical exam at initial consultation revealed symmetric bilateral testicular enlargement (40mm on day of cinacalcet treatment 73), increased penile length (40mm on day 73, 65mm on day 117), and Tanner G3P2. Diagnostic evaluation included the following:

- Testosterone levels: >0.7 nmol/L (normal for age and gender 0.28±0.01 nmol/L)
- Follicle stimulating hormone (FSH): "normal"
- Luteinizing hormone (LH): 1.1-4.1 IU/L (normal values for age and gender: 0.17-0.6 IU/L)
- Serum estradiol level: "normal"
- Anti-Müllerian hormone (AMH): 68-126 pmol/L (normal values for age and gender >200 pmol/L)
- Inhibin B serum levels: 319-406 ng/L (normal local values for age and gender 42-268 ng/L)
- Dehydroepiandrosterone sulphate (DHAS):2022-3205 nmol/L (normal values for age and gender 320±250 nmol/L)

- Two magnetic resonance imaging (MRI) studies of the brain and hypothalamic pituitary axis: normal
- "Adrenal aetiology of precocious puberty was excluded by normal levels of steroids"
- Adrenal ultrasound: normal
- Tumor markers (α-fetoprotein, human chorionic gonadotropin [hCG]): negative
- Retrospective evaluation of baseline serum sexual and adrenal hormones prior to cinacalcet and after lanthanum carbonate initiation revealed increased serum testosterone, DHAS, and LH levels with decreased AMH
- Other: no mutation in the LH receptor or in GNAS gene
- Skeletal age: 74 months at chronological age 61 months
- Growth velocity: Accelerated 0.5 standard deviation to the mean within 6 months

Two to three weeks after cinacalcet discontinuation, pubarche symptoms stabilized and frequency of erections decreased. Six months after discontinuation, "biological data progressively normalized" and physical findings improved to Tanner G2P2. At 7 months post discontinuation, testosterone increased in association with increased LH so the patient was treated with triptorelin. After 4 months of triptorelin therapy, testosterone serum levels remained high but stable and clinical symptoms moderately improved.

Reviewer comments: Pubertal delay is common among children with chronic illnesses,[9] however, the medical literature has case reports of central precocious puberty in children with chronic renal failure.[10] The patient's signs on physical exam and diagnostic findings are consistent with precocious puberty. Increased testicular size, testosterone and LH favor diagnosis of central precocious puberty.[11,12] Notably, DHAS elevation suggests possible contribution of adrenal androgens but normal adrenal ultrasound and unspecified "steroids" for evaluation of adrenal etiology does not favor adrenal abnormalities. Despite the available details provided (e.g., normal MRI studies to rule out central nervous system lesions, normal hCG to rule out germ cell tumors), the narrative lacks information needed to evaluate the etiology of this patient's precocious puberty such as family history, complete physical exam findings, thyroid studies, growth chart, gonadotropin releasing hormone (GnRH) stimulation test, additional imaging studies (e.g., imaging of testicles, liver, or retroperitoneum), or additional genetic tests. Causality assessment for precocious puberty and cinacalcet is further complicated by return of precocious puberty signs and symptoms despite initial improvement after cinacalcet discontinuation, and report of baseline aberrancy in testosterone, DHAS, and LH levels prior to cinacalcet therapy. An expanded search of the FAERS database for all reports received by FDA through January 21, 2020 with the PTs "precocious puberty" and "incomplete precocious puberty" retrieved one additional case describing a 3-year-old with possible precocious puberty. The case reported multiple competing suspect drugs, provided no objective diagnostic findings/measurements to confirm diagnosis of precocious puberty, and contained no narrative detail to discern temporal relationship between cinacalcet and the concomitant medications to precocious puberty symptoms.

4 DISCUSSION

DPV-I identified no new pediatric safety signals associated with cinacalcet from reports submitted to the FAERS database. In addition, there were no increased severity or frequency of any labeled adverse events, and there were no deaths directly attributed to cinacalcet. In our case series there were no U.S. cases identified in FAERS and the two cases with an unlabeled adverse event are from foreign sources. One case described a patient who experienced increased LFTs after initiating therapy with cinacalcet. However, the patient received multiple medications labeled for elevated LFTs and had underlying co-morbidities that may have contributed to the elevation in LFTs. Additionally, a high-level review of similar reports in the adult population described patients on multiple medications, many labeled for increasing LFTs, or the reports did not contain sufficient information to attribute causality to cinacalcet. The second case described a patient with precocious puberty. This case described hormonal abnormalities prior to cinacalcet exposure, lacked complete diagnostic data and history, and described negative dechallenge with cinacalcet. An expanded FAERS search for precocious puberty did not retrieve cases that support the signal. At this time, there is insufficient evidence to identify precocious puberty as a potential signal for cinacalcet.

5 CONCLUSION

DPV-I did not identify any new pediatric safety concerns for cinacalcet at this time.

6 RECOMMENDATION

Cinacalcet is not indicated for use in pediatric patients. DPV-I recommends no regulatory action at this time. DPV-I will continue to monitor all adverse events associated with the use of cinacalcet including precocious puberty.

7 REFERENCES

1. Lubas W. Clinical Review NDA: 21866/S-023 (Cinacalcet). 2017. Retrieved from: https://www.fda.gov/media/106866/download

2. A Randomized, Double-blind, Placebo Controlled Study to Assess the Efficacy and Safety of Cinacalcet HCl in Pediatric Subjects with Chronic Kidney Disease and Secondary Hyperparathyroidism Receiving Dialysis. (2019). Retrieved from: https://clinicaltrials.gov/ct2/show/NCT01277510?id=20070208&draw=2&rank=1 (Identification No. NCT01277510)

3. A Randomized, Open-label, Controlled Study to Assess the Efficacy and Safety of Cinacalcet HCl in Pediatric Subjects With Secondary Hyperparathyroidism and Chronic Kidney Disease Receiving Dialysis. (2020). Retrieved from: https://clinicaltrials.gov/ct2/show/NCT02138838?term=20130356&draw=2&rank=2 (Identification No. NCT02138838)

4. An Open-label, Single-arm Study to Assess the Safety & Tolerability of Cinacalcet in Addition to Standard of Care in Pediatric Subjects Age 28 Days to < 6 Yrs With Chronic Kidney Disease & Secondary Hyperparathyroidism Receiving Dialysis. Retrieved from: https://clinicaltrials.gov/ct2/show/study/NCT01439867?id=NCT02341417+OR+NCT01290029+OR+NCT01439867+OR+NCT01277510+OR+NCT02138838&draw=2&rank=3&load=cart (Identification No. NCT01439867)

5. FDA.gov. New Pediatric Labeling Information Database. June 2020. Retrieved from: https://www.accessdata.fda.gov/scripts/sda/sdDetailNavigation.cfm?sd=labelingdatabase&id=5305DC6723CE296BE053554DA8C0160D&rownum=1

6. U.S. Food and Drug Administration. Guidance for Industry: Pediatric Information Incorporated into Human Prescription Drug and Biological Product Labeling. March 2019. Available at: https://www.fda.gov/media/84949/download.

7. Sensipar (cinacalcet) [package insert]. Thousand Oaks, CA: Amgen Inc. Revised 29Mar19.

8. Bacchetta J, Plotton I, Ranchin B, Vial T, Nicolino M, Morel Y, Cochat P. Precocious puberty and unlicensed paediatric drugs for severe hyperparathyroidism. Nephrol Dial Transplant. 2009. 24: 2595–2598.

9. Pozo J et al. Delayed puberty in chronic illness. Best Practice & Research Clinical Endocrinology & Metabolism. 2002;16(1):73-90.

10. Loh KC et al. Central precocious puberty and chronic renal failure: a reversible condition post renal transplantation. JPEM.1997;10(5):539-545.

11. Bradley SH et al. Precocious puberty. BMJ. 2020;368; l6597.

12. Carel JC and Leger L. Precocious puberty. NEJM. 2008;358: 2366-2377.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=2)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	5/29/2009	7015009	2	SPV1-2009-00955	Expedited (15-Day)	5	Male	France	DS
	9/27/2007	6428936 (Duplicate)	5	FR-AMGEN-UK244302	Expedited (15-Day)	4.9	MALE	France	HO, OT
2	5/16/2011	7945511	5	IT-AMGEN-ITACT2011023918	Expedited (15-Day)	3	MALE	Italy	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: HO=hospitalization, DS=Disability, OT=other medically significant

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBRA L RYAN
07/27/2020 09:22:30 AM

IVONE E KIM
07/27/2020 09:24:03 AM

CARMEN CHENG
07/27/2020 09:31:48 AM

CINDY M KORTEPETER
07/27/2020 09:45:32 AM