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Pediatric Postmarketing Pharmacovigilance Review

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Product Name: Zemplar (paricalcitol)

**Pediatric Labeling
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Zemiplar (paricalcitol) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with paricalcitol in pediatric patients less than 17 years of age.

The FDA approved paricalcitol injection on April 17, 1998 and it is currently indicated for the prevention and treatment of secondary hyperparathyroidism in patients 5 years of age and older with chronic kidney disease (CKD) on dialysis. The FDA approved paricalcitol oral capsules on May 26, 2005 and it is currently indicated for adults and pediatric patients 10 years of age and older for the prevention and treatment of secondary hyperparathyroidism associated with CKD stages 3 and 4 and CKD stage 5 in patients on hemodialysis or peritoneal dialysis. This review was prompted by pediatric labeling approved on October 18, 2016 that expanded the indication of paricalcitol capsules to include use in pediatric patients ages 10 to 16 years for treatment of secondary hyperparathyroidism associated with CKD stages 3 and 4 and CKD stage 5 in patients on hemodialysis or peritoneal dialysis.

DPV reviewed all serious FAERS reports with paricalcitol use (injections, capsules) in the pediatric population less than 17 years of age received by FDA from April 17, 1998 through March 5, 2019, and identified two reports for discussion. The reports described single serious and unlabeled adverse events of appendicitis and peritonitis, respectively. No specific pattern of adverse events was noted and both reports contained insufficient information for causality assessment.

DPV did not identify any new pediatric safety concerns for paricalcitol at this time.

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of paricalcitol.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Zemlar (paricalcitol) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with paricalcitol in pediatric patients less than 17 years of age.

1.1 PEDIATRIC REGULATORY HISTORY

Paricalcitol is a synthetic, biologically active vitamin D2 analog available for intravenous and oral use. The FDA initially approved paricalcitol injection on April 17, 1998 in adult patients for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. The FDA approved paricalcitol oral capsules on May 26, 2005 in adult patients for prevention and treatment of secondary hyperthyroidism associated with chronic kidney disease (CKD) stage 3 and 4; paricalcitol oral capsules were approved for the same indication in adults with CKD stage 5 on hemodialysis or peritoneal dialysis on June 29, 2009. Currently FDA-approved indications of paricalcitol are listed by formulation in Table 1.

	Paricalcitol injection	Paricalcitol oral capsules
Indications	Prevention and treatment of secondary hyperparathyroidism in patients 5 years of age and older with chronic kidney disease on dialysis	<ul style="list-style-type: none">• Adults and pediatric patients 10 years of age and older for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stages 3 and 4• Adults and pediatric patients 10 years of age and older for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5 in patients on hemodialysis or peritoneal dialysis
Available strengths	0.006 mg/ml single-dose vial, 0.002 mg/ml single-dose vial, 0.01 mg/2 ml multiple-dose vial	1 mcg capsule, 2 mcg capsule

This review was prompted by pediatric labeling approved on October 18, 2016 that expanded the indication of paricalcitol capsules to include use in pediatric patients ages 10 to 16 years for treatment of secondary hyperparathyroidism associated with CKD stages 3 and 4 and CKD stage 5 in patients on hemodialysis or peritoneal dialysis.

The efficacy and safety of paricalcitol injection in the treatment of secondary hyperparathyroidism associated with CKD have been established in pediatric patients 5 years of age and older receiving hemodialysis. The use of paricalcitol injection in these age groups was

supported by a randomized, double-blind, placebo-controlled investigation that enrolled patients aged 2 to 20 years who had been receiving hemodialysis (ClinicalTrials.gov Identifier: NCT00053547).^{1,2,3} The primary efficacy endpoint was the proportion of patients in each group who achieved two consecutive reductions in intact parathyroid hormone (iPTH) levels $\geq 30\%$ from baseline. Sixty percent of the paricalcitol group had two consecutive 30% decreases from baseline iPTH levels compared with 21% in the placebo group ($P = 0.06$). There was no difference from baseline to final visit in calcium (Ca), phosphorus (P), or Ca x P product values in either group. There were no deaths in this study, no subject withdrew from the study due to an adverse event, and there were no clinically meaningful differences between groups in the reporting of adverse events.

The efficacy and safety of paricalcitol capsules in pediatric patients 10 to 16 years of age is supported by evidence from adequate and well controlled studies in adults with CKD, a 12-week double-blind placebo-controlled randomized multicenter study in 36 pediatric patients 10 to 16 years of age with stage 3/4 CKD, and safety data from a 12-week open-label single-arm multicenter study in 13 pediatric patients 10 to 16 years of age with stage 5 CKD receiving peritoneal dialysis or hemodialysis.^{4,5,6} In the stage 3/4 CKD study (ClinicalTrials.gov Identifier: NCT01382212), the primary efficacy endpoint was the percentage of participants who achieved two consecutive $\geq 30\%$ reductions of iPTH levels from baseline during the 12-week double-blind treatment period. Among those treated with paricalcitol, 27.8% achieved this threshold compared with no patients in the placebo group. Efficacy of paricalcitol capsules in pediatric patients 10 to 16 years with CKD stage 5 was extrapolated using adult pharmacokinetic data in the stage 5 CKD population, pediatric pharmacokinetic data from the stage 3/4 CKD study, and data from the stage 5 CKD safety study (ClinicalTrials.gov Identifier: NCT01382212).^{4,7} There were no deaths in either the stage 3/4 or stage 5 CKD study. The FDA clinical review concluded that the safety profile in the trials was consistent with the known safety profile established for paricalcitol in adult patients and for the whole class of vitamin D analogs. No new, population-specific safety signals were identified in the paricalcitol pediatric program.

The Division of Drug Risk Evaluation (DDRE) (which is now called DPV) previously evaluated postmarketing adverse event reports from the FAERS database for paricalcitol injection in pediatric patients.⁸ DDRE's evaluation, dated April 20, 2005, was prompted by the pediatric labeling changes on March 31, 2004 to add information regarding use of paricalcitol injection in pediatric patients with CKD stage 5 on dialysis. DDRE did not identify any postmarketing adverse event reports of safety concerns for paricalcitol injection in pediatric patients. FDA presented DDRE's evaluation to the Pediatric Advisory Committee (PAC) on June 29, 2005.⁹

1.2 RELEVANT LABELED SAFETY INFORMATION

The following safety information is an excerpt from the Zemplar capsules labeling:¹⁰

4 CONTRAINDICATIONS

ZEMPLAR capsules should not be given to patients with evidence of

- hypercalcemia or
- vitamin D toxicity [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

Excessive administration of vitamin D compounds, including ZEMPLAR capsules, can cause over suppression of PTH, hypercalcemia, hypercalciuria, hyperphosphatemia, and adynamic bone disease.

5.1 *Hypercalcemia*

Progressive hypercalcemia due to overdosage of vitamin D and its metabolites may be so severe as to require emergency attention [*see Overdosage (10)*]. Acute hypercalcemia may exacerbate tendencies for cardiac arrhythmias and seizures and may potentiate the action of digitalis. Chronic hypercalcemia can lead to generalized vascular calcification and other soft-tissue calcification. Concomitant administration of high doses of calcium-containing preparations or thiazide diuretics with ZEMPLAR may increase the risk of hypercalcemia. High intake of calcium and phosphate concomitant with vitamin D compounds may lead to serum abnormalities requiring more frequent patient monitoring and individualized dose titration. Patients also should be informed about the symptoms of elevated calcium, which include feeling tired, difficulty thinking clearly, loss of appetite, nausea, vomiting, constipation, increased thirst, increased urination and weight loss.

Prescription-based doses of vitamin D and its derivatives should be withheld during ZEMPLAR treatment to avoid hypercalcemia.

5.2 *Digitalis Toxicity*

Digitalis toxicity is potentiated by hypercalcemia of any cause. Use caution when ZEMPLAR capsules are prescribed concomitantly with digitalis compounds.

5.3 *Laboratory Tests*

During the initial dosing or following any dose adjustment of medication, serum calcium, serum phosphorus, and serum or plasma iPTH should be monitored at least every two weeks for 3 months, then monthly for 3 months, and every 3 months thereafter.

In pre-dialysis patients, ZEMPLAR capsules may increase serum creatinine and therefore decrease the estimated GFR (eGFR). Similar effects have also been seen with calcitriol.

5.4 *Aluminum Overload and Toxicity*

Aluminum-containing preparations (e.g., antacids, phosphate binders) should not be administered chronically with ZEMPLAR, as increased blood levels of aluminum and aluminum bone toxicity may occur.

8 USE IN SPECIFIC POPULATIONS

8.4 *Pediatric Use*

The safety and effectiveness of ZEMPLAR capsules have been established in pediatric patients 10 to 16 years of age for the prevention and treatment of secondary hyperparathyroidism associated with Stage 3, 4, and 5 CKD.

Use of ZEMPLAR capsules in this age group is supported by evidence from adequate and well controlled studies in adults with CKD, a 12-week double-blind placebo-controlled randomized multicenter study in 36 pediatric patients 10 to 16 years of age with CKD Stages 3 and 4, and safety data from a 12-week open-label single-arm multicenter study in 13 pediatric patients 10 to 16 years of age with CKD Stage 5 receiving peritoneal dialysis or hemodialysis. The pharmacokinetics of paricalcitol in Stage 5 CKD pediatric patients appear to be similar to those observed in Stage 3 and 4 pediatric patients [see *Clinical Pharmacology (12.3) and Clinical Studies (14.1)*].

Adverse reactions reported in these pediatric studies are consistent with the known safety profile of ZEMPLAR capsules and with what has been reported in adult clinical studies [see *Adverse Reactions (6.1)*].

Safety and effectiveness of ZEMPLAR capsules in pediatric patients under the age of 10 years have not been established.

The labeling for Zemplar injection contains similar safety highlights but lists an additional contraindication in patients with known hypersensitivity to paricalcitol or any of the inactive ingredients.¹¹ In addition, the Zemplar injection labeling contains additional safety information regarding use in pediatric patients 5 years of age and older, listed below:

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and efficacy of ZEMPLAR for the prevention and treatment of secondary hyperparathyroidism associated with CKD have been established in pediatric patients 5 years of age and older with CKD on dialysis. Use of ZEMPLAR in pediatric patients 5 years of age and older is supported by evidence from an adequate and well-controlled study in 29 patients, 5 to 19 years of age, with CKD on hemodialysis [see *Clinical Studies (14)*].

The safety and efficacy of ZEMPLAR have not been established in pediatric patients less than 5 years old.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of Search	March 6, 2019
Time Period of Search	April 17, 1998 [†] - March 5, 2019
Search Type	FBIS Product-Manufacturer Reporting Summary
Product Terms	Product Name: Zemplar [‡] Product Active Ingredient: Paricalcitol [‡] NDA: 020819, 021606

Table 2. FAERS Search Strategy*	
MedDRA Search Terms (Version 21.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database.	
† U.S. Approval date of Zemplar injection	
‡ Includes capsule and injection dosage forms	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from April 17, 1998 through March 5, 2019 with paricalcitol.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from April 17, 1998 through March 5, 2019 with Paricalcitol			
	All reports (U.S.)	Serious[†] (U.S.)	Death (U.S.)
Adults (≥ 17 years)	4,849 (703)	4,438 (302)	2,604 (106)
Pediatrics (0 - <17 years)	38 [‡] (4)	34[‡] (0)	22 [‡] (0)
* 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, and other serious important medical events.			
‡ Report counts include 15 additional reports of pediatric deaths that were identified among reports not reporting an age.			

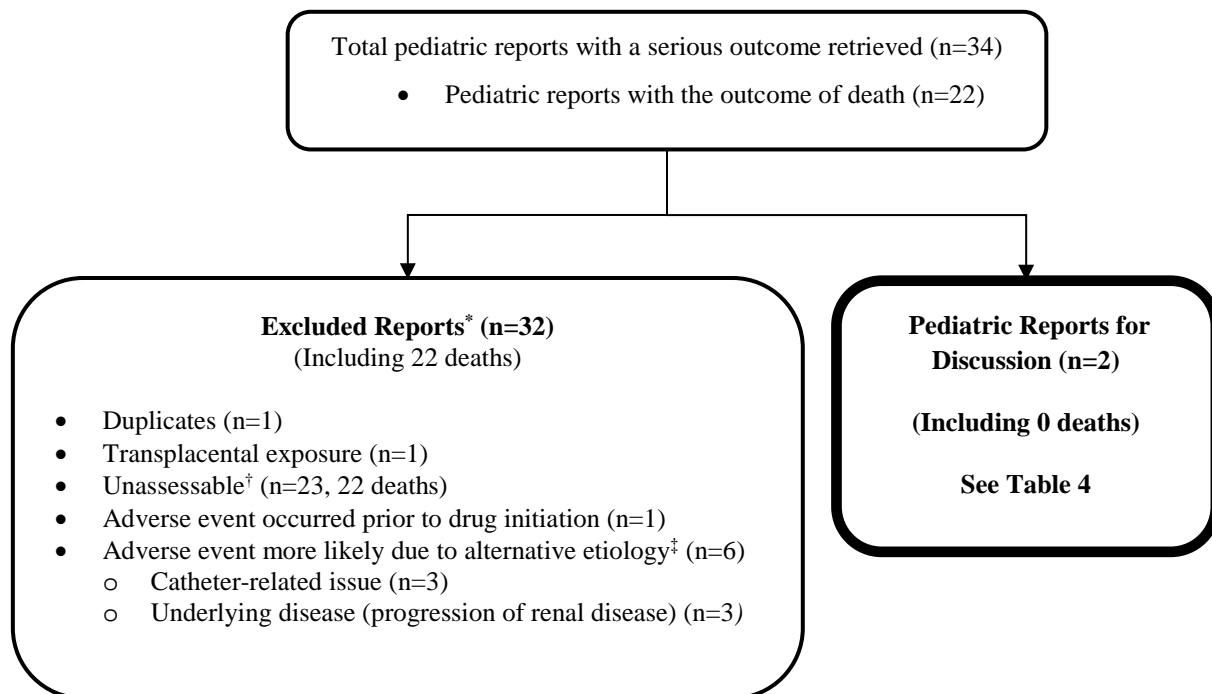
3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 34 serious pediatric reports from April 17, 1998 through March 5, 2019. All 34 serious reports were of patients from foreign countries.

We reviewed all 34 FAERS pediatric reports with a serious outcome. We excluded reports from the case series of this review for the following reasons: duplicates (n=1), transplacental exposure (n=1), unassessable due to insufficient information reported (n=23), adverse event occurred prior to paricalcitol initiation (n=1), and adverse event more likely due to alternative etiology (e.g., catheter-related issue, underlying disease) (n=6). We summarize the remaining two cases in the sections below.

Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with Paricalcitol



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

[†] Reports cannot be assessed for causality because there is insufficient information reported (e.g., unknown time to event, concomitant medications and comorbidities, clinical course and outcome). Seven of the 22 reports with a death stated the patients were on dialysis, and few cases specified patients experienced cardiorespiratory arrest (n=2) or cerebrovascular event (n=1). All cases lacked additional information about clinical course and diagnostic evaluation.

[‡] Reports where adverse events were more likely due to alternative etiologies described patients with catheter-related issues [catheter infection (n=1), catheter replacement procedures (n=2)] or complications from underlying renal failure [uremic encephalopathy, fluid overload, pulmonary edema, and convulsive crisis (n=1); osteomalacia and myopathy (n=1); and hypertensive crisis with abnormal phosphorous and parathyroid hormone levels (n=1)].

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of the two pediatric cases.

Table 4 summarizes the two FAERS cases in pediatric patients with paricalcitol reporting a serious outcome received by FDA from April 17, 1998 through March 5, 2019.

FAERS#	10717900	12196931
Year of Report	2015	2016
Age (years)	16	16
Sex	Male	Male

Table 4. Characteristics of the FAERS Serious Pediatric Cases with Paricalcitol Received by FDA from April 17, 1998 through March 5, 2019 (n=2)		
FAERS#	10717900	12196931
Country	Argentina	Ecuador
Reported Reason for Use	Hyperparathyroidism secondary	Hyperparathyroidism secondary
Serious Outcome*	Other Serious	Hospitalization
Preferred Terms	<i>Appendicitis</i>	<i>Abdominal pain, Peritonitis, Vomiting</i>
* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. A case may have more than one serious outcome.		

3.1.4 Summary of Fatal Pediatric Cases (n=0)

We did not include any fatal pediatric adverse event reports in our case series.

3.1.5 Summary of Non-Fatal Pediatric Serious Cases (n=2)

We identified two serious FAERS cases with paricalcitol in the pediatric population reporting a non-fatal serious outcome. Both cases were foreign and reported unlabeled events, but contained insufficient information to assess causality. We did not identify patterns or trends suggestive of new safety signals in our pediatric cases. Both cases are summarized below.

FAERS# 10717900, 2015, Argentina, Other serious: A consumer reported that a 16-year-old male patient developed appendicitis 166 days after starting intravenous paricalcitol (dose not reported) for secondary hyperparathyroidism. Past medical history and concomitant medications were not reported. The patient’s relative (relationship unspecified) reported that the patient underwent surgery for appendicitis and paricalcitol was changed to sevelamer due to the operation. The patient’s relative did not know if the change in drug was permanent and decision to continue paricalcitol would be made after unspecified tests were performed. The outcome of the event was reported as recovering.

Reviewer comment: Appendicitis is common, occurring at a rate of approximately 90 to 100 patients per 100,000 inhabitants per year in developed countries, and peaks typically in the second or third decade of life.¹² This case does not contain additional information that indicates this patient’s clinical course is aberrant from the usual clinical course of appendicitis. The case contained insufficient information such as comorbid conditions, concomitant medications, clinical history, reason for change in drug therapy, rechallenge, and pathology findings from the appendectomy; therefore, causality between the appendicitis and use of paricalcitol cannot be adequately assessed.

FAERS# 12196931, 2016, Ecuador, Hospitalization: A consumer reported a 16-year-old male patient developed peritonitis 132 days after initiating paricalcitol 2 mcg capsules “interday” for secondary hyperparathyroidism. Past medical history included arterial hypertension and secondary hyperparathyroidism. Concomitant medications included erythropoietin, amlodipine, vitamin B complex, vitamin C, folic acid, and calcium. The patient experienced abdominal pain,

vomiting, and peritonitis and was admitted to the nephrology service. The patient was treated with oxacillin, recovered, and was discharged. Intravenous paricalcitol was initiated the following month. The date of oral paricalcitol discontinuation and reason for change to intravenous paricalcitol was not reported.

Reviewer comment: Patients with chronic renal failure have immune system dysregulation and may be more susceptible to infections;¹³ however, peritonitis, in and of itself, is not common. Peritoneal dialysis is a common dialysis treatment modality for pediatric patients with end-stage renal disease, and peritonitis is the most common significant complication of chronic peritoneal dialysis in the pediatric population.¹⁴ However, the report does not specify whether the patient underwent peritoneal dialysis. In addition, the case lacks additional information that would rule out other leading causes of peritonitis, such as rupture or perforation along the gastrointestinal tract, other sources of inflammation (e.g., pancreatitis, diverticulitis), trauma, and cirrhosis. Despite the temporal relationship between paricalcitol initiation and peritonitis, the case contained insufficient information to adequately assess causality, such as comorbid conditions, clinical history, route of dialysis, and dechallenge or rechallenge information.

4 DISCUSSION

DPV reviewed all serious FAERS reports with paricalcitol use (injections, capsules) in the pediatric population less than 17 years of age received by FDA from April 17, 1998 through March 5, 2019, and identified two reports for discussion. The reports described single serious and unlabeled adverse events of appendicitis and peritonitis, respectively. No specific pattern of adverse events was noted and both reports contained insufficient information for adequate causality assessment.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for paricalcitol at this time.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of paricalcitol.

7 REFERENCES

1. Colman E. Clinical review of NDA 20819 Zemplar (paricalcitol) injection. March 31, 2004.
2. Greenbaum LA, Benador N, Goldstein SL, et al. Intravenous paricalcitol for treatment of secondary hyperparathyroidism in children on hemodialysis. *Am J Kidney Dis.* 2007;49(6):814-823.
3. Safety and Effectiveness of Zemplar Injection in Decreasing iPTH Levels in Pediatric ESRD Subjects on Hemodialysis. (2006). Retrieved from <https://clinicaltrials.gov/ct2/show/NCT00053547?term=zemplar+children&rank=2> (Identification No. NCT00053547).
4. Zemskova M. Cross-discipline team leader review NDA 021606 Zemplar (paricalcitol) capsules. October 13, 2016.
5. Safety and Efficacy of Paricalcitol Capsules in Decreasing Serum Parathyroid Hormone Levels in Children Aged 10-16 With Chronic Kidney Disease (CKD) (2018). Retrieved from <https://clinicaltrials.gov/ct2/show/NCT01020487?term=paricalcitol&cond=pediatric&rank=3> (Identification No. NCT01020487).
6. Webb NJ, Lerner G, Warady BA, et al. Efficacy and safety of paricalcitol in children with stages 3 to 5 chronic kidney disease. *Pediatr Nephrol.* 2017;32(7):1221-1232.
7. A Study to Evaluate the Safety of Paricalcitol Capsules in Pediatric Subjects Ages 10 to 16 With Stage 5 Chronic Kidney Disease Receiving Peritoneal Dialysis or Hemodialysis (2018). Retrieved from <https://clinicaltrials.gov/ct2/show/NCT01382212?term=paricalcitol&cond=pediatric&draw=1&rank=1> (Identification No. NCT01382212).
8. Pamer C. One year post-pediatric exclusivity postmarketing adverse event review Zemplar (paricalcitol), NDA 20819. April 20, 2005.
9. Food and Drug Administration Pediatric Advisory Committee Briefing Information. June 29, 2005. Retrieved from <https://wayback.archive-it.org/7993/20170404062504/https://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4152b1.htm>.
10. Zemplar (paricalcitol) capsules [product label]. North Chicago, IL: AbbVie Inc.; October 2016.
11. Zemplar (paricalcitol) injection [product label]. North Chicago, IL: AbbVie Inc.; November 2018.
12. Bhangu A, Soreide K, Di Saverio S, et al. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *Lancet*, 2015;386(100000):1278-1287.
13. Syed-Ahmed M, Narayanan, M. Immune Dysfunction and Risk of Infection in Chronic Kidney Disease. *Adv Chronic Kidney Dis.* 2019;26(1):8-15.
14. Chua A, Warady BA. Chronic peritoneal dialysis in children. In: Niaudet P, ed. *UpToDate*. Waltham, MA: UpToDate Inc. Retrieved from https://www.uptodate.com/contents/chronic-peritoneal-dialysis-in-children?search=peritonitis%20children&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H263453046. (Accessed on June 3, 2019.)

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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	1/16/2015	10717900	1	AR-ABBVIE-15P-007-1333346-00	Expedited (15-Day)	16.66	MALE	Argentina	OT
2	3/21/2016	12196931	2	EC-ABBVIE-16P-047-1587788-00	Expedited (15-Day)	16.82	MALE	Ecuador	HO
<p>*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, or a congenital anomaly/birth defect, and 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, OT=Other medically significant</p>									

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