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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance

Date:	November 6, 2020
Safety Evaluator:	Mohamed Mohamoud PharmD, MPH, BCPS 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:	Cotempla XR-ODT (methylphenidate extended release orally disintegrating tablets)
Pediatric Labeling Approval Date:	June 19, 2017
Application Type/Number:	NDA 205489
Applicant:	Neos Pharmaceuticals
OSE RCM #:	2020-727

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Cotempla XR-ODT (methylphenidate extended-release orally disintegrating tablet) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Cotempla XR-ODT in the pediatric population.

Cotempla XR-ODT (methylphenidate extended-release orally disintegrating tablet) is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 17 years of age. The FDA approved Cotempla XR-ODT on June 19, 2017. The safety and effectiveness of Cotempla XR-ODT in patients below 6 years of age have not been established. Additionally, the long-term efficacy of methylphenidate in pediatric patients has not been established.

DPV-I reviewed all FAERS reports associated with Cotempla XR-ODT in the pediatric population (ages 0 to < 18 years), received by FDA from approval of Cotempla XR-ODT through March 15, 2020. There were no fatal cases reported with Cotempla XR-ODT. The majority of FAERS reports for Cotempla XR-ODT described adverse events that were consistent with the known adverse events described in Cotempla XR-ODT's approved prescribing information. Furthermore, we did not identify an increase in severity in the labeled adverse events associated with Cotempla XR-ODT.

Of the five cases that described serious unlabeled adverse events, there were no new safety signals identified. All of the serious unlabeled events were confounded by the patient's underlying comorbidities, concurrent medication use, contained insufficient information for assessment, or had a more compelling alternative cause. As a result, no pediatric safety signals were identified at this time. DPV-I will continue postmarketing surveillance of adverse events associated with Cotempla XR-ODT use in the pediatric population.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Cotempla XR-ODT (methylphenidate extended-release orally disintegrating tablet) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Cotempla XR-ODT in pediatric patients.

1.1 REGULATORY HISTORY

Cotempla XR-ODT (methylphenidate extended-release orally disintegrating tablet) is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 17 years of age.[1] Cotempla XR-ODT was approved by the FDA on June 19, 2017. The safety and effectiveness of Cotempla XR-ODT in pediatric patients below 6 years of age have not been established. Additionally, the long-term efficacy of methylphenidate in pediatric patients has not been established.[1] Cotempla XR-ODT is supplied as extended-release orally disintegrating tablet in three strengths 8.6 mg, 17.3 mg and 25.9 mg. The recommended starting dose for pediatric patients 6 to 17 years of age is 17.3 mg given orally once daily in the morning. Daily dosage may be increased weekly in increments of 8.6 mg to 17.3 mg per day. Daily dosage above 51.8 mg is not recommended. This review was triggered by pediatric studies completed under PREA for Cotempla XR-ODT at the time of initial approval.[1]

The efficacy of Cotempla XR-ODT was evaluated in a laboratory classroom study conducted in 87 pediatric patients (aged 6 to 12 years) with ADHD. Following the washout of previous methylphenidate medications, there was an open-label dose-optimization period for 4 weeks to reach the optimal or maximum dose. After one week, subjects then entered a one-week randomized, double-blind, parallel group treatment period with the individually optimized dose of Cotempla XR-ODT or placebo. The primary efficacy endpoint was the average of the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale. SKAMP is a validated 13-item teacher rated scale that assesses manifestations of ADHD in a classroom setting. The SKAMP-combined scores test day average was statistically significantly lower (improved) with Cotempla XR-ODT compared to placebo.[1]

The pharmacokinetics of Cotempla XR-ODT administration were studied in pediatric patients (6-17 years of age) with ADHD under fasting conditions. After a single oral dose of 51.8 mg Cotempla XR-ODT, plasma concentrations of methylphenidate in children (6-12 years of age) were approximately twice the concentration observed in adults. Exposure levels in adolescent patients (13 to 17 years of age) were similar to those in adults. Body weight normalized clearance values were similar across the age groups.[1]

Notably, Cotempla XR-ODT was issued a Complete Response by FDA on November 6, 2015 based upon differences between the formulation used in the clinical trials and the formulation intended for commercial use. There was no bioavailability/bioequivalence study conducted to bridge this difference. On December 19, 2016, Neos Therapeutics, Inc. submitted the results of a bioavailability/bioequivalence study which compared the clinical trial formulation to the

formulation intended for commercial use. This study indicated an adequate bridge between the two formulations leading to Cotempla XR-ODT's approval on June 19, 2017.[2]

1.2 RELEVANT LABELED SAFETY INFORMATION

The Cotempla XR-ODT labeling contains the following safety information within the Highlights of Prescribing Information.[1]

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- **CNS stimulants, including COTEMPLA XR-ODT, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence (5.1, 9.2, 9.3)**
- **Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)**

WARNINGS AND PRECAUTIONS

- *Serious Cardiovascular Reactions*: Sudden death has been reported in association with CNS stimulants at recommended doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease. (5.2)
- *Blood Pressure and Heart Rate Increases*: Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic. (5.3)
- *Psychiatric Adverse Reactions*: Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to COTEMPLA XR-ODT use. (5.4)
- *Priapism*: Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms or prolonged penile erections or priapism are observed. (5.5)
- *Peripheral Vasculopathy, including Raynaud's Phenomenon*: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.6)
- *Long-term Suppression of Growth*: Monitor height and weight at appropriate intervals in pediatric patients. (5.7)

ADVERSE REACTIONS

Based on accumulated data from other methylphenidate products, the most common (>5% and twice the rate of placebo) adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased. (6)

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	March 16, 2020
Time period of search	June 19, 2017† - March 15, 2020
Search type	FBIS Quick Query
Product terms	Product name: Cotempla XR-ODT
Product NDA	205489
MedDRA Search Terms (Version 22.0)	All Preferred Terms (PTs)

Table 1. FAERS Search Strategy*
* See Appendix A for a description of the FAERS database. † Approval date of Cotempla XR-ODT Abbreviations: FBIS= FDA Business Intelligence System, MedDRA=Medical Dictionary for Regulatory Activities

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 approval of Cotempla XR-ODT to March 15, 2020.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From Approval of Cotempla XR-ODT to March 15, 2020

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	6 (2)	4 (0)	0 (0)
Pediatrics (0 - ≤17 years)	44 (39)	11(6)	0 (0)

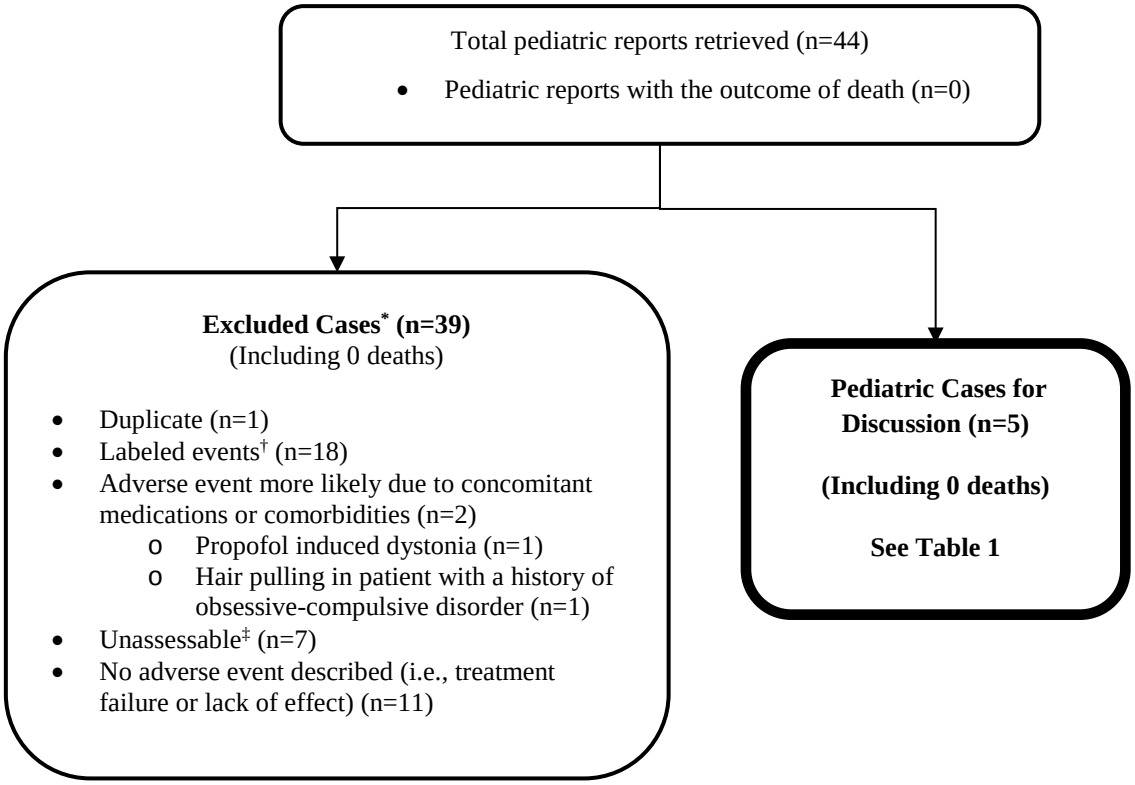
* May include duplicates and transplacental exposures, and have not been assessed for causality

† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.

3.1.2 Selection of Pediatric Cases in FAERS

Our FAERS search retrieved 44 pediatric reports from June 19, 2017 to March 15, 2020. DPV-I reviewed all 44 pediatric reports and excluded reports from further analysis if they were coded with labeled Preferred Terms (PTs) that did not reflect an apparent increase in severity of the labeled events. We further excluded reports from the case series for various reasons, such as duplicate reports, the adverse event was unlikely to be causally related to the use of Cotempla XR-ODT (e.g., co-morbid diseases or concomitant medications provide a more likely explanation for the adverse events), no adverse event described (i.e., treatment failure or lack of effect), and unassessable cases (i.e., cases that cannot be clinically assessed for causality because information is insufficient or lacking). We summarize the remaining cases in the sections below. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Pediatric Cases with Cotempla XR-ODT



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above
† Includes labeled neurological, psychiatric, skin and subcutaneous, and vascular adverse events
‡ Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, or clinical course and outcome).

3.1.3 Characteristics of Pediatric Cases

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

Table 3 summarizes the five FAERS cases in pediatric patients with Cotempla XR-ODT received by FDA from June 19, 2017 to March 15, 2020.

Table 3. Characteristics of the FAERS Pediatric Cases with Cotempla XR-ODT Received by FDA From June 19, 2017 to March 15, 2020 (N=5)		
Age (n=5)	6- <12 years 12- <17 years	3 2
Sex	Male Female	1 4
Country	United States Foreign	1 4
Reported reason for use	ADHD	5
Serious outcome*	Hospitalization	2

	Other Serious	4

* 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. A case can have more than one serious outcome.
Abbreviation: ADHD = Attention deficit hyperactivity disorder

3.1.4 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event reports associated with Cotempla XR-ODT.

3.1.5 Summary of Non-Fatal Serious Pediatric Cases (N=5)

The non-fatal pediatric cases reported the following serious unlabeled adverse events: accidental exposure to methylphenidate extended-release leading to hyponatremia and polydipsia, tongue biting and ulceration, dystonia, precocious puberty, and a drug interaction between methylphenidate and indomethacin resulting in visual hallucination. We identified these five unlabeled serious adverse events of interest in the pediatric population with the use of Cotempla XR-ODT.

FAERS#14301727v1, MCN: US-NEOS THERAPEUTICS, LP-2017NEO00110, USA, 2017[3]

Unlabeled Event: Polydipsia, Hyponatremia (n=1)

A previously healthy 8-year-old male (weight 23 kg) with ADHD on 20 mg lisdexamfetamine was admitted to the emergency department (ED) with altered mental status 15 hours after accidental ingestion of his 10-year-old brother‘s 36 mg long-acting methylphenidate. Approximately 3 hours after ingestion the patient was noted to be combative, disoriented, and drinking copious amounts of water. On arrival to the ED he was noted to be diaphoretic, flushed, and combative to obtain water. It is estimated he drank three to four gallons of water prior to arriving in the ED. Due to his agitation, he was given a dose of lorazepam and fell asleep. He was then discharged home 8 hours post-ingestion but was still drowsy and continued to have altered mental status. At 13 hours post-ingestion he returned to ED with multiple episodes of tonic-clonic seizures, emesis, hypothermia, and urinary incontinence. Due to his severely altered mental status he was intubated and transferred to the pediatric intensive care unit (PICU). On arrival to the PICU the patient had documented sodium of 115 (units not reported). He was then given 250 mL of 3% NaCl bolus, which brought his sodium to 127 (units not reported). Initial post correction evaluation revealed low plasma osmolality (246, units not reported), normal urine osmolarity (450), and normal urine sodium. A computed tomography of the head was performed, which demonstrated no evidence of acute trauma or cerebral edema. After correction of sodium to 132, the patient continued to have altered mental status. Pediatric neurology performed a 24-hour electroencephalography (EEG) and found no seizure activity. Due to his temperature instability, a lumbar puncture was performed, and broad-spectrum antibiotics were initiated. After 48 hours of negative cerebrospinal fluid findings, antibiotics were discontinued. Eighteen hours post ingestion the patient was more alert and had significant improvement in his mental status and was extubated. Thirty-six hours post ingestion the patient returned to his baseline and was discharged 60 hours post ingestion with no residual sequelae.

Reviewer comments: The overdosage section of methylphenidate products states that the signs and symptoms of acute methylphenidate overdosage result primarily in the overstimulation of the CNS causing excessive sympathomimetic effects which may include vomiting, agitation,

convulsions and hallucinations among other symptoms.[1,4] In this case, the patient ingested long acting methylphenidate in more than the recommended dose (i.e., 1.5 mg/kg). However, it is difficult to determine whether these symptoms are the result of the immediate effect of the long-acting methylphenidate overdose or the effect of combined acute methylphenidate with chronic amphetamine use. This case was also identified in the published literature; the authors concluded the patient likely had psychogenic (secondary) polydipsia. Cotempla XR-ODT is labeled for the onset of new psychotic or manic symptoms. To identify whether there is a potential safety signal, we searched the medical literature using PubMed and retrieved no additional reports of polydipsia/hyponatremia with methylphenidate products. Additionally, DPV-I searched the FAERS database for additional cases in pediatric patients using the PTs polydipsia/hyponatremia through May 22, 2020 reported with methylphenidate and identified 9 cases. Each of the 9 cases was limited by insufficient information or alternative causes (e.g., anticonvulsants, CNS tumor).

FAERS#15068842v1, MCN: TR-NEOS THERAPEUTICS, LP-2018NEO00074, Turkey, 2018[5]

Unlabeled Event: Tongue biting, Tongue ulceration(n=1)

A 12-year-old female with a family history significant for obsessive-compulsive disorder bit her tongue and lip multiple times after starting treatment with methylphenidate. She was diagnosed with ADHD (inattentive subtype) four years ago and was treated with Osmotic Release Oral System Methylphenidate (OROS) methylphenidate 18 mg/day; she bit her tongue after starting treatment. At that time, she was switched to atomoxetine but did not experience any clinical benefit and the medication was discontinued. She was switched to OROS methylphenidate 27 mg/day, which was later increased to 36 mg/day. Two weeks after the dose increase, she bit off the tip of her tongue and the drug was discontinued. An EEG evaluation was done and the tongue biting was deemed not to be due to an epileptic episode. After some time, the patient was restarted on immediate release (IR) methylphenidate 10 mg/day. After starting methylphenidate IR, she involuntarily bit her lower lip and the medication was discontinued. After a five-week drug free period and the healing of the ulcer, methylphenidate IR 10 mg/day was started again, and the patient subsequently bit off the lateral side of her tongue the day the dose was increased to 20 mg/day. The medication was then discontinued with no reoccurrence of tongue or lip biting over the following two months. A psychiatric evaluation did not reveal any psychotic, psychosocial stressors or mood disturbances in the patient's life. No other medications were initiated, and the patient was referred to a counseling program for the management of her ADHD symptoms.

Reviewer comments: The case reports a plausible temporal relationship to methylphenidate in addition to positive dechallenge and rechallenge. Tongue biting/ulceration is not a labeled adverse event in the prescribing information of methylphenidate products. However, compulsive behaviors and stereotyped movement disorders such as motor tics are generally associated with stimulants.[6] Some methylphenidate products are labeled for bruxism and are contraindicated in patients with motor tics or with family history or diagnosis of Tourette's syndrome.[4] For completeness, DPV-I searched the FAERS database for additional cases in pediatric patients using the PTs tongue biting/ulceration through April 28, 2020 reported with methylphenidate and identified six cases. Each of the six cases was limited by insufficient information or alternative cause (e.g., epilepsy)

FAERS #15154435v1, MCN: TR-NEOS THERAPEUTICS, LP-2018NEO00086, Turkey, 2018[7]

Unlabeled Event: Dystonia (n=1)

A seven-year-old girl was brought to the ED with complaints of hyperactivity, inattentiveness, excessive talking, excitement and difficulty to remain focused on school work. She was diagnosed with ADHD according Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and she was prescribed methylphenidate IR 5 mg twice daily. After the third dose of methylphenidate, she developed dystonic involuntary movements characterized by turning the neck sideways and by twisted facial muscles. Routine laboratory assessments and magnetic resonance imaging were normal. The patient had no significant history of head trauma, acute/chronic diseases, or susceptibility to intoxication. The patient was diagnosed with methylphenidate-induced acute dystonia. Methylphenidate was discontinued and she was administered intramuscular biperiden (0.4mg/kg). Her symptoms reduced within 12 hours and entirely resolved after three days.

Reviewer comments: The case reports a plausible temporal relationship to methylphenidate and a positive dechallenge. Methylphenidate is not labeled for dystonia but is labeled for dyskinesia in its prescribing information.[1] Dystonia due to methylphenidate treatment has been generally reported during combined treatments with antipsychotics.[8] On June 2020, the Office of Surveillance and Epidemiology (OSE) conducted a comprehensive integrated postmarket safety review to evaluate acute dystonic reactions associated with products used to treat ADHD, including methylphenidate and found insufficient evidence to support the association of acute dystonia with ADHD stimulants, including methylphenidate, at this time.[9]

FAERS#16890028v1, MCN: TR-NEOS THERAPEUTICS, LP-2019NEO00045, Turkey, 2019[10]

Unlabeled Event: Precocious puberty (n=1)

A female aged 7-years and 11 months was reported to have precocious puberty after 12 months of methylphenidate treatment dosed at 0.5 mg/kg/dose three times daily (maximum 60 mg) for ADHD. The child was noted to have Tanner 2 breast development "and rapidly progressing precocious puberty". The child's weight was at the >97th percentile and height was between the 75th-90th percentile. Body mass index (BMI) and BMI percentile were not reported. Family history was notable for ADHD. Diagnostic evaluation revealed the following: basal luteinizing hormone (LH) 0.66 IU/L (normal 0.2-5.0 IU/L), peak LH 23.76 IU/L (normal 12-80 IU/L), estradiol (E2) 1 pg/ml (normal 2-18 pg/ml), prolactin 6.55 ng/ml (normal levels not reported), thyroid function test results "euthyroid", pelvic ultrasound showing "pubertal changes", and bone age reported as "9-year-old". The child was started on gonadotropin-releasing hormone (GnRH) analog treatment.

Reviewer comments: The case describes a female child who was treated with a GnRH analog for development of premature thelarche. Treatment selection suggests diagnosis of gonadotropin-dependent precocious puberty, but the case lacks details for a thorough assessment. For example, there is no information on axillary or pubic hair development to provide a global clinical assessment of secondary sexual characteristics, it is not possible to assess BMI with the

available information, reported reference lab values do not specify pubertal or prepubertal norms, and it is unclear what is meant by "rapidly progressing precocious puberty" or ultrasound findings of "pubertal changes." For completeness, DPV-I searched the FAERS database for additional cases in pediatric patients using the PT precocious puberty through May 19, 2020 reported with methylphenidate and identified 13 unique pediatric cases. One case did not describe symptoms related to precocious puberty, two cases reported diagnostic evaluation that ruled out precocious puberty, and 10 cases were unassessable due to insufficient information (e.g., no reported symptoms, no physical examination, no clinical evaluation, no diagnostic information, no interpretable diagnostic findings).

FAERS#17395599v1, MCN:TR-NEOS THERAPEUTICS, LP-2020NEO00008, Turkey, 2020[11]

Unlabeled Event: Drug Interaction: hallucinations (n=1)

A 14-year-old female was seen in clinic with complaints of attention deficit, lack of concentration in school lessons, forgetfulness and procrastination, lack of being organized, excessive talking and impulsivity. The patient was diagnosed with ADHD, and 27 mg of long acting methylphenidate treatment daily was initiated. After one month, the methylphenidate dose was increased to 36 mg daily with no drug related problems in the subsequent two follow-up clinic visits over two months. Subsequently, the patient presented to the hospital with complaints of visual hallucinations - "seeing strange things". The symptoms began 48 hours prior to her admission to the hospital. She did not have any personal or family history of psychiatric disease, trauma or illicit drug use. She had been using long-acting methylphenidate for a total of three months when she presented with visual hallucinations. She also started using indomethacin four days prior due to intense dysmenorrhea. She used indomethacin before for headaches and abdominal pain prior to starting treatment with methylphenidate with no complaints. Indomethacin was discontinued and the patient's visual hallucinations disappeared within 48 hours. The patient was continued on long acting methylphenidate and the visual hallucinations did not occur again during the follow-up clinic visits. The reporting physician thought that visual hallucinations were due to a pharmacodynamic drug interaction between long acting methylphenidate and indomethacin.

Reviewer comments: The case reports a possible drug interaction between long acting methylphenidate and indomethacin. Visual hallucination only emerged when indomethacin was concomitantly used with long acting methylphenidate and subsided after indomethacin was discontinued. In addition, the patient had previously used each agent as monotherapy with no reported problems. Methylphenidate is labeled for psychiatric adverse reactions in its prescribing information.[1] Moreover, CNS stimulants at recommended doses may cause psychotic or manic symptoms (e.g., visual hallucinations) in patients with no prior history of psychotic illness or mania. Methylphenidate and psychotic adverse events are rare; the events occur acutely and after months of use and abate only after the cessation of methylphenidate.[12,13] The mechanism by which methylphenidate may cause psychotic adverse events is unclear. However, the increase of dopamine in the synaptic cleft is a possible risk factor for the association of psychotic symptoms including hallucinations with methylphenidate. Furthermore, there have been reports that nonsteroidal anti-inflammatory drugs (NSAIDs), including indomethacin, can also induce psychotic symptoms by inhibiting prostaglandin synthesis and thus indirectly increase dopamine levels which may cause psychotic symptoms.[14] The reported psychotic

adverse events in this case may have been caused by each agent alone or possibly by the combination of both agents. For completeness, a literature search of "Drug interaction between methylphenidate and NSAIDs" in PubMed did not yield any additional case reports. Furthermore, DPV-I searched the FAERS database for additional cases in pediatric and adult patients using the PTs Drug interaction and hallucination through April 25, 2020 reported with methylphenidate and indomethacin and did not retrieve any additional cases.

4 DISCUSSION

DPV-I reviewed all the FAERS reports associated with Cotempla XR-ODT use in the pediatric population (ages 0 to < 18 years) from approval of Cotempla XR-ODT through March 15, 2020. Since approval of Cotempla XR-ODT the majority of the FAERS reports described adverse events that were consistent with the known adverse events described in Cotempla XR-ODT's approved prescribing information. We did not identify an increase in severity in the labeled adverse events associated with Cotempla XR-ODT. There were no deaths reported with Cotempla XR-ODT. Of the total FAERS reports evaluated, we identified five cases describing serious unlabeled events as adverse events of interest that warranted further investigation. Notably, these cases report the use of methylphenidate products (i.e., other than Cotempla XR-ODT).

Of the five cases describing serious unlabeled adverse events, there were no new safety signals identified. All five serious unlabeled cases had missing clinical information or reported events that may be sequelae to other labeled events. An expanded search for the five serious unlabeled adverse events in pediatric patients reported in our series did not identify additional well-documented cases. Singular cases of hyponatremia/polydipsia, tongue biting/ulceration, precocious puberty, and hallucination from drug interaction between methylphenidate and indomethacin do not support new pediatric safety signals at this time.

5 CONCLUSION

DPV-I did not identify any pediatric safety concerns for Cotempla XR-ODT at this time.

6 RECOMMENDATION

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 Cotempla XR-ODT.

7 REFERENCES

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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=5)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	12/19/2017	14301727	1	US-NEOS THERAPEUTICS, LP-2017NEO00110	Expedited (15-Day)	8	Male	USA	HO,OT
2	6/26/2018	15068842	1	TR-NEOS THERAPEUTICS, LP-2018NEO00074	Expedited (15-Day)	12	Female	Turkey	OT
3	7/17/2018	15154435	1	TR-NEOS THERAPEUTICS, LP-2018NEO00086	Expedited (15-Day)	7	Female	Turkey	OT
4	10/7/2019	16890028	1	US-NEOS THERAPEUTICS, LP-2017NEO00110	Expedited (15-Day)	7	Female	Turkey	OT
5	2/10/2020	17395599	1	TR-NEOS THERAPEUTICS, LP-2020NEO00008	Expedited (15-Day	14	Female	Turkey	HO

*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, OT=other medically significant

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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/

MOHAMED A MOHAMOUD
11/06/2020 12:03:50 PM

IVONE E KIM
11/06/2020 12:05:43 PM

CARMEN CHENG
11/06/2020 12:10:13 PM

CINDY M KORTEPETER
11/06/2020 01:18:53 PM