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Office of Surveillance and Epidemiology**

Pediatric Postmarketing Pharmacovigilance Review

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Product Names: Dyanavel XR (amphetamine suspension) extended release
Adzenys XR-ODT (amphetamine tablet) orally disintegrating

**Pediatric Labeling
Approval Date** 10/19/2015 (Dyanavel XR)
01/27/2016 (Adzenys XR-ODT)

Application Type/Number: NDA 208147 (Dyanavel XR)
NDA 204326 (Adzenys XR-ODT)

Applicant/Sponsor: Tris Pharma Inc (Dyanavel XR)
Neos Therapeutics (Adzenys XR-ODT)

OSE RCM #: 2018-304

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for Dyanavel XR[®] (amphetamine suspension, extended-release) and Adzenys XR-ODT[®] (amphetamine tablet, orally disintegrating) in pediatric patients.

Dyanavel XR[®] was first approved in October 19, 2015 and is indicated for Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 to 17 years old. Adzenys XR-ODT[®] was first approved in January 27, 2016 and is indicated for ADHD in patients aged 6 to 17 years old.

The Division of Pharmacovigilance (DPV) evaluated all FAERS reports of adverse events in the pediatric population for Dyanavel XR received between October 19, 2015 to December 26, 2017 and Adzenys XR-ODT received between January 27, 2016 to December 26, 2017. We identified four cases with a serious outcome (2 Dyanavel XR and 2 Adzenys XR-ODT). No deaths were reported. The four cases reported adverse events consistent with the known risks described in labeling (i.e., overdose, respiratory distress as part of hypersensitivity reaction) or had limited information which precluded a meaningful causality assessment (i.e., suicidal ideation without information on abuse or dependence, comorbidities, and concomitant medications).

We evaluated lack of effect as an adverse event of interest because both Dyanavel XR and Adzenys XR-ODT are new dosage forms for amphetamine XR. We identified 15 non-serious cases reporting lack of effect, 7 with Dyanavel XR and 8 with Adzenys XR-ODT. Our review of these cases did not identify any compelling information that supports a product quality issue.

There is no evidence that there are pediatric safety concerns with Dyanavel XR or Adzenys XR-ODT at this time. DPV-I will continue to monitor adverse events associated with Dyanavel XR and Adzenys XR-ODT use.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Dyanavel XR and Adzenys XR-ODT (amphetamine extended-release) are central nervous system stimulants indicated for the treatment of ADHD in patients aged 6 to 17 years old. Dyanavel XR was approved by the FDA on October 19, 2015. It is supplied as an extended-release suspension containing 2.5 mg amphetamine base per ml. Adzenys was approved by the FDA on January 27, 2016. It is supplied as extended-release orally disintegrating tablets in 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 16.7 mg, and 18.8 mg. The dosage and administration for Dyanavel XR and Adzenys XR-ODT are summarized in Table 1.1.

Table 1.1: Amphetamine XR dosage and administration			
Brand Name	Starting dose	Dose increase	Maximum
Dyanavel XR	2.5 mg or 5 mg once daily in the morning	Increments of 2.5 mg to 10 mg per day	20 mg per day
Adzenys XR-ODT	6.3 mg once daily in the morning	Increments of 3.1 mg or 6.3 mg at weekly intervals	18.8 mg per day (6-12 years) 12.5 mg per day (13-17 years)

This Pediatric Research Equity Act (PREA) review was triggered by pediatric studies completed for Dyanavel XR and Adzenys XR-ODT at the time of initial approval.

DYANAVAL XR

The safety and effectiveness of Dyanavel XR have been established in pediatric patients with ADHD ages 6 to 17 years of age in two adequate and well-controlled clinical trials:

- 1) A double-blind, randomized, placebo-controlled study in pediatric patients 6 to 12 years of age with ADHD [National Clinical Trial Number (NCT) 02083783]

The SKAMP-combined score from pre-dose showed improvement at 4 hours post-dosing with Dyanavel XR compared to placebo (primary efficacy endpoint).^a The SKAMP-combined change scores from pre-dose showed improvement at all time points (1 to 13 hours post-dose) with Dyanavel XR compared to placebo (secondary efficacy endpoints). The most commonly reported adverse reactions were epistaxis, allergic rhinitis, and upper abdominal pain.

^a SKAMP is a 13-item teacher-rated scale that assesses manifestations of ADHD in the classroom setting.

- 2) A single-dose, open-label pharmacokinetic (PK) study in pediatric patients 6 to 12 years of age with ADHD.^b

The sponsor used a modeling report to simulate the exposure and PK profile in adolescent patients (13-17 years old).¹ This was considered adequate to characterize the safety and efficacy of Dyanavel XR in adolescent patients with ADHD.

ADZENYS XR-ODT

The safety and effectiveness of Adzenys XR-ODT have been established in pediatric patients with ADHD ages 6 to 17 years of age in three adequate and well-controlled clinical trials:

- 1) A double-blind, randomized, placebo-controlled, parallel-group study in pediatric patients 6 to 12 years of age with ADHD.^c
- 2) A double-blind, randomized, placebo-controlled, parallel-group study in pediatric patients 13 to 17 years of age with ADHD.^c
- 3) A single-dose, open-label PK study in pediatric patients (6-12 years) and adolescents (13-17 years) with ADHD.^b

The safety of Adzenys XR-ODT relies on previous safety and efficacy findings for Adderall XR [mixed salts of a single-entity amphetamine product extended-release (MAS ER) capsules], originally approved in 2001.² In the controlled clinical studies, patients who received MAS ER showed improvements on the ADHD-RS-IV total score compared to patients on placebo.^d The most common adverse reactions were loss of appetite, insomnia, abdominal pain, weight loss, and nervousness.

^b NCT numbers are unavailable (registry requirements do not apply for Phase 1 investigations)

^c Two randomized clinical trials for Adzenys XR-ODT were conducted with Adderall XR as the listed drug. NCT numbers are unavailable (studies were completed in 2001 prior to inception of the registry in 2005).

^d ADHD-RS-IV is an 18-item parent-rated or teacher-rated scale that measures the symptoms of ADHD as described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES³

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

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

----- CONTRAINDICATIONS -----

- Known hypersensitivity to amphetamine products or other ingredients in DYANAVEL XR (4)
- Use of monoamine oxidase inhibitor (MAOI) or within 14 days of the last MAOI dose (4, 7.1)

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

- **Serious Cardiovascular Reactions:** Sudden death has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients 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 arrhythmia, or coronary artery disease (5.2)
- **Blood Pressure and Heart Rate Increases:** Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic (5.3)
- **Psychiatric Adverse Reactions:** May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use (5.4)
- **Long-Term Suppression of Growth:** Monitor height and weight in pediatric patients during treatment (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)
- **Serotonin Syndrome:** Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdose situations. If it occurs, discontinue DYANAVEL XR and initiate supportive treatment (5.7, 17).

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

Most common adverse reactions observed with amphetamine products: dry mouth, anorexia, weight loss, abdominal pain, nausea, insomnia, restlessness, emotional lability, dizziness, tachycardia (6.1)

The labeling for Adzenys XR-ODT is similar to Dyanavel XR with the exception of the "Adverse Reactions" section where the reactions are categorized by pediatric age [(6 to 12) and (13 to 17) years old]:⁴

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

- Pediatric patients ages 6 to 12 years: Most common adverse reactions (≥5% and with a higher incidence than on placebo) were loss of appetite, insomnia, abdominal pain, emotional lability, vomiting, nervousness, nausea, and fever. (6.1)
- Pediatric patients ages 13 to 17 years: Most common adverse reactions (≥5% and with a higher incidence than on placebo) were loss of appetite, insomnia, abdominal pain, weight loss, and nervousness. (6.1)

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy

	Dyanavel XR	Adzenys XR-ODT
Date of Search	December 26, 2017	December 26, 2017
Time Period of Search	October 19, 2015* - December 26, 2017	January 27, 2016† - December 26, 2017
Search Type	Quick Query	Quick Query
Product Name	Product Name: Dyanavel XR	Product Name: Adzenys XR-ODT
Search Parameters	NDA 208147	NDA 204326

* US approval date for Dyanavel XR

† US approval date for Adzenys XR-ODT

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 Total adult and pediatric FAERS reports* from October 19, 2015 to December 26, 2017 with Dyanavel XR

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	1 (1)	1 (1)	0 (0)
Pediatrics (0 - <18 years)	30 (30)	2‡ (2)	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, and other serious important medical events.

‡ See Figure 2.3.1

Table 2.2.2 Total adult and pediatric FAERS reports* from January 27, 2016 to December 26, 2017 with Adzenys XR-ODT

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (≥ 18 years)	26 (25)	11 (10)	1 (0)
Pediatrics (0 - <18 years)	41 (40)	2 [‡] (2)	0 (0)

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

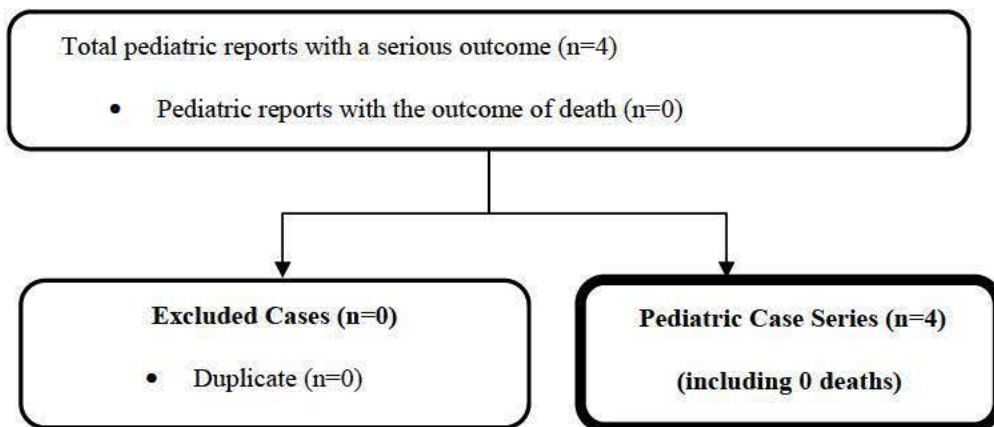
[†] For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

[‡]See Figure 2.3.1

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 4 pediatric reports with a serious outcome (See Tables 2.2.1 and 2.2.2). See **Figure 2.3.1** below for the specific selection of cases to be summarized in **Sections 2.5 and 2.6**.

Figure 2.3.1 Selection of Serious Pediatric Cases with Dyanavel XR and Adzenys XR-ODT



2.2.3 Characteristics of Pediatric Case Series

Appendix B lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 2.2.3 Characteristics of Pediatric Case Series with Dyanavel XR and Adzenys XR-ODT (n=4)

Age	2- < 6 years	1
	6- <12 years	2
	12- < 17 years	1
Sex	Male	3
	Female	1

Table 2.2.3 Characteristics of Pediatric Case Series with Dyanavel XR and Adzenys XR-ODT (n=4)

Country	United States	4
Reported reason(s) for use*	ADHD	4
	Autism spectrum disorder	1
Serious outcome [†]	Life-threatening	1
	Hospitalized	1
	Other serious	2

* A case could have more than one reported reason for use

[†] 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. Reports may have more than one outcome.

2.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

No pediatric deaths were reported for Dyanavel XR or Adzenys XR-ODT.

2.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=4)

2.4.1 Dyanavel XR (N=2)

2.4.1.1 Intentional overdose (n=1)

FAERS Case# 14149258 describes a 5-year-old male on Dyanavel XR for Asperger syndrome. After an unknown duration of treatment with Dyanavel XR, he consumed the “whole bottle” of Dyanavel XR as the “taste was good”. He experienced tremors, insomnia, vomiting, and agitation. The patient was immediately taken to the emergency room, sedated with diazepam, and hospitalized for two days. At the time of the report, the patient’s condition was stable.

Reviewer’s comments: Intentional overdose is an unlabeled term; however, based on the patient’s age and reason reported for overdose, it is possible that this was an unintentional event. The Overdosage section of labeling describes manifestations of overdose including tremor and vomiting, consistent with the events described in the report. Additionally, Dyanavel XR was prescribed for an off-label use as it is not indicated for Asperger syndrome or pediatric patients younger than 6 years of age with ADHD.

2.4.1.2 Respiratory distress (n=1)

FAERS Case# 13372687 describes a 16-year-old male who experienced respiratory distress 20 minutes after taking a first dose of 2 ml (total of 5 mg) of Dyanavel XR. Diphenhydramine and epinephrine were administered in the ambulance and his breathing returned to normal after he arrived to the emergency department. His medical history was significant for autism, depression, anxiety, and an unspecified oral surgery eleven days prior to the event. Concomitant

medications included citalopram, gabapentin, multivitamin, fish oil, melatonin, calcium citrate, and vitamin D3.

Reviewer's comments: The temporal relationship between Dyanavel XR and respiratory distress followed by recovery after drug discontinuation with medical treatment is consistent with a hypersensitivity reaction. Hypersensitivity reactions, including anaphylaxis and angioedema, are labeled in the Contraindications and Adverse Reaction sections of the label.

2.4.2 Adzenys XR-ODT (N=2)

2.4.2.1 Suicidal ideation (n=2)

FAERS Case# 13114569 describes an 8-year-old male who received Adzenys XR-ODT 3.1 mg daily for ADHD. Concomitant medication included unspecified vitamin. The dose was increased to 12.5 mg daily over an unknown period of time. One week after initiation of Adzenys, the patient felt “emotionally bad”, “cried a lot and didn't know why”, “made bad choices at school”, and had suicidal thoughts of “better if I die”. Two weeks later, Adzenys was discontinued after the patient alerted the physician. The patient improved and was initiated on a different unspecified ADHD medication.

FAERS Case# 12947693 describes a 7-year-old female who received Adzenys XR-ODT 6.3 mg for ADHD. Medical history was also significant for unspecified psychotic disorder. Two weeks after starting Adzenys, the patient became hostile, aggressive, and “went to the kitchen and grabbed a knife to cut herself”. After drug discontinuation hostility and aggression improved.

Reviewer's comments: The two cases support a temporal association between initiation of the drug and onset of suicidal ideation. Additionally, there is a positive dechallenge in both cases. However, missing clinical information (i.e., unknown patient comorbidities in FAERS Case# 13114569 and unknown concomitant medications in FAERS Case# 12947693) limits our assessment. Of note, FAERS Case# 12947693 is also confounded by the patient's underlying psychotic disorder. Suicidal ideation is a labeled event under the “Drug Abuse and Dependence” section of the label, but the cases do not provide sufficient information to assess whether this event occurred in the context of abuse or dependence. Depression is labeled in the “Adverse Reactions” section of the label.

2.5 ADVERSE EVENT OF INTEREST: LACK OF EFFECT (N=15)

DPV evaluated cases reporting lack of effect associated with Dyanavel XR and Adzenys XR-ODT use as both these products are new dosage forms for amphetamine XR. DPV identified 15 cases [Dyanavel XR (7), Adzenys XR-ODT (8)] reporting a lack of effect among the non-serious pediatric adverse event reports.

Of the seven Dyanavel XR cases, two reported a short duration of action (therapeutic effect lasted less than eight hours after administration). One case reported lack of effect due to reduced viscosity of the liquid; however, it was unclear if the bottle was shaken prior to administration. In the four remaining cases limited clinical information precluded a meaningful assessment.

Of the eight Adzenys XR-ODT cases, two reported a short duration of action where the patient chewed or swallowed the tablet prior to dose dissolution. Five cases provided limited clinical information that precluded a meaningful assessment.

Six of the 15 cases reporting lack of effect with the use of Dyanavel XR and Adzenys XR-ODT provided lot number information; however, no trend was noted and overall no product quality issue has been identified. None of the 15 cases reported switching from a different amphetamine formulation to Dyanavel XR or Adzenys XR-ODT.

Generally, it is difficult in most cases to attribute lack of efficacy to a particular product. It is important to note that ‘drug ineffective’ and related preferred terms are the most common group of adverse events reported for all cases submitted to FAERS. The preferred term ‘drug ineffective’ alone accounts for approximately 6% to 7% of all adverse event terms reported in FAERS cases.⁵ Thus, this group of AE terms has a markedly high background rate, and is experienced or suspected by many patients. This largely reflects the heterogeneity and complexity of medical conditions, as well as the variability of clinical responses to therapeutic products among individuals. Many conditions are not fully amenable to treatments, and many are chronic, episodic, and progressive.

3 DISCUSSION

We identified four pediatric adverse event reports of Dyanavel XR (2) and Adzenys XR-ODT (2) with a serious outcome. The four reports describe adverse events that are consistent with the known risks described in labeling (e.g., overdose, respiratory distress as part of hypersensitivity reaction) or had limited information which precluded a meaningful causality assessment (i.e., suicidal ideation without information on abuse or dependence, comorbidities, and concomitant medications).

We further explored lack of effect as an adverse event of interest because both Dyanavel XR and Adzenys XR-ODT are new dosage forms for amphetamine XR. Our search did not identify any compelling cases that support a product quality issue.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths associated with Dyanavel XR or Adzenys XR-ODT.

4 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with Dyanavel XR or Adzenys XR-ODT at this time.

5 RECOMMENDATIONS

DPV-I recommends no regulatory action at this time and will continue to monitor adverse events associated with Dyanavel XR and Adzenys XR-ODT use.

6 REFERENCES

1. Kumi K, Zhang L, Krudys K, Zhu H. Amphetamine Extended Release Oral Suspension (Dyanavel XR). Clinical Pharmacology Review, September 21, 2015.
2. Snyder D. Amphetamine Extended Release (ER) Orally Disintegrating Tablets (ODT), (Adzenys XR-ODT). Memorandum and Pediatric Labeling Review, December 9, 2015
3. Tris Pharma Inc. Dyanavel XR Package Insert. May 2017.
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5. Misu T, Kortepeter CM, Muñoz MA, Wu E, Dal Pan GJ. An Evaluation of "Drug Ineffective" Postmarketing Reports in Drug Safety Surveillance. *Drugs Real World Outcomes*. 2018 Feb 23. doi: 10.1007/s40801-018-0131-3.

7 APPENDICES

7.1 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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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.

7.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DYANA VEL XR AND ADZENYS XR-ODT (N=4)

DYANA VEL XR (N=2)		
FAERS CASE NUMBER	FAERS VERSION NUMBER	MANUFACTURER CONTROL NUMBER
14149258	3	US-TRIS PHARMA, INC-2017TRISPO00423
13372687	1	
ADZENYS XR-ODT (N=2)		
FAERS CASE NUMBER	FAERS VERSION NUMBER	MANUFACTURER CONTROL NUMBER
13114569	2	US-NEOS THERAPEUTICS, LP-2016NEO00066
12947693	1	US-NEOS THERAPEUTICS, LP-2016NEO00053

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