CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	204325
Priority or Standard	Standard
Submit Date(s)	15 November 2016
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PDUFA Goal Date	15 September 2017
Division / Office	DPP/ODE I
Reviewer Name(s)	Bernard A. Fischer, MD
Review Completion Date	July 31, 2017
Established Name	Amphetamine extended release oral suspension, 1.25 mg/mL
(Proposed) Trade Name	Adzenys ER
Therapeutic Class	Stimulant
Applicant	Neos Therapeutics, Inc.
Formulation(s)	Suspension
Dosing Regimen	Starting dose 6.3 mg (5 mL) daily; maximum for ages 6 to 12 years old is 18.8 mg (15 mL) daily, for ages 13 to adult is 12.5 mg (10 mL) daily
Indication(s)	Attention Deficit/Hyperactivity Disorder
Intended Population(s)	Ages 6 years and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Applicant has demonstrated bioequivalence to the listed drug (Adderall XR). No new safety findings were identified that would indicate a difference in the risk-benefit considerations for this form of amphetamine to treat attention deficit hyperactivity disorder. Therefore, I recommend approval of this application.

1.2 Risk-Benefit Assessment

There are a number of stimulant-based treatments for ADHD available at this time. However, the added benefit of another long-acting oral solution amphetamine option, with no known increased risk, supports the approval of this application.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant's Adzenys XR oral disintegrating tablet (ODT; NDA-204326) has three post-marketing requirements (PMRs) in children ages 4 to less than 6 years old with ADHD:

- A single-dose, open-label, randomized pharmacokinetic study
- A randomized, double-blind, placebo-controlled, flexible-dose titration study
- A one-year open-label safety study

I recommend the same PMRs for the Applicant's Adzenys ER oral solution. The Applicant can use the data for the ODT PMRs to satisfy the oral solution PMRs if they conduct a small bridging study (which can enroll healthy adults). If, for any reason, the Applicant withdraws the ODT from the market prior to completing the ODT PMRs, they will then have to complete the PMRs with the oral solution.

2 Introduction and Regulatory Background

Neos Therapeutics has submitted a 505(b)(2) application for an extended release amphetamine oral suspension referencing listed drug Adderall XR.

2.1 Product Information

The product is a suspension of dextro- and levoamphetamine [(b) (4)] for oral administration. [(b) (4)] which allows for delayed release. A suspension dose of 18.8 mg is equivalent to 30 mg of Adderall XR; the suspension can be dosed as 5, 10, 15, 20, 25, or 30 Adderall XR-equivalent-milligrams. It has a shelf-life of 24 months and is orange-flavored via [(b) (4)].

2.2 Table of Currently Available Treatments for Proposed Indication

Although behavioral therapies are available for ADHD, the mainstay of treatment remains pharmacological. Most approved drugs are psychostimulants, although several antidepressants are used off-label (e.g., desipramine, nortriptyline, imipramine, and bupropion).

Table 1. Currently Available ADHD Medications.

Class	Active Moiety	Dosage Form	Strength
Stimulant	Methamphetamine	Tablet	5, 10 mg
		Tablet, extended release	5, 10 mg
	Methylphenidate	Tablet	2.5, 5, 10 mg
		Tablet, chewable	2.5, 5, 10 mg
		Tablet, extended release	10, 18, 20, 27, 36, 54 mg
		Tablet, extended release, chewable	20, 30, 40 mg
		Capsule, extended release	5, 10, 15, 20, 25, 30, 35, 40, 50, 60 mg
		Transdermal	10, 15, 20, 30 mg/9hrs
		Suspension, extended release	5 mg/mL
		Solution	5, 10 mg/mL
	Dexmethylphenidate	Tablet	2.5, 5, 10 mg
		Capsule, extended release	5, 10, 15, 20, 25, 30, 35, 40 mg
	Amphetamine	Suspension, extended release	2.5 mg/mL
		Tablet	5, 10 mg
		Tablet, extended release, orally disintegrating	EQ 3.1, 6.3, 9.4, 12.5, 15.7, 18.8 mg base
	Dextroamphetamine	Tablet	2.5, 5, 7.5, 10, 15, 20, 30 mg
		Capsule, extended release	5, 10, 15 mg
		Solution	5 mg/mL
	Mixed Amphetamine Salts	Capsule, extended release	Total active ingredients: 5, 10, 15, 20, 25, 30 mg
		Tablet	Total active ingredients: 5, 7.5, 10, 12.5, 15, 20, 30 mg
	Lisdexamfetamine	Tablet, chewable	10, 20, 30, 40, 50, 60 mg
		Capsule	10, 20, 30, 40, 50, 60, 70 mg

Table 1. continued

Class	Active Moiety	Dosage Form	Strength
Non-stimulant	Atomoxetine	Capsule	10, 18, 25, 40, 60, 80, 100 mg
	Clonidine	Tablet	0.1, 0.2, 0.3 mg
		Tablet, extended release	0.1 mg
		Transdermal	0.1, 0.2, 0.3 mg/24 hrs
	Guanfacine	Tablet	EQ 1, 2, 3 mg base
		Tablet, extended release	EQ 1, 2, 3, 4 mg base

2.3 Availability of Proposed Active Ingredient in the United States

Amphetamine is currently Schedule II in the United States. It is available by prescription as a brand-name product and generic in a variety of formulations (see Table 1). Adderall XR, the reference listed drug (RLD), has been approved in the United States since October 2001.

2.4 Important Safety Issues with Consideration to Related Drugs

Amphetamines carry a boxed warning for abuse and dependence as well as sudden death and serious cardiovascular adverse reactions when misused. Other warnings and precautions include risk of increased blood pressure, psychosis or mania, long-term suppression of growth, seizure, peripheral vasculopathy (including Raynaud's phenomenon), serotonin syndrome (when combined with serotonergic agents or in an overdose setting), blurred vision, and exacerbation of tics. Other adverse reactions include loss of appetite, insomnia, abdominal pain, nausea and vomiting, nervousness, headache, dry mouth, and fever.

2.5 Summary of Presubmission Regulatory Activity

The following meetings were held between the Division and the Applicant:

- Pre-IND Type B meeting on January 13, 2011
- End-of-Phase 2 (EOP2) Type B meeting on May 02, 2013
- Pre-NDA Type B meeting on June 19, 2014
- Written Response Only (WRO) Type C meeting in December 2015

During the pre-IND and EOP2 meetings, the Division and the Applicant agreed on a development program that could lead to NDA review. The Division agreed that the Applicant could conduct adult pharmacokinetic studies with Adderall XR 30 mg, the RLD dose, even though the Adderall XR label specifies 20 mg as the adult dose. It was also agreed that the pediatric study would occur after some data was obtained from adult studies.

The Applicant conducted three bioequivalence and food effect studies with a "clinical trial formulation" of the product. During the pre-NDA meeting, the Division and the Applicant discussed differences between this clinical trial product formulation and the

commercial-scale product formulation. Levels of the controlling excipient in the commercial product differed from those of the clinical trial formulation by greater than (b) (4) percent ((b) (4) percent versus (b) (4) percent, respectively). Therefore, the Agency required a bioequivalence study of the commercial formulation with the reference listed drug (Adderall XR) and a food effect study. The Division clarified this requirement via the WRO meeting and a follow-up email from the regulatory project manager in December 2105.

2.6 Other Relevant Background Information

The Applicant submitted an amphetamine orally disintegrating tablet (ODT) formulation NDA (204,326) in December 2012, but was the subject of a Complete Response due to Chemistry Manufacturing and Controls (CMC) issues. Specifically, there were problems with tablet hardness and disintegration failures. The Applicant addressed these concerns and the Division approved the application in January 2016.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The application was submitted via eCTD. All required datasets were included. The Applicant did not prospectively submit individual case report forms (CRFs) since there were no deaths or serious adverse events. On examination, preferred terms appeared to accurately reflect investigator verbatim terms.

3.2 Compliance with Good Clinical Practices

The Quality Assurance Unit from Worldwide Clinical Trials Early Phase Services, LLC, inspected and audited study sites to assure compliance with Good Clinical Practices. FDA's Office of Study Integrity and Surveillance recommended accepting the study data without an on-site inspection.

3.3 Financial Disclosures

Was a list of clinical investigators provided: Yes ☒ No ☐

Total number of investigators identified: 28

Number of investigators who are Applicant employees (including both full-time and part-time employees): 0 (Applicant used CRO)

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A

Significant payments of other sorts: N/A

Proprietary interest in the product tested held by investigator: N/A

Significant equity interest held by investigator in sponsor of covered study: N/A

Is an attachment provided with details of the disclosable financial interests/ arrangements:	Yes ☐	No ☐	N/A ☒
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐	N/A ☒

Number of investigators with certification of due diligence (FDA 3454, box 3) 0

Is an attachment provided with the reason: Yes ☐ No ☐ N/A ☒

4 Significant Issues from Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

At filing, the CMC reviewer requested data concerning product stability data, the length of time the product must be shaken to re-suspend, and the ability to dispense accurate doses via a variety of measuring instruments. The Applicant submitted data to address these concerns.

4.2 Clinical Microbiology

At filing, the Applicant was asked to perform a risk assessment to identify potential sources for introduction of Burkholderia cepacia complex organisms (BCC), or to provide this data if it already exists. The Applicant submitted data to address these concerns.

4.3 Preclinical Pharmacology-Toxicology

During the Filing Meeting, the pharmacology-toxicology reviewer noted that some of the inactive ingredients exceeded the Inactive Ingredient Database (IID) limits at the time of filing; namely, sorbitol, propylene glycol, and xanthan gum. In their response, the

Applicant referenced the January 2017 IID update. All three inactive ingredients are now within the acceptable levels cited by the updated IID. However, there have been case reports of intestinal necrosis linked to the combination of sodium polystyrene sulfonate and concomitant use of (b) (4) percent sorbitol; see 7.7 Additional Safety Issue.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Amphetamines increase extracellular dopamine via action on the dopamine active transporter and by triggering dopamine-containing vesicles to release. The pathological basis for ADHD is currently unknown— as is the reason for stimulant efficacy in the disorder.

4.4.2 Biopharmaceutics/Pharmacokinetics

Pharmacokinetic parameters were within acceptable limits to establish bioequivalence between the Adzenys clinical trial formulation, the commercial formulation, and the RLD (see Table 2).

Table 2. Mean (SD) PK Parameter Ranges for Adzenys and RLD.

Drug	Population	AUC_{last} (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{½}$ (hr)
d-Amphetamine					
Adzenys Clinical Trial	Child, ADHD	1061 (229)	68 (12)	5.3 (1.6)	12.7 (6.0)
Adzenys Clinical Trial	Healthy Adult	820-979 (161-207)	43-51 (8-10)	5.0-5.3 (0.7-1.9)	11.8-12.4 (1.8-2.1)
Adzenys Commercial	Healthy Adult	891-930 (144-189)	43-49 (7-8)	4.8-4.9 (1.0-1.8)	11.4-12.0 (1.9-2.5)
Adderall XR	Healthy Adult	848-970 (146-213)	43-51 (9-10)	4.6-8.0 (1.5-2.5)	11.8-12.6 (1.5-2.4)
l-Amphetamine					
Adzenys Clinical Trial	Child, ADHD	380 (88)	24 (4)	5.9 (2.0)	15.3 (14.4)
Adzenys Clinical Trial	Healthy Adult	289-354 (60-86)	13-16 (2-3)	5.1-5.9 (0.9-2.1)	14.5-15.6 (2.8-3.1)
Adzenys Commercial	Healthy Adult	316-327 (54-71)	14-15 (2)	5.0-5.6 (1.1-2.6)	14.1-14.6 (2.7-3.6)
Adderall XR	Healthy Adult	287-339 (54-85)	13-15 (3)	4.8-8.2 (1.5-2.6)	14.5-15.6 (2.5-3.7)

4.5 Controlled Substances

Amphetamine is currently DEA schedule II and is a known drug of abuse.

4.6 Pediatric and Maternal Health

The Division of Pediatric and Maternal Health examined the submitted data from both the Applicant's studies and literature review and made labeling recommendations. Information on a national pregnancy registry was added to the patient hand-out.

5 Sources of Clinical Data

5.1 Table of Clinical Trials

Table 3. Clinical Studies Supporting NDA Submission.

Study Number	Description	Population and Formulation
NT0201.1004	Single-dose Single treatment: -Oral suspension (30 mg[a]), fasted	Children (6-12 yrs) with ADHD Clinical trial formulation
NT0201.1005	Single-dose 4 treatment crossover: -3 formulations of oral suspension (30 mg), fasted -Adderall XR(30 mg), fasted	Healthy adults 3 Test formulations including Clinical trial formulation (Test 2)
NT0201.1006	Single-dose food effect study 3 treatment crossover: -Oral suspension (30 mg), fed and fasted -Adderall XR (30 mg), fed	Healthy adults Clinical trial formulation
NT0201.1007	Single-dose food effect study 3 treatment crossover: -Commercial formulation (30 mg), fed and fasted -Clinical trial formulation (30 mg), fasted	Healthy adults Clinical trial formulation versus commercial formulation
NT0201.1008	Single-dose 2 treatment crossover: -Commercial formulation (30 mg), fasted -Adderall XR(30 mg), fasted	Healthy adults Commercial trial formulation

[a]30 Adderall XR-equivalent mg = 18.8 mg of the Adzenys ER oral suspension.

5.2 Review Strategy

As per Table 3, the Applicant did not conduct efficacy studies. This review focuses on the safety record of the bioequivalence (BE) and food effect studies as per Table 4.

Table 4. Material Reviewed.

Material Submitted	eCDT Sequence Number	Submission Date
NDA	0000	NOV 15, 2016
Clinical Overview	0004	JAN 11, 2017
Response to Information Request	0014	JUL 06, 2017

6 Review of Efficacy

The Applicant did not conduct any clinical efficacy studies; this application relies on the findings of efficacy and safety from the RLD, Adderall XR (NDA 021,303), and the BE and food effect studies described above.

7 Review of Safety

Safety Summary

Given the extensive safety experience to date with amphetamine, the relatively brief duration of the bioequivalence and food effect studies (single dose studies), and the subject population (mostly healthy adult volunteers), these studies are not expected to produce meaningful new safety data that could be extrapolated to the clinical use of Adzenys.

There were no deaths or non-fatal serious adverse events in any of the studies submitted to support this application. Two subjects discontinued the study early due to adverse events as described below (see 7.3.3 Dropouts and Discontinuations). No new, unlabeled safety signals were identified.

The most commonly reported AEs in Applicant-conducted studies (greater than or equal to 5 percent of total exposures) were nausea and vomiting (7 percent of Adderall XR exposures) and decreased appetite (5 percent of Adderall XR and Clinical Trial Formulation exposures).

7.1 Methods

7.1.1 Studies Used to Evaluate Safety

I used all submitted studies (NT0201.1004, NT0201.1005, NT0201.1006, NT0201.1007, and NT0201.1008) to evaluate safety. I also referred to a placebo-controlled study of Adderall XR in children (Study 381.201) from the Adderall XR NDA (021,303) for data on pulses as described below (see 7.4.3 Vital Signs).

7.1.2 Categorization of Adverse Events

The Applicant categorized adverse events using MedDRA versions as follows:

- NT0201.1004, version 17.0
- NT0201.1005, version 14.1
- NT0201.1006, version 15.1
- NT0201.1007, version 18.1
- NT0201.1008, version 19.0

In my review, AEs in gastrointestinal and cardiovascular systems were examined by system organ class as well as by preferred terms. Other AEs, such as those with multiple possible etiologies (e.g., headaches), were analyzed as preferred terms separately from their assigned system organ class. Terms that appeared to represent similar concepts (e.g., excitation and increased energy) were combined for analysis.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

I combined the adult studies (NT0201.1005, NT0201.1006, NT0201.1007, and NT0201.1008) to compare the safety of the clinical trial and commercial formulations of the proposed product to the RLD. Because the Applicant's studies were cross-over, I counted AE occurrences separately for each study arm even though the same individuals were participating in multiple arms. I examined Study NT0201.1004, the study in children, separately.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

All studies were single-dose; adult studies were cross-over. All drug doses were either 30 mg (RLD) or 30 Adderall XR-equivalent mg.

Mean BMI for the children in study NT0201.1004 was 17.4 ± 2.4 kg/m^2. In this study, there were nine children in the 6 to 7 years-old subgroup and ten each in the 8 to 10 and 11 to 12 years-old subgroups. See Table 5 for other participant demographics across all five studies.

Table 5. Participant Demographics.

		NT0201.				
		-1004 N=29	-1005 N=44	-1006 N=30	-1007 N=48	-1008 N=42
Age, years	M (SD)	8.8 (2)	42.5 (16)	35.8 (14)	46.0 (15)	43.7 (13)
	Range	6-12	18-70	20-68	19-73	20-70
Female Sex, % (n)		24% (7)	46% (20)	43% (13)	56% (27)	55% (23)
Race, % (n)	Asian	0	0	3% (1)	4% (2)	5% (2)
	Black/African-American	65% (19)	18% (8)	7% (2)	27% (13)	26% (11)
	White	35% (10)	73% (32)	90% (27)	65% (31)	67% (28)
	Other	0	9% (4)[a]	0	4% (2)[b]	2% (1)[c]
Hispanic, % (n)		35% (10)	48% (21)	67% (20)	48% (23)	52% (22)

[a]3 Native American/American Indian, 1 native Hawaiian.
[b]1 Native American/American Indian, 1 multiracial.
[c]1 Native American/American Indian.

Based on 2015 U.S. Census Department data, Hispanics (18 percent of the U.S. Population) were over-represented in the Applicant's studies. African-Americans (13 percent of the U.S. Population) were under-represented in some studies and over-represented in others. ADHD is more often diagnosed in white children[1,2], which could also exaggerate the differences in the study sample demographics compared to the U.S. population potentially receiving the drug. However, reflection of the diagnosed U.S. population is arguably less important in pharmacokinetic studies without an efficacy endpoint. Although sex, racial, and ethnic differences have been observed in pharmacokinetic parameters[3], these differences are also less important in cross-over studies where each subject acts as his or her own control. Therefore, I would not expect subjects' demographics to have impacted these bioequivalence studies.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and In Vitro Testing

Not Applicable.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

The studies conducted were bioequivalence studies. No new information was presented on amphetamine metabolism, clearance, or drug interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

To assess for increased blood pressure and pulse, investigators measured these vital signs at screening, pre-dose, and 4, 8, 12, 24, 36, 48, and 60 hours after dosing in all studies. Some studies had more frequent vital signs (e.g., study NT0201.1005 also measured blood pressure and pulse at 1 and 6 hours). Subjects received study drug in an inpatient setting to monitor closely for AEs. Laboratory tests, physical exams, and electrocardiograms (EKGs) were also collected pre- and post-doses.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during the studies.

7.3.2 Nonfatal Serious Adverse Events

No nonfatal serious adverse events occurred during the studies.

7.3.3 Dropouts and Discontinuations

See Table 6 for dropouts and discontinuations.

Table 6. Discontinuations and Dropouts.

Study	Subject	Discontinuation Reason
NT0201.100**4**	None	N/A
NT0201.100**5**	115	Positive urine drug screen at period 2 check-in
	123	Positive urine pregnancy at period 4 check-in
	125	Withdrew consent for personal preference after period 4
	133	Withdrew after period 2 (Adderall XR) for multiple AEs: jitteriness, headache, myalgia, thirst, abdominal cramp, dry skin, fatigue, dizziness, diarrhea, blepharitis, irregular menses, and vomiting
	138	Withdrawn by investigator for dental abscess
NT0201.100**6**	110	Withdrew after period 1 (Clinical Trial Formulation, Fasted) for AE of vomiting
NT0201.100**7**	1129	Withdrawn during period 2 for study non-compliance
	1148	Withdrew consent for personal preference during period 3
NT0201.100**8**	None	N/A

Nausea and vomiting are labeled adverse events and there was no indication of increased frequency with Adzenys compared to the RLD (see 7.4.1 Common Adverse Events).

7.3.4 Significant Adverse Events

No adverse events were labeled as severe. Subject NT0201.1005-001-1135 was listed as having "clouded sensorium" related to Adderall XR from 0700 on October 6 to 1600 on October 7, 2012. No additional information was submitted. An IR was sent to the

Applicant to request the CRFs for this subject during this period. The CRFs were submitted, but contained no additional details regarding the event.

7.3.5 Submission-Specific Primary Safety Concerns

There were no submission-specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

There was no placebo administered during the submitted studies and so AEs can only be compared among active treatments. There was no signal for unusual or increased rates of AEs with Adzenys compared to the RLD (see Tables 7 and 8).

Table 7. Adverse Events in Adzenys Child Study (NT0201.1004).

Age Bracket (yrs)	Cardiac	GI	
	Tachycardia[a]	Nausea	Vomiting
6-7	7	0	0
8-9	7	1	1
10-12	8	0	2
Total	10 (35%)	1 (3%)	3 (10%)

[a]Tachycardia reported by the investigator as an AE. See 7.4.3 Vital Signs for more information on measured pulse.

Table 8. Combined Adverse Events from Adzenys Adult Studies.

Adverse Events	Reference (Adderall XR)			Commercial Formulation			Clinical Trial Formulation			Test 1 n=43	Test 3 n=40
	Fed n=71	Fasted n=42	Total n=113	Fed n=47	Fasted n=89	Total n=136	Fed n=71	Fasted n=77	Total n=148		
GI System Organ Class	16	6	**22 (19%)**	1	3	**4 (3%)**	16	4	**20 (14%)**	19 (44%)	19 (48%)
Abdominal Distension/ Flatulence	-	-	**0**	-	-	**0**	1	-	**1**	2	1
Abdominal Pain	3	1	**4 (4%)**	-	-	**0**	3	-	**3 (2%)**	3	2
Dyspepsia	-	-	**0**	-	-	**0**	-	-	**0**	1	0
Nausea/Vomiting	4	4	**8 (7%)**	-	1	**1**	2	3	**5 (3%)**	4	4
Constipation	-	-	**0**	-	-	**0**	-	-	**0**	0	1
Diarrhea	2	-	**2 (2%)**	-	-	**0**	1	-	**1**	2	3
Decreased Appetite	5	1	**6 (5%)**	1	2	**3 (2%)**	7	-	**7 (5%)**	6	6
Dry Mouth	2	-	**2 (2%)**	-	-	**0**	2	1	**3 (2%)**	1	2
Cardiac System Organ Class	1	-	**1**	-	2	**2 (1%)**	1	3	**4 (3%)**	0	1
Chest Pain	-	-	**0**	-	-	**0**	-	1	**1**	0	0
Tachycardia[a]	-	-	**0**	-	-	**0**	-	2	**2 (1%)**	0	0
Palpitations	1	-	**1**	-	-	**0**	1	-	**1**	0	1
Prolonged QRS	-	-	**0**	-	1	**1**	-	-	**0**	0	0
Arthralgia/Myalgia/ Muscle Stiffness	1	-	**1**	-	-	**0**	2	1	**3 (2%)**	0	0
Bruxism/Muscle Spasm or Contraction/Tremor	-	1	**1**	1	-	**0**	-	2	**2 (1%)**	0	1
"Dizziness"	3	-	**3 (3%)**	-	-	**0**	-	1	**1**	3 (7%)	0
Dysesthesia/Paresthesia	-	-	**0**	-	-	**0**	1	2	**3 (2%)**	0	0
Excitation/Agitation/ Increased Energy/ Increased Attentiveness/ Anxiety/Jitteriness	3	1	**4 (4%)**	2	2	**4 (3%)**	4	6	**10 (7%)**	3 (7%)	2 (5%)
Euphoria	1	-	**1**	2	1	**4 (3%)**	1	3	**4 (3%)**	0	0
Fatigue/Somnolence/ Relaxation/Decreased Concentration	2	1	**3 (3%)**	-	2	**2 (1%)**	1	-	**1**	2 (5%)	1
Flushing/Hot Flash	-	2	**2 (2%)**	-	-	**0**	-	1	**1**	0	1
Headache	3	-	**3 (3%)**	1	2	**3 (2%)**	3	3	**6 (4%)**	3 (7%)	6 (15%)
Infection/Inflammation	3	-	**3 (3%)**	-	-	**0**	-	2	**2 (1%)**	1	0
Insomnia	1	-	**1**	1	-	**1**	1	1	**2 (1%)**	2 (5%)	1

[a]Tachycardia reported by the investigator as an AE. See 7.4.3 Vital Signs for more information on measured pulse.

There was no statistical difference between the AE of euphoria in the RLD and the Adzenys Commercial Formulation (X^2=1.26, p=0.26). There was no statistical difference between the excitation-related AEs in the RLD and the Adzenys Clinical Trial Formulation (X^2=1.06, p=0.30).

7.4.2 Laboratory Findings

I examined pediatric subject laboratory values and no out-of-range value represented a clinically meaningful pattern that would indicate a new safety signal. Adult laboratory values that were out-of-range after exposure to study drugs are presented in Table 9. Individual adult values were also examined for clinical significance and none demonstrated a clinically significant pattern that would indicate a potential new safety signal.

Table 9. Number of Adult Subjects (N=162) with Out-of-Range Laboratory Values.

Test	High	Low	Test	High	Low
Hematocrit	-	8 (5%)	Albumin	1	2 (1%)
Leukocytes	2 (1%)	-	Bilirubin	-	-
Basophils	-	-	BUN	11 (7%)	-
Eosinophils	5 (3%)	-	Creatinine	3 (2%)	-
Lymphocytes	4 (2%)	-	Calcium	-	2 (1%)
Monocytes	2 (1%)	-	Chloride	1	4 (2%)
Neutrophils	1	4 (2%)	Potassium	-	1
Platelets	3 (2%)	-	Sodium	-	15 (9%)
ALT	4 (2%)	-	Glucose	33 (20%)	-
AST	5 (3%)	-	LDH	3 (2%)	6 (4%)
Alk. Phos.	2 (1%)	-	Urate	-	-

7.4.3 Vital Signs

Investigators reported tachycardia as an AE in two studies: 10 pediatric subjects in study NT0201.1004 and 2 adult subjects in study NT0201.1006. All subjects with reported tachycardia were on the Adzenys Clinical Trial Formulation.

When I examined the complete NT0201.1004 vital signs dataset, I identified an additional 12 pediatric subjects with pulses during the study over 100 bpm and at least 10 bpm over their baseline (see Table 10 for Applicant-reported and reviewer-identified subjects with tachycardia).

Table 10. Tachycardia (Beats per Minute) in Study NT0201.1004.

Subject	Pre-dose HR	Peak HR	Hrs Post-dose	Peak - BL	Resolution HR	Hrs Post-dose
Applicant-Reported Cases						
1001 (8 yo)	90	119	2	29	117	24
1002 (11 yo)	64	117	6	53	92	12
1003 (11 yo)	90	100	6	10	86	8
1009 (8 yo)	97	140	6	43	101	24
1012 (7 yo)	82	122	12	40	85	24
1014 (9 yo)	72	110	8	38	85	24
1016 (11 yo)	72	117	6	45	93	24
1017 (7 yo)	75	110	2	35	95	10
1018 (8 yo)	74	106	6	32	93	8
1019 (7 yo)	105	138	12	33	83	24
Reviewer-Identified Similar Cases						
1005 (10 yo)	76	102	2	26	80	24
1006 (10 yo)	58	100	12	42	78	24
1011 (7 yo)	67	120	10	53	95	12
2001 (6 yo)	85	105	4	20	88	6
2003 (9 yo)	106	119	6	13	108	24
2010 (9 yo)	81	101	2	20	84	8
2012 (9 yo)	83	134	10	51	90	24
2013 (10 yo)	88	128	6	40	94	24
2015 (11 yo)	76	125	6	49	94	24
2017 (7 yo)	84	123	2	39	87	24
2018 (7 yo)	86	120	10	34	92	12
2019 (11 yo)	79	114	2	35	85	24

It is difficult to interpret the tachycardia observed in study NT0201.1004. There is no comparison arm and no discernable pattern in timing. To better provide context for these findings, I examined the results of Study 381.201 from NDA-021,303 (Adderall XR). This randomized, placebo-controlled study examined Adderall IR and several doses of XR in children with ADHD. Select data from that study is reproduced in Table 11. It appears that children receiving placebo had increases in heart rate comparable to stimulant-treated children; up to 133 bpm.

Drawing from the medical literature, I found a 10-year study of more than 500 children with ADHD that compared heart rates with and without stimulants. Children receiving stimulant medications had increased heart rates compared to those receiving non-stimulant treatment, but differences were modest (mean pulse of 84 ± 12 versus 79 ± 12 bpm).[4] This finding, and the tachycardia observed in the placebo arm of Study 381.201

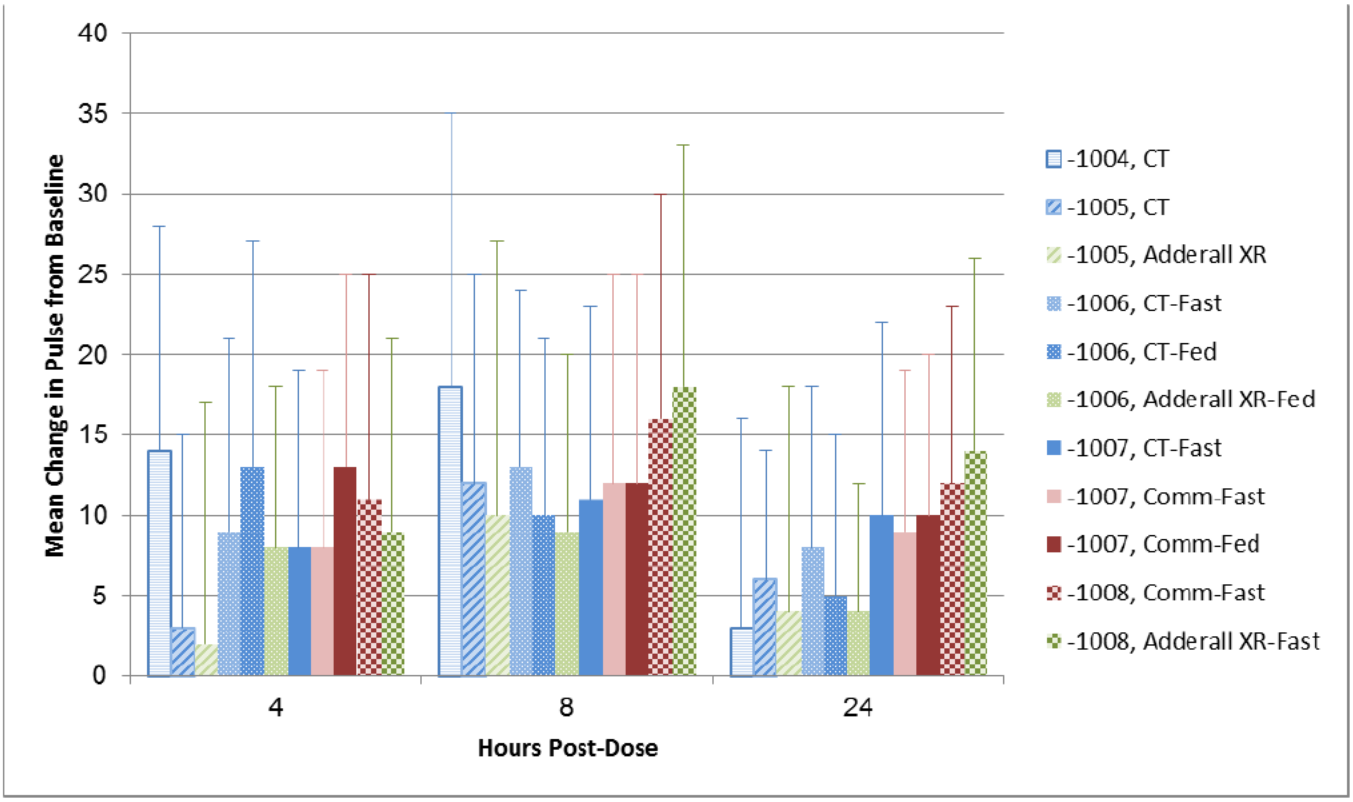
from NDA-021,303 (Adderall XR), gives some indication that tachycardia in children is not specific to treatment with stimulant medications.

Table 11. Select Heart Rate Data from Study 381.201; NDA-021,303 (Adderall XR).

	Adderall XR (30 mg)			Placebo		
	n	Mean (SD)	Min - Max	n	Mean (SD)	Min - Max
Pre-Dose	52	87 (13)	53 – 119	55	90 (13)	59 – 119
1.5 hours	50	97 (15)	44 – 129	53	99 (12)	68 – 125
4.5 hours	50	102 (12)	77 – 131	53	107 (15)	67 – 129
7.5 hours	50	100 (14)	71 – 140	52	103 (13)	70 – 133

Tachycardia was also reported as an AE in two adult subjects in study NT0201.1006 (peak heart rates of 125 and 133 bpm). However, mean pulse rates in all subjects across all treatments in all studies were similar (see Figure 1 for representative data).

Figure 1. Mean Pulse Changes from Baseline during all Applicant Studies.



CT=Adzenys Clinical Trial Formulation; Comm=Adzenys Commercial Formulation

Mean blood pressure results for all studies are presented in Table 12. The maximum individual systolic blood pressure reading in any child subject was 130 mmHg, which was pre-dose. The maximum individual diastolic blood pressure reading in any child subject was 71 mmHg, which was seen in various subjects at 4, 8, and 12 hours post-

dose. Adult subjects with at least one blood pressure reading outside of the range 90 to 170 mmHg/50 to 100 mmHg were as follows:

- Systolic blood pressure greater than 170 mmHg: 3 (2 percent)
- Systolic blood pressure less than 90 mmHg: 31 (19 percent)
- Diastolic blood pressure greater than 100 mmHg: 2 (1 percent)
- Diastolic blood pressure less than 50 mmHg: 15 (9 percent)

Overall, there was no clear signal for elevated blood pressure related to any treatment arm in the Applicant's studies.

Table 12. Peak Mean (SD) Blood Pressure Results for all Applicant Studies.

Study	Treatment	Peak Mean Systolic Blood Pressure (mmHg)	Hrs Post-dose	Peak Mean Diastolic Blood Pressure (mmHg)	Hrs Post-dose
NT0201.1004	Clinical Trial Formulation	110 (9)	4	71 (5)	4
NT0201.1005	Test 1	124 (13)	12	75 (10)	24
	Clinical Trial Formulation	124 (14)	6	74 (8)	12
	Test 3	123 (14)	4	75 (9)	24
	Adderall XR	121 (15)	6	75 (9)	24
NT0201.1006	Clinical Trial Formulation- Fasted	124 (13)	12	73 (9)	8
	Clinical Trial Formulation- Fed	127 (12)	12	76 (7)	6
	Adderall XR- Fed	126 (14)	6	75 (10)	8
NT0201.1007	Commercial Formulation- Fed	128 (12)	12	77 (10)	12
	Commercial Formulation- Fasted	124 (15)	4	75 (9)	12
	Clinical Trial Formulation- Fasted	124 (14)	4	75 (9)	36
NT0201.1008	Commercial Formulation- Fasted	125 (13)	4	77 (7)	12
	Adderall XR- Fasted	123 (13)	4	77 (8)	36

7.4.4 Electrocardiograms (EKGs)

There were no clinically significant EKG findings in studies NT0201.1004, NT0201.1005, NT0201.1006, or NT0201.1008. A 38-year-old African American female subject in study NT0201.1007 developed a widened QRS complex during the study (after the treatment period with the Clinical Trial Formulation, fasted). A cardiologist determined the abnormality was benign and idiopathic (e.g., unrelated to stimulant treatment).

7.4.5 Special Safety Studies/Clinical Trials

Not Applicable.

7.4.6 Immunogenicity

Not Applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not Applicable.

7.5.2 Time Dependency for Adverse Events

Not Applicable.

7.5.3 Drug-Demographic Interactions

Not Applicable.

7.5.4 Drug-Disease Interactions

Not Applicable.

7.5.5 Drug-Drug Interactions

Not Applicable; data as per RLD.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not Applicable.

7.6.2 Human Reproduction and Pregnancy Data

One pregnancy was reported during the study, but no labeling updates are proposed from this single experience.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not Applicable; data as per RLD.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not Applicable; data as per RLD.

7.7 Additional Safety Issue

Both sodium polystyrene sulfonate (SPS) and (b) (4) percent sorbitol are inactive ingredients in the Adzenys ER oral suspension. SPS is an FDA-approved treatment for hyperkalemia as an orally- or rectally-administered cation exchange agent. SPS suspensions had historically been constituted in sorbitol. Sorbitol, as an osmotic laxative, prevents SPS-induced constipation and impaction.

There are case reports of intestinal necrosis, including some deaths, linked to the use of SPS for hyperkalemia. Many of these reports suggest that suspending the SPS in a (b) (4) percent sorbitol solution increases the risk of developing necrosis (see references 5 and 6 for examples). Based on these reports and a rat study supporting a risk of SPS+ (b) (4) percent sorbitol[7], the Divisions of Cardiovascular and Renal Products (DCRP) and Gastroenterology and Inborn Errors Products (DGIEP) advised SPS manufacturers to remove sorbitol from any pre-mixed formulations and to warn against using it for the resuspension of the SPS powder.

Exposures to SPS and (b) (4) percent sorbitol are considerably higher when used to treat hyperkalemia versus as an inactive ingredient in the Adzenys formulation (see Table 13).

Table 13. Comparative sodium polystyrene and sorbitol doses.

	Hyperkalemia	Adzenys ER	Inactive Ingredient Database Limit

sodium polystyrene sulfonate	(b) (4)
(b) (4) % sorbitol	

There was no specific gastrointestinal AE signal in the submitted studies, but most exposures were limited to a single dose. I reviewed multiple other NDA applications and could find no other orally administered liquid with both SPS and sorbitol (oseltamivir, omeprazole, methylphenidate, amphetamine, oxycodone, morphine, lamotrigine, carbamazepine, and valproate).
Based on the nature of the evidence (case reports), the difference in indication, and the large difference in exposures, I do not believe that the Division needs to issue a Complete Response for this application. However, I do recommend that language be inserted into labeling mentioning that intestinal necrosis has been seen with the SPS and sorbitol combination; see 9.2 Labeling Recommendations.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

[1]Morgan PL, Hillemeier MM, Farkas G, Maczuga S. Racial/ethnic disparities in ADHD diagnosis by kindergarten entry. J Child Psychol Psychiatry 2014; 55(8):905-13.

[2]Morgan PL, Staff J, Hillemeier MM, Farkas G, Maczuga S. Racial and ethnic disparities in ADHD diagnosis from kindergarten to eighth grade. Pediatrics 2013; 132(1):85-93.

[3]Anderson GD. Sex and racial differences in pharmacological response: Where is the evidence? Pharmacogenetics, pharmacokinetics, and pharmacodynamics. J Women's Health 2005; 14(1):19-29.

[4]Vitiello B, et al. Blood pressure and heart rate over 10 years in the Multimodal Treatment Study of Children with ADHD. Am J Psychiatry 2012; 169(2):167-77.

[5]Lillemoe KD, et al. Intestinal necrosis due to sodium polystyrene (Kyexalate) in sorbitol enemas: Clinical and experimental support for the hypothesis. Surgery 1987; 101(3):267-72.

[6]McGowan CE, et al. Intestinal necrosis due to sodium polystyrene sulfonate (Kayexalate) in sorbitol. South Med J 2009; 102(5):493-7.

[7]Ayoub I, et al. Colon necrosis due to sodium polystyrene sulfonate with and without sorbitol: An experimental study in rats. PLoS One 2015; DOI:10.1371/journal.pone.0137636.

9.2 Labeling Recommendations

Clinically, no labeling changes are recommended to the RLD's boxed warning, warnings and precautions, or adverse reactions specific to this formulation. Because altering the suspension's pH could change the pharmacokinetic parameters of the drug, CMC and clinical have recommended wording to advise patients not to mix the suspension with foods or other liquids prior to consuming Adzenys. Data on blood pressure will conform to the approved Adzenys ODT label.

Based on the possible risk of intestinal necrosis with the concomitant exposure to sodium polystyrene sulfonate and (b) (4) percent sorbitol, I suggest something similar to the following language be added to the Warnings and Precautions section of the label:

Cases of intestinal necrosis, including some deaths, have been reported with the concomitant use of sodium polystyrene sulfonate and (b) (4) % sorbitol. In these cases, patients were administered sodium polystyrene sulfonate to treat hyperkalemia at doses greater than 200 times the amount present in Adzenys ER oral suspension. However, no absolute safe levels for the interaction of sodium polystyrene sulfonate and (b) (4) % sorbitol have been established.

9.3 Advisory Committee Meeting

This 505(b)(2) application relies on the findings of safety and efficacy of Adderall XR and there were no questions for an Advisory Committee.

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/s/

BERNARD A FISCHER
08/28/2017

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