APPLICATION NUMBER:

204325Orig1s000

NON-CLINICAL REVIEW(S)
PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 204325
Supporting document/s: Supporting Document Number 1, eCTD
Sequence Number 0000
Applicant’s letter date: November 15, 2016
CDER stamp date: November 15, 2016
Product: Amphetamine XR-OS; Amphetamine extended- release oral suspension (1.25 mg/mL)
Indication: Attention Deficit Hyperactivity Disorder (ADHD)
Applicant: Neos Therapeutics Inc
Review Division: Division of Psychiatry Products
Reviewer: Deepa B. Rao DVM, PhD
Supervisor/Team Leader: Ikram Elayan, PhD
Division Director: Mitchell V. Mathis MD
Project Manager: Brendan Muoio, Pharm D

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204325 are owned by Neos Therapeutics Inc or are data for which Neos Therapeutics Inc has obtained a written right of reference. Any information or data necessary for approval of NDA 204325 that Neos Therapeutics Inc does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug’s approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 204325.
# TABLE OF CONTENTS

1 EXECUTIVE SUMMARY .............................................................................................................................. 5  
1.1 INTRODUCTION ........................................................................................................................................ 5  
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS ........................................................................... 5  
1.3 RECOMMENDATIONS .............................................................................................................................. 6  
8 USE IN SPECIFIC POPULATIONS .................................................................................................................... 6  
8.1 PREGNANCY ........................................................................................................................................... 6  
8.2 LACTATION ............................................................................................................................................ 8  
8.3 FEMALES AND MALES OF REPRODUCTIVE POTENTIAL ................................................................. 8  
8.4 PEDIATRIC USE .................................................................................................................................... 8  
8.5 GERIATRIC USE .................................................................................................................................. 9  
12 CLINICAL PHARMACOLOGY ........................................................................................................................... 9  
12.1 MECHANISM OF ACTION .................................................................................................................... 9  
12.2 PHARMACODYNAMICS ......................................................................................................................... 9  
13 NONCLINICAL TOXICOLOGY ......................................................................................................................... 9  
13.1 CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY ................................................. 9  
13.2 ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY ......................................................................... 10  
2 DRUG INFORMATION ...................................................................................................................................... 10  
2.1 DRUG ....................................................................................................................................................... 10  
2.2 RELEVANT INDS, NDAS, AND DMFS ................................................................................................. 12  
2.3 DRUG FORMULATION ............................................................................................................................ 12  
2.4 COMMENTS ON NOVEL EXCIPIENTS ............................................................................................... 13  
2.5 COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN .......................................................... 14  
2.6 PROPOSED CLINICAL POPULATION AND DOSING REGIMEN ..................................................... 15  
2.7 REGULATORY BACKGROUND ............................................................................................................... 15  
3 STUDIES SUBMITTED .................................................................................................................................. 15  
3.3 PREVIOUS REVIEWS REFERENCED .................................................................................................... 15  
4 PHARMACOLOGY ......................................................................................................................................... 15  
4.1 PRIMARY PHARMACOLOGY .................................................................................................................. 15  
11 INTEGRATED SUMMARY AND SAFETY EVALUATION ........................................................................... 15  
12 REFERENCES ............................................................................................................................................... 17
Table of Tables

Tables 1 and 2: Composition of Drug Formulation for Amphetamine XR-OS (excerpted from the applicant’s submission) .......................................................................................................................... 12
Table 2: Continued - Composition of Drug Formulation for Amphetamine XR-OS (excerpted from the applicants submission) ........................................................................................................... 13
Table 3: List of Excipients ................................................................................................................................. 14
Abbreviations

ADHD   Attention Deficit Hyperactivity Disorder  
AERS   Adverse Event Reporting System  
CNS   Central Nervous System  
IID   Inactive Ingredient Database  
MAS   Mixed Amphetamine Salts  
MRHD   Maximum Recommended Human Dose  
RLD   Reference Listed Drug
1 Executive Summary

1.1 Introduction

NDA 204325 is a 505(b)(2) application filed by Neos Therapeutics Inc., towards seeking approval for their new extended release oral formulation of amphetamine as Amphetamine XR-OS (under the tradename Adzenys ER). The new formulation is an oral suspension containing 18.8 mg of amphetamine (base) in 15 mL. The proposed indication is for treatment in patients ≥ 6 years old diagnosed with Attention Deficit Hyperactivity Disorder (ADHD). This Amphetamine XR-OS drug product is similar to another drug product, namely, Adzenys™ XR-ODT (orally disintegrating tablet) that was also developed by Neos Therapeutics and approved by the FDA in January 27, 2016.

Data in support of the current application is limited to published literature and clinical bioequivalence studies. Adderall® XR 30 mg (NDA 021303 owned by Shire Development Inc.) is the identified reference listed drug (RLD) product.

From a nonclinical perspective, Adzenys ER appears to be reasonably safe for approval.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies have been submitted with this application.

Safety information for nonclinical studies is based on findings from published literature, information owned by the applicant under Adzenys™ XR-ODT (NDA 204326), and the RLD (Adderall® XR 30 mg under NDA 21303).

There are no safety concerns with the active ingredient.

There are no new novel excipients. All listed excipients are lower than that used in other FDA-approved products and/or lower than the maximum potency per unit dose for the same oral route of administration as listed in FDA’s IID (as updated on July 5, 2017 per reviewer evaluation). See Table 3 below (see Quality review for more details).

It should be noted that toxicity (intestinal necrosis) has been reported in published literature with the concomitant use of two excipients present in the sponsor’s drug product, namely, sorbitol and sodium polystyrene sulfonate (see Section 2.4). At the FDA, a similar issue has been previously evaluated by the Division of Cardiovascular and Renal Products. We defer to our clinical team for risk mitigation and evaluation.

The proposed label from the applicant was reviewed and modified to include summary statements and nonclinical findings from reproductive and juvenile animal toxicology studies for the active ingredient – amphetamine. The inclusion of this data was based on studies reviewed under Adderall XR 30 mg (RLD), and/or Adzenys XR-ODT (owned by the applicant).
Other labeling changes in the nonclinical sections (Sections 8 and 13) include modifications to the safety margins. Safety margins were calculated by comparing the base form of amphetamine in the toxicology studies or published literature to the proposed dose of Amphetamine XR-OS (base form) in the most sensitive and appropriate population age group of patients. All proposed nonclinical changes to the version dated July 31, 2017 in Sharepoint were accepted by the applicant.

From a nonclinical perspective, Adzenys ER appears to be reasonably safe for approval.

1.3 Recommendations

1.3.1 Approvability

Given the long history of clinical use of the active ingredient, safety information available from the RLD, Adderall® XR 30 mg, lack of novel excipients, and the use of excipients in reasonable amounts (compared to FDA’s IID and/or use in other FDA approved drug products), Adzenys-XR appears to be reasonably safe for approval from a nonclinical perspective.

1.3.3 Labeling

Sections 8, 12.1, 12.2, and 13 have been excerpted from the applicant’s submission (word file titled “Draft Labeling Text – Word” dated 02/2017 under Module 1.14.1.3). Proposed changes are underlined and italicized in blue below. It should be noted that the following label changes documented in this review are work-in-progress. The proposed changes shown below are to the most updated version of the label (version in Sharepoint titled “NDA 204325 draft-labeling-text-redline SUBMITTED 7.31.2017”), and may not reflect the finalized label (pending at this time) accurately.

**************Start of Label Excerpt ************

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AMPHETAMINE XR-OS during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388.

Risk Summary

The limited available from published literature and postmarketing reports on the use of prescription amphetamine in pregnant women are insufficient to inform a drug-associated risk of major congenital malformations or miscarriage. Adverse
pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines (see Clinical Considerations).

No effects on morphological development were observed in embryo-fetal development studies with oral administration of amphetamine to rats and rabbits during organogenesis at doses and times, respectively, the maximum recommended human dose (MRHD) of 12.5 mg/day (as base) given to adolescents, on a mg/m² basis. However, in a pre- and post-natal development study, amphetamine (d- to l-ratio of 3:1) administered orally to pregnant rats during gestation and lactation caused a decrease in pup survival and a decrease in pup body weight that correlated with a delay in developmental landmarks at clinically relevant doses of amphetamine. In addition, adverse effects on reproductive performance were observed in pups whose mothers were treated with amphetamine Long-term neurochemical and behavioral effects have been reported in published animal developmental studies using clinically relevant doses of amphetamine [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Amphetamines, such as AMPHETAMINE XR-OS, cause vasoconstriction and thereby may decrease placental perfusion. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. Infants born to amphetamine dependent mothers have an increased risk of premature delivery and low birth weight.

Monitor infants born to mothers taking amphetamines for symptoms of withdrawal, such as feeding difficulties, irritability, agitation, and excessive drowsiness.

Data

Animal Data

Amphetamine (d- to l-enantiomer ratio of 3:1) had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 4 and 20 times, respectively, the MRHD of 12.5 mg/day (as base), given to adolescents, on a mg/m² basis. Infants born to amphetamine dependent mothers have an increased risk of premature delivery and low birth weight. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 15 times the MRHD) given to adolescents on a mg/m² basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.
A study was conducted in which pregnant rats received daily oral doses of amphetamine (d- to l-enantiomer ratio of 3:1) of 2, 6, and 10 mg/kg from gestation day 6 to lactation day 20. These doses are approximately 1, 4, and 6 times the MRHD of 12.5 mg/day (as base) given to adolescents, on a mg/m² basis. All doses caused hyperactivity and decreased weight gain in the dams. A decrease in pup survival was seen at all doses. A decrease in pup body weight was seen at 6 and 10 mg/kg which correlated with delays in developmental landmarks, such as preputial separation and vaginal opening. Increased pup locomotor activity was seen at 10 mg/kg on day 22 postpartum but not at 5 weeks postweaning. When pups were tested for reproductive performance at maturation, gestational weight gain, number of implantations, and number of delivered pups were decreased in the group whose mothers had been given 10 mg/kg.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d, l-), at doses similar to those used clinically, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

8.2 Lactation

Risk Summary

Based on limited case reports in published literature, amphetamine (d- or d, l-) is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant. Long term neurodevelopmental effects on infants from stimulant exposure are unknown. It is possible that large dosages of amphetamine might interfere with milk production, especially in women whose lactation is not well established. Because of the potential for serious adverse reactions in nursing infants, advise patients that breastfeeding is not recommended during treatment with AMPHETAMINE XR-OS.

8.4 Pediatric Use

Safety and effectiveness have been established in pediatric patients with ADHD ages 6 to 17 years of age in three adequate and well-controlled clinical trials of up to 4 weeks in duration [see Adverse Reactions (6.1), Clinical Pharmacology (12), Clinical Studies (14)]. Safety and efficacy in pediatric patients younger than 6 years of age with ADHD have not been established.
Long-Term Growth Suppression

Growth should be monitored during treatment with stimulants, including AMPHETAMINE XR-OS, and children who are not growing or gaining weight as expected may need to have their treatment interrupted [see Warnings and Precautions (5.5)].

Juvenile Animal Toxicity Data

Juvenile rats treated with mixed amphetamine salts early in the postnatal period through sexual maturation demonstrated transient changes in motor activity. Learning and memory was impaired at approximately 10 times the maximum recommended human dose (MRHD) given to children on a mg/m² basis. No recovery was seen following a drug free period. A delay in sexual maturation was observed at a dose approximately 10 times the MRHD given to pediatric patients on a mg/m² basis, although there was no effect on fertility.

In a juvenile developmental study, rats received daily oral doses of amphetamine (d to l enantiomer ratio of 3:1) of 2, 6, or 20 mg/kg on days 7-13 of age; from day 14 to approximately day 60 of age these doses were given for total daily doses of 4, 12, or 40 mg/kg. The latter doses are approximately 1, 3, and 10 times the MRHD of 18.8 mg/day (as base) given to children on a mg/m² basis. Post-dosing hyperactivity was seen at all doses; motor activity measured prior to the daily dose was decreased during the dosing period but the decreased motor activity was largely absent after an 18 day drug-free recovery period. Performance in the Morris water maze test for learning and memory was impaired at the 40 mg/kg dose, and sporadically at the lower doses, when measured prior to the daily dose during the treatment period; no recovery was seen after a 19 day drug-free period. A delay in the developmental milestones of vaginal opening and preputial separation was seen at 40 mg/kg but there was no effect on fertility.

8.5 Geriatric Use

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
No evidence of carcinogenicity was found in studies in which \(d,l\)-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 3, 2, and (equivalent) times, respectively, the maximum recommended human dose of 18.8 mg/day (as base) given to children, on a mg/m\(^2\) basis.

Mutagenesis
Amphetamine, in the enantiomer ratio (d- to l- ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test \textit{in vivo} and was negative when tested in the E. coli component of the Ames test \textit{in vitro}. \(d,l\)-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the \textit{in vitro} sister chromatid exchange and chromosomal aberration assays.

Impairment of Fertility
Amphetamine, in the enantiomer ratio (d- to l- ratio of 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day [approximately 12.4 times the maximum recommended human dose of 12.5 mg/day (as base) given to adolescents on a mg/m\(^2\) basis].

13.2 Animal Toxicology and/or Pharmacology
Acute administration of high doses of amphetamine (\(d\)- or \(d,l\)-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown.

************************************************************************End of Label Excerpt*************************************************************************

2 Drug Information

2.1 Drug
The applicant’s states that their Amphetamine XR-OS formulation contains amphetamine with a 3:1 enantiomeric mixture of \(d\)-amphetamine and \(l\)-amphetamine.

CAS Registry Number:

Generic Names:
Chemical Name:

Code Names:
Amphetamine XR-OS

Molecular Formula/Molecular Weight:

Reviewer Note:

Pharmacologic Class
Central Nervous System (CNS) Stimulant
2.2 Relevant INDs, NDAs, and DMFs

IND 110281
Product Name: (b)(4) Amphetamine (b)(4)
Applicant: Neos Therapeutics Inc.
Indication: ADHD
Status: Active since September 1, 2011

NDA 21303
Product Name: Adderall® XR
Applicant: Shire Development Inc
Indication: ADHD
Status: Approved on October 11, 2001

NDA 204326
Product Name: Adzenys™ XR-ODT
Applicant: Neos Therapeutics Inc.
Indication: ADHD
Status: Approved on January 27, 2016

2.3 Drug Formulation

The applicant states that Amphetamine XR-OS (18.8 mg of amphetamine base per 15 mL of suspension or 1.25 mg of amphetamine base per mL of suspension), was formulated (b)(4)

Tables 1 and 2: Composition of Drug Formulation for Amphetamine XR-OS (excerpted from the applicant’s submission)
2.4 Comments on Novel Excipients

There are no new novel excipients.

All listed excipients are lower than that used in other FDA-approved products and/or lower than the maximum potency per unit dose for the same oral route of administration as listed in FDA's IID (as updated on July 5, 2017 per reviewer evaluation). See Table 3 below (see Quality review for more details).

Published literature and cases from the Adverse Event Reporting System (AERS) include toxicity (intestinal necrosis) reports with the concomitant use of sorbitol and sodium polystyrene sulfonate. Reports include clinical cases (McGowan et al, 2009; Thomas et al, 2009; Lillemoe et al, 1987), as well as in studies in rats from published literature (Ayoub et al, 2015; Romolo and Williams 1979). At the FDA, the safety issue has been reviewed for other NDAs and ANDAs by an Interdisciplinary Review Team in the Division of Cardiovascular and Renal Products (see TSI # 518 dated July 25, 2010). It appears that our understanding of the factors impacting toxicity based on the available data is limited and unclear, and the decision is a case by case basis. We defer to our clinical team for risk mitigation and evaluation on the concomitant use of sorbitol and sodium polystyrene sulfonate in this sponsor’s drug product. Recommendations include reformulation with water, contraindicating use in patients with or at risk for
constipation/fecal impaction and in susceptible populations (bowel disease, elderly, pediatric etc), discontinuation of therapy in patients who develop constipation, include language in label to address this risk.

Table 3: List of Excipients

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Function</th>
<th>Maximum Level of Excipient in Maximum Daily Dose of Finished Product (mg)</th>
<th>Maximum Level per IID (mg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polystyrene Sulfonate, USP</td>
<td>(0)(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyethylene Glycol</td>
<td>(0)(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methacrylic Acid and Methyl Methacrylate Copolymer, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triethyl Citrate, NF</td>
<td>(0)(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citric Acid, USP</td>
<td>(0)(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propylene Glycol, USP</td>
<td>(0)(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylparaben, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propylparaben, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xanthan Gum, FCC</td>
<td>(0)(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetable Oil, FCC</td>
<td>(0)(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorbitol</td>
<td>(0)(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orange</td>
<td>(0)(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural Orange</td>
<td>(0)(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucrose, NF</td>
<td>(0)(4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*IID Database Updated January 10, 2017

**Reviewer Note (For Internal Use Only):**

2.5 Comments on Impurities/Degradants of Concern

No nonclinical studies on impurities were conducted, and no specific impurities were identified to be of concern from the Quality evaluation.

For a complete review, refer to the Quality review for this NDA.
2.6 Proposed Clinical Population and Dosing Regimen
Patients diagnosed with ADHD aged ≥ 6 years.

2.7 Regulatory Background
This Amphetamine XR-OS drug product (oral suspension) under NDA 204325 is similar to another drug product, namely, Adzenys™ XR-ODT (orally disintegrating tablet) that was developed by Neos Therapeutics and approved by the FDA in January 27, 2016.

IND 110281 is the original application by Neos Therapeutics Inc., for an oral suspension formulation of Amphetamine.

Data in support of the current application includes:
1) Literature reviews conducted for Adzenys™ XR-ODT (under NDA 204326 also owned by Neos Therapeutics Inc.) covering the period between September 2001 and April 2012.
2) Additional literature reviews covering the period between April 2012 and March 2017 conducted under the current application (NDA 204325).
3) Clinical bioequivalence studies conducted under the current application (NDA 204325).
4) Adderall® XR 30 mg (NDA 021303 owned by Shire Development Inc.) is the identified RLD product.

3 Studies Submitted
No nonclinical studies have been submitted.

3.3 Previous Reviews Referenced
Pre-NDA Meeting Minutes from IND 110281 (dated July 2, 2014).

4 Pharmacology

4.1 Primary Pharmacology
Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The exact mode of therapeutic action in ADHD is not known.

11 Integrated Summary and Safety Evaluation
Given the initial studies conducted under IND 110281 for an oral suspension formulation of amphetamine, and currently marketed oral tablets under Adzenys™ XR (NDA 204326 approved on January 27, 2016), Neos Therapeutics Inc., is now seeking
approval for an oral suspension formulation of Amphetamine XR-OS (under the
tradename Adzenys ER).

Amphetamine XR-OS contains amphetamine sulfate and dextroamphetamine sulfate
with a 3:1 enantiomeric mixture of \textit{d}-amphetamine and \textit{l}-amphetamine, which is similar
to the RLD product Adderall® XR 30 mg (NDA 21303).

No nonclinical studies were submitted.

Data in support of the current application includes:
1) Literature reviews conducted for AdzenysTM XR-ODT (under NDA 204326 also
owned by Neos Therapeutics Inc.).
2) Additional literature reviews to cover the period between April 2012 and March
2017 conducted under the current application (NDA 204325).
3) Clinical bioequivalence studies conducted under the current application (NDA
204325).
4) Adderall® XR 30 mg (NDA 021303 owned by Shire Development Inc.) is the
identified RLD product.

Nonclinical review confirms that the active ingredient and ratio of enantiomers (d:l is 3:1
in base form) in Amphetamine XR-OS is the same as in Adderall® XR, the RLD for the
current application.

There are no new novel excipients. All listed excipients are lower than that used in other
FDA-approved products and/or lower than the maximum potency per unit dose for the
same oral route of administration as listed in FDA’s IID (as updated on July 5, 2017 per
reviewer evaluation). See Table 3 above (see Quality review for more details).

It should be noted that toxicity (intestinal necrosis) has been reported in published
literature with the concomitant use of two excipients present in the sponsor’s drug
product, namely, sorbitol and sodium polystyrene sulfonate. Published literature
includes clinical cases (McGowan et al, 2009; Thomas et al, 2009; Lillemoe et al, 1987),
as well as in studies in rats from published literature (Ayoub et al, 2015; Romolo and
Williams 1979). Cases from the Adverse Event Reporting System (AERS) include
multiple reports from NDA and/or ANDAs. The safety issue has been reviewed by an
Interdisciplinary Review Team in the Division of Cardiovascular and Renal Products
(see TSI # 518 dated July 25, 2010). It appears that our understanding of the factors
impacting toxicity based on the available data is limited and unclear, and the decision is
a case by case basis. We defer to our clinical team for risk mitigation and evaluation on
the concomitant use of sorbitol and sodium polystyrene sulfonate in this sponsor’s drug
product. Recommendations include reformulation with water, contraindicating use in
patients with or at risk for constipation/fecal impaction and in susceptible populations
(bowel disease, elderly, pediatric etc), discontinuation of therapy in patients who
develop constipation, include language in label to address this risk.

No nonclinical studies on impurities were conducted, and no specific impurities were
identified to be of concern from the Quality evaluation.
Given the long history of clinical use of the active ingredient, safety information available from the RLD Adderall® XR 30 mg, lack of novel excipients, and the use of excipients in reasonable amounts (compared to FDA’s IID and/or use in other FDA approved drug products), Adzenys ER appears to be reasonably safe for approval from a nonclinical perspective.

12 References

Ayoub I, Oh MS, Gupta R, McFarlane M, Babinska A, Salifu MO. Colon necrosis due to sodium polystyrene sulfonate with and without sorbitol: an experimental study in rats. PLOS One, September 28, 2015. DOI:10.1371/journal.pone.0137636


This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEEPA B RAO
08/10/2017

IKRAM M ELAYAN
08/10/2017