CENTER FOR DRUG EVALUATION AND RESEARCH

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OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Memorandum

Date: October 14, 2015 **Date consulted:** February 23, 2015

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To: Division of Psychiatry Products (DPP)

Drug: Dyanavel XR (amphetamine extended-release) Oral Suspension

NDA: 208147

Applicant: Tris Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

Materials Reviewed:

- DPMH consult request dated September 3, 2015, DARRTS Reference ID 3815377.
- Sponsor's submitted background package for NDA 208147, Dyanavel XR.
- DPMH consult review of Vyvanse (lisdexamfetamine dimesylate) capsules, NDA 21977. Jeanine Best, MSN, RN, PNP and Carrie Ceresa, Pharm D, MP. November 1, 2011. DARRTS Reference ID 3037737.
- DPMH consult review of Aptensio XR-NDA 205831. Miriam Dinatale, D.O. March 16, 2015, DARRTS Reference ID 3715876.

Consult Question:

DPP requests DPMH to "review what the sponsor submitted regarding PLLR and let us know if it is acceptable."

INTRODUCTION

The Division of Psychiatry Products (DPP) consulted the Division of Pediatric and Maternal Health (DPMH) on September 3, 2015, to provide input for appropriate labeling of the pregnancy and lactation subsections of Dyanavel XR (amphetamine extended-release) Oral Suspension labeling to comply with Pregnancy and Lactation Labeling Rule format.

REGULATORY HISTORY

Dyanavel XR (amphetamine) is a central nervous system (CNS) stimulant. On December 18, 2014, Tris Pharmaceuticals, Inc., submitted a 505 (b)(2) New Drug Application (NDA 208147) for Dyanavel XR (amphetamine) Extended-Release Oral Suspension to obtain approval to market Dyanavel XR for the proposed indication of the treatment of Attention-Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older. The current NDA relies on safety and efficacy information previously reviewed and approved by the Agency for the reference listed drug (RLD) Adderall (amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate, dextroamphetamine sulfate) tablets, NDA 011522. However, since the RLD is currently discontinued, the applicant relied on a product available as a generic, Dextroamphetamine saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate and Amphetamine Sulfate Tablets as a reference product.

BACKGROUND

ADHD and Pregnancy

ADHD affects 4.4% of adults in the United States and is associated with an elevated risk of poorer general and mental health, substance abuse, and impaired work performance. There have been no studies evaluating the course of ADHD in pregnancy and the postpartum period. While many women with ADHD can stop their medications during pregnancy without adverse effects, for other women, functional impairment may be severe. Some women with ADHD may be at an increased risk of motor vehicle accidents and have severe impairments in occupational, school and work functioning.[1]

It is estimated that 30% of patients continue ADHD medications into adulthood. In an ongoing case-control surveillance study, Slone Epidemiology Center's Birth Defects Study (BDS), the prevalence of ADHD medication use was analyzed. In this study, 29,540 women were interviewed between 1998 and 2014, and there were 87 reported exposures to an ADHD medication. Although the overall prevalence of use of any ADHD medication was 0.3%, there was a marked increase in the prevalence of use over the period of the study, from 0.2% for women with last menstrual period (LMP) dates in 1997-1998 to 1.3% for women with LMP dates in 2013. The most commonly reported ADHD medication was amphetamine mixed salts (57.5%), followed by methylphenidate (29.9%). Of the 87 women who were exposed to an ADHD medication, all but one used it during the first trimester; 18 continued use into the second trimester, and 11 continued use into the third trimester. In a recent letter to the editor, Louik *et*

[1] Freeman, MP. ADHD and pregnancy. Am J Psychiatry. 2014; 171 (7): 723-8.

al., noted that although the use of ADHD medications in pregnancy is increasing, there is lack of information regarding potential fetal risks in humans.[2]

Amphetamine and Drug Characteristics

Amphetamines are non-catecholamine sympathomimetic amines with central nervous system stimulant activity and are indicated for the treatment of ADHD and narcolepsy in adults and children. The mechanism of action in ADHD is unknown. Amphetamines are thought to block the reuptake of norepinephrine and dopamine by presynaptic neurons and increase the release of dopamine and norepinephrine into the extraneuronal space.

Dyanavel (amphetamine) XR is a 3.2 to1 ratio of *d*- to *l*-amphetamine in an extended-release oral suspension. Amphetamine has a molecular weight of 135.2 Daltons, a pH of 9.9 and a half-life of 10.43 hours for dextroamphetamine (*d*-amphetamine) and 12.14 hours for levoamphetamine (*l*-amphetamine).[3]

Common adverse events seen in children and adults who take amphetamine, regardless of immediate-release or extended-release formulations, include: dry mouth, anorexia, weight loss, abdominal pain, nausea, insomnia, restlessness, emotional lability, dizziness and tachycardia.

Pregnancy and Nursing Mothers Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[4] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[5] format to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION

Nonclinical Experience

The applicant did not perform additional nonclinical studies for Dyanavel (amphetamine) XR and relied on data for Adderall (NDA 011522) to develop labeling for Dyanavel XR. Overall, there were no effects on embryofetal morphological development that were observed in animal reproductive studies with oral administration of amphetamine to rats and rabbits during organogenesis at doses 1.5 and 10 times, respectively, the maximum recommended human dose. However, published prenatal and early postnatal animal studies have reported long-term neurochemical and behavioral effects (learning and memory deficits, altered locomotor activity,

[2] Louik et al. Increasing use of ADHD medications in pregnancy. Pharmacoepidemiology and Drug Safety. 2015; 24: 218-220.
[3] Applicant proposed Dyanavel XR (amphetamine) labeling. Section 12 Clinical Pharmacology.
[4] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[5] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

changes in sexual function) when rodents were given amphetamine doses similar to those used clinically (specific doses not specified). The reader is referred to the full Pharmacology/Toxicology review by Ikram Elayan, Ph.D. for further details.

Amphetamine and Pregnancy

The National Toxicology Program (NTP) established the Center for the Evaluation of Risks to Human Reproduction (CERHR)[6] in 1998. The NTP-CERHR conducted an evaluation of amphetamines and pregnancy by searching PubMed and Toxline databases (using the search terms *d*- and *l*-amphetamine and *d*-methamphetamine and pregnancy) for all studies done prior to December 31, 2004, and published the NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Amphetamines in July 2005. The applicant considered the NTP-Monograph to be complete and focused their literature review on studies that were completed between January 1, 2005 and July 31, 2015. DPMH also performed a search of the Drugs and Lactation Database (LactMed)[7] and Pubmed, and no additional published literature on amphetamine use in pregnancy has been reported since December 31, 2004.

National Toxicology Program Center for Evaluation of Risks to Human Reproduction (2005)[8]

A 13-member expert panel reviewed literature published before December 31, 2004 regarding the use of amphetamines and methamphetamines during pregnancy. The expert panel made the following conclusions about amphetamine:

- Human data are insufficient for an evaluation of the developmental toxicity of amphetamine following prenatal exposure.
- There are sufficient data to conclude that intraperitoneal injection of amphetamine in pregnant mice at doses of 50 mg/kg body weight/day given between gestational days 9 and 11 increases the incidence of malformations (microphthalmia, amelia, excencephaly, cleft lip) in the offspring.
- Several rat and mouse studies reported effects on fetal or neonatal viability, but the evidence is not sufficient to permit conclusions due to limitations of the studies.
- Based on the experimental animal data, the expert panel was concerned that neurobehavioral alterations due to prenatal amphetamine exposure could be seen in humans in both therapeutic and non-therapeutic settings.

The expert panel made the following conclusions about methamphetamine:

- There is no interpretable human data on methamphetamine use during pregnancy and developmental toxicity.

[6] CERHR is a publicly accessible resource for information about adverse reproductive and/or developmental effects associated with exposure to a drug or chemical. The CERHR convenes a scientific expert panel that meets in a public forum to review and discuss scientific literature on a particular drug or chemical and provides an opinion of the degree to which exposure to a chemical/drug is hazardous to humans.

[7] http://toxnet.nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[8] NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Amphetamines, March 2005

- There is sufficient data from experimental animal studies to conclude that methamphetamine induces reduced pup weights, reduced litter sizes, and neurobehavioral alterations (abnormal neurobehavioral test results) in rats exposed to methamphetamine *in utero*.
- Based on the animal data, the expert panel had concerns about potential adverse perinatal outcomes and neurobehavioral alterations due to prenatal methamphetamine exposure in humans in both therapeutic and non-therapeutic settings.

Overall, the expert panel concluded that the available data are limited due to inadequate study design, outdated methods and insufficient numbers of patients treated only with amphetamines. There were no additional studies found by the applicant or DPMH in their search of published literature. See Appendix B, C, and D for the NTP expert panel review of strengths and weaknesses of the studies reviewed.

Discussion

DPMH reviewed the NTP-CERHR Expert Panel Report on Reproductive and Developmental Toxicity of Amphetamines. The NTP expert panel noted that published literature regarding amphetamine exposure during pregnancy and the risk of congenital abnormalities and infant withdrawal symptoms is inconsistent.[9,10,11,12,13] In addition, the NTP expert panel noted that many of the studies they reviewed involve confounding factors (illicit use of amphetamines and concurrent use of other illicit drugs, alcohol, and tobacco) and that long term neurodevelopment effects of amphetamine exposure during pregnancy are unknown. The NTP expert panel's review of the published literature shows that there are insufficient data to make a clear statement about the safety of amphetamine. Besides what the NTP expert panel had reviewed, there is no new information in published literature to update the Pregnancy section of amphetamine labeling.

Published literature about amphetamine abuse during pregnancy notes that amphetamine can cause prematurity and low birth weight.[14,15,16,17,18] Overall, the mechanism by which amphetamine crosses the placenta and affects the developing fetus is complex, and there are

[9] Nora, et al. Dexamphetamine: a possible environmental trigger in cardiovascular malformations. Lancet 1970; 1: 1290-1

[10] Milkovich L and Van den Berg BJ: Effects of antenatal exposure to anorectic drugs. Am J Obstet Gynecol 129:637-42, 1977.

[11] Heinonen, OP.; Slone, D.; Shapiro, S. Birth defects and drugs in pregnancy. Littleton, Mass: Publishing Sciences Group; 1977.

[12] Levin JN: Amphetamine ingestion with biliary atresia. J Pediatr 1971; 79:130

[13] Felix RJ, Chambers CD, Dick LM, Johnson KA, Jones KL. Prospective pregnancy outcome in women exposed to amphetamines. Teratology 2000;61: 441. Abstract

[14] Eriksson, M., Larsson, G., Winbladh, B. and Zetterström, R. The Influence of Amphetamine Addiction on Pregnancy and the Newborn Infant. Acta Paediatr Scand 1978; 67: 95-99.

[15] Larsson, G., Eriksson, M. and Zetterström, R. Amphetamine addiction and pregnancy. Psychosocial and medical aspects. Acta Psychiatr Scand 1979; 60: 334-46.

[16] Eriksson, M., Larsson, G. and Zetterström, R. Amphetamine addiction and pregnancy. II. Pregnancy, delivery and the neonatal period. Socio-medical aspects. Acta Obstet Gynecol Scand 1981; 60: 253-9.

[17] Furara, et al. The outcome of pregnancy associated with amphetamine use. Journal Obstet Gynaecol. 1999. 19(4): 377-80.

[18] Little BB et al: Methamphetamine abuse during pregnancy: outcome and fetal effects. Obstet Gynecol 72 (4):541-4, 1988.

theories that explain the actions of amphetamine at the placenta and effects on the fetus. Serotonin and norepinephrine receptors are located in the placenta and remove norepinephrine and serotonin from the intervillous space (maternal blood). Amphetamine is competitive inhibitor of serotonin and norepinephrine receptors and prevents the transport of serotonin and norepinephrine (both are vasoconstrictors) into the syncytiotrophoblast.[19] In turn, amphetamine enters the placental cells via the receptors and results in serotonin and norepinephrine accumulation in the intervillous space. Accumulation of norepinephrine and serotonin leads to increased sympathetic activity and results in the following:

- cardiac stimulation and hypertension in the mother
- vasoconstriction of blood vessels and decreased blood flow to the placenta increasing the risk for intrauterine growth restriction
- stimulation of uterine contractions increasing the risk of premature delivery.

In addition, since amphetamine is thought to cross the placenta, it is believed that once amphetamine reaches the developing fetus, amphetamine causes cardiac stimulation and vasoconstriction of blood vessels in the fetus, similar to what is seen in the mother, resulting in hypertension in the fetus and affecting fetal growth and development.[20,21,22,23] This information has been reviewed by DPMH in a prior review by Jeanine Best, MSN, RN, PNP and Carrie Ceresa , PharmD, MPH[24] and is also present in current amphetamine labeling, which states:

> Amphetamines, such as DYANAVEL XR, can cause vasoconstriction and thereby decrease placental perfusion. Premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers. Monitor infants born to mothers taking amphetamines for symptoms of withdrawal, such as feeding difficulties, irritability, agitation, and excessive drowsiness.

Based on the information discussed above, DPMH proposes the following changes to the "Clinical Considerations" section of labeling:

> Amphetamines, such as DYANAVEL XR, may cause vasoconstriction, including vasoconstriction of placental blood vessels, and may increase the risk for intrauterine growth restriction. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. Premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers. Monitor infants born to mothers taking amphetamines for symptoms of withdrawal, such as feeding difficulties, irritability, agitation, and excessive drowsiness.

[19] Syncytiotrophoblast: is the outer layer of the trophoblast that actively invades the uterine wall forming the outermost fetal component of the placenta.
[20] Ganapathy, Vadivel. Drugs of abuse and human placenta. Life Sciences. 2011; 88 (21-22): 926-930.
[21] Salisbury, et al. Fetal Effects of Psychoactive Drugs. Clinics in Perinatology. 2009. 36 (3): 595-619.
[22] Ross, et al. Developmental Consequences of Fetal Exposure to Drugs: What We Know and What We Still Must Learn. Neuropsychopharmacology Reviews. 2015; 40: 61-87.
[23] Ramamoorthy, et al. Human placental monoamine transporters as targets for amphetamines. American Journal of Obstet Gynecol. 1995; 173: 1782-7.
[24] DPMH consult review of Vyvanse (lisdexamfetamine dimesylate) capsules. Jeanine Best, MSN, RN, PNP and Carrie Ceresa, Pharm D, MP. November 1, 2011. DARRTS Reference ID 3037737.

Amphetamine and Lactation

The characteristics of amphetamine suggest that amphetamine is present in breast milk. Amphetamine has low protein-binding of 15-40% (medications with protein-binding less than 90% are more extensively excreted into breastmilk), a low molecular weight of 135.2 Daltons (drugs with molecular weights less than 800 Daltons are more readily transferred to the milk compartment), and a high pH of 9.9 (a higher pH means that more drug may be present in breast milk than in plasma). [25]

The NTP-CERHR conducted an evaluation of amphetamines and lactation and searched PubMed and Toxline databases for studies done prior to December 31, 2004, and presented a case study of a lactating mother being treated with amphetamine for narcolepsy (see description of case report below in Steiner, *et al*). The NTP-expert panel concluded that amphetamine does pass into breast milk in humans and would expose the infant to the drug. The applicant considered the NTP-Monograph to be complete and focused their literature review on studies that were completed between January 1, 2005 and July 31, 2015. DPMH also performed a search of the Drugs and Lactation Database (LactMed)[26] and Pubmed. A review of the available published literature is provided below.

LactMed (accessed 9/10/2015)

When amphetamines are given at clinical doses, there is no evidence that nursing infants have been adversely affected. However, the effect of amphetamines on the neurological development of breastfed infants has not been studied. LactMed discourages breastfeeding in mothers who are abusing amphetamines.[27]

The American Academy of Pediatrics Committee on Drugs (2013)

The American Academy of Pediatrics (AAP) Committee on Drugs 2013 reports that amphetamine exposure via illicit use in the breastfeeding infant has resulted in cases of infant hypertension, tachycardia and seizures. In animal studies of postnatal exposure, long-term behavioral effects (learning and memory deficits), as well as altered locomotor activity, have been observed. Because current published data are insufficient to determine the long-term effects on infants exposed to stimulants through breast milk, the AAP recommends that amphetamines not be used by breastfeeding women.[28]

[25] Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.

[26] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[27] Lactmed. Amphetamines. http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~RlRu5g:1. Accessed 9/9/2015

[28] American Academy of Pediatrics: Committee on Drugs. The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on Selected Topics. Pediatrics. 2013; 132 (3): e796-809.

Medications and Mother's Milk: A Manual of Lactational Pharmacology (2012)
In Hale's Medication and Mother's Milk, Dr. Thomas Hale, a breastfeeding expert, classifies breastfeeding as "probably safe" with clinical doses of dextroamphetamine taken by a breastfeeding woman but "hazardous" if dextroamphetamine was abused. [29]

Ohman, *et al*. (2015)
In a case report (Ohman, *et al*.), a woman with narcolepsy was taking racemic amphetamine 35mg daily during pregnancy and breastfeeding (exclusive breastfeeding for six months). Maternal and infant plasma and breast milk samples were taken at two, five and nine weeks postpartum, and breastmilk samples of amphetamine were 74 mcg/L, 82 mcg/L and 82mcg/L, respectively. The calculated relative infant dose (RID) was 2% of the maternal weight-adjusted dosage. The absolute infant dose was 11to 12.4 mcg/kg daily. Infant plasma concentrations at two, five and nine weeks were 3.1, 2 and 1.4 mcg/L, respectively. These values were 15%, 7% and 5% of the maternal plasma concentrations. The mother and infant were followed until the infant was ten months old; no adverse effects were seen in the breastfed infant and psychomotor development were normal up to 10 months of age. The authors concluded that further studies of amphetamine use in lactation are needed.[30]

Ilett, *et al*. (2007)
In a case series (Ilett, *et al*.), four lactating women (mean age 35, range 27-40 years old) were treated with a single dose of dexamphetamine 18mg/day (range 15-45 mg/day) for ADHD. The women had been on dexamphetamine for an average of 48 months before the studied commenced. The infants ranged from 3 to 10 months of age. There was no discussion of whether the infants were exclusively breastfed or if any infants received supplementation with formula. In two women, venous blood samples were taken just before the first morning dose of dexamphetamine and at 2, 4, 6, 7 or 8 and 24 hours post-dose. In the other two women, a single blood sample was taken 3-4 hours after the first dose. The mothers collected milk samples just before the morning dose and then after each time their infant fed during the next 24 hours (six-eight feeds) The estimated RID averaged 5.7% (range 3.9-13.8%) of the maternal weight-adjusted dosage and the milk/plasma ratio average 3.3 (range between 1.9 and 5.3). In three infants tested, dexamphetamine in plasma was undetected in one infant (limit of detection 1 microgram/L and present in the other two infants (18 microgram/L and 2 microgram/L). Infant health was evaluated by the mother and referring physician. In two of the cases, a full clinical exam, including the Denver development assessment, was performed by a neonatologist. There were no adverse effects seen in infants. The authors concluded that dexamphetamine readily transfers into breast milk. Since the relative infant doses were, on average, less than 10%, the authors concluded that dexamphetamine use would be considered "safe" for a short period of time; however, medium to long-term consequence of dexamphetamine exposure during lactation are unknown. The authors noted that although there were no adverse infant effects noted, the sample size was small, and study findings support using caution if dexamphetamine is used during lactation.[31]

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[29] Hale, Thomas. Medications and Mother's Milk: A Manual of Lactational Pharmacology, 15th edition. Hale Publishing, L.P. 2012
[30] Ohman, et al. Narcolepsy Treated with Racemic Amphetamine during Pregnancy and Breastfeeding. Journal of Human Lactation. 2015. 31; 374-376.
[31] Ilett, et al. Transfer of dexamphetamine into breastmilk during treatment for attention deficit hyperactivity disorder. British Journal of Clinical Pharmacology. 2007. 63 (3): 371-5.

Reviewer comments:
The studies reviewed identify a range of concentrations of amphetamine in breast milk between 3.9% and 13.8% of the maternal concentration. The lowest RID (3.9%) and the highest RID (13.8%) were seen in infants whose mothers were taking 15mg/day of dexamphetamine. There is no information about the age of the infant who had the highest RID (only the age range for all five infants was listed) or if the infant was solely breastfed or being supplemented with formula. Infants who are supplemented with formula may be exposed to less drug per kg of body weight compared to infants who are solely breastfed. There may be differences in breast milk lipid content that can contribute to differences in drug partitioning between serum and breast milk.[32]

Steiner, *et al*. (1984)
In another case report (Steiner, *et al*.), a 36 year-old lactating female with a ten year history of narcolepsy was treated with a daily dose of amphetamine 20mg throughout pregnancy and a normal male infant was born at 39 weeks and was breastfed. The maternal dose of amphetamine 20mg was divided four times daily (10 AM, 12PM, 2PM, 4PM). Maternal amphetamine plasma, urine and breastmilk samples from the mother and infant urine samples (12-hour urine collection) were obtained on post-partum days 10 and 42. The milk/plasma ratio ranged from 2.8 to 3 on day 10 and between 6.6 to 7.5 on day 42. The infant's health and development were monitored over a period of 24-months, and no adverse effects were seen. The authors concluded that amphetamines should not be used for long periods of time in breast feeding mothers due to concerns for possible effects of amphetamines on normal psycho-behavioral development.[33]

Reviewer comments:
In the case report reviewed above, the milk/plasma (M/P) ratio ranged from 2.8 to 7.5. In general, a M/P ratio <1 indicates that the drug appears in breast milk in concentrations less than in plasma, a M/P ratio of 1 indicates that the drug levels in breast milk are similar to those in plasma, and a M/P >1 indicates that the drug is concentrated in breast milk. The M/P ratio calculation has limitations. M/P concentrations are often static measurements in time; however, milk composition and pH frequently change, even over the course of the same breastfeeding session, which causes the M/P concentration to change. Also, the way in which the M/P ratio is derived may affect the results. Many times the peak milk concentration is compared to the peak plasma concentration; however, these two concentrations were not taken at the same time, and this may provide an inaccurate M/P ratio.[34] *In addition, the M/P ratio of 7.5 may reflect an outlier and may not be representative of the usual findings.*

Discussion
Overall, all of the published studies and sources discussed above (NTP-CERHR, AAP, LactMed, Dr. Hale) note that amphetamine is present in breastmilk and that a breastfeeding infant will be exposed to the drug. Although there have been no adverse events seen with clinical use of amphetamine, there have been serious adverse events (hypertension, tachycardia and seizures) seen in breastfeeding infants whose mothers abuse amphetamine. In addition, there is no information on the long-term neurodevelopmental effects on infants from stimulant exposure during breastfeeding. Given the lack data on long-term neurodevelopmental effects and the

[32] DPMH Review Vyvanse (lisdexamfetamine dimesylate). Leyla Sahin, MD. March 31, 2008.
[33] Steiner, et al. Amphetamine Secretion in Breast Milk. Eur J Clin Pharmacol. 1984; 27 (1): 123-124.
[34] Black, Rebecca. The Management of Breastfeeding, Volume 4. 1998. Jones & Bartlett Learning.

potential risks on a breastfed infant exposed to amphetamine, labeling for Dyanavel XR will remain consistent with labeling for other amphetamines and will recommend that the drug should not be used by a breastfeeding mother. DPP was in agreement with this approach.

DPMH notes that the lactation labeling language reflects adverse events observed with breastfed infants whose mothers abuse amphetamine; however, the same level of risk may not exist for breastfed infants of mothers who use the drug as prescribed. An alternate approach to the lactation labeling may instead advise for a risk/benefit discussion between the patient and the prescriber, with special mention of clinical considerations when the drug is abused. In the future, if more information becomes available about amphetamine use during lactation in the ADHD (or narcolepsy) population, the lactation labeling language may be re-visited to focus on adverse outcomes associated with amphetamine use as prescribed.

Amphetamine and Females and Males of Reproductive Potential
The NTP-CERHR conducted an evaluation of amphetamines and methamphetamines and their effects on reproduction and development in humans and searched PubMed and Toxline databases for studies done prior to December 31, 2004. The applicant focused their literature review on studies that were completed between January 1, 2005 and July 31, 2015. Neither the NTP-monograph, the applicant nor DPMH found any published studies on the reproductive effects of amphetamines or methamphetamines in humans.

In animal studies, amphetamine did not adversely affect fertility or early embryonic development in rats at doses up to 7.7 times the maximum recommended human dose of methylphenidate (20mg/day). The reader is referred to the full Pharmacology/Toxicology review by Ikram Elayan, Ph.D. for further details.

Overall, there are no controlled human studies that evaluate possible reproductive toxicity of amphetamine or methamphetamine, and animal data are insufficient for an evaluation of possible reproductive toxicity following exposure to amphetamine or methamphetamine.

CONCLUSIONS
Dyanavel XR (amphetamine) has been updated to comply with the PLLR. A review of published literature revealed no new data with amphetamine use in pregnant or lactating women. DPMH has the following recommendations for Dyanavel XR (amphetamine) labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of Dyanavel XR (amphetamine) labeling was formatted in the PLLR format to include the "Risk Summary," "Clinical Considerations," and "Data" subsections[35].
- **Lactation, Section 8.2**
  - The "Lactation" subsection of Dyanavel XR (amphetamine) labeling was formatted in the PLLR format to include the "Risk Summary" subsection[36].

[35] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

- **Patient Counseling Information, Section 17**
  - The "Patient Counseling Information" section of Dyanavel XR (amphetamine) labeling was updated to correspond with changes made to sections 8.1 and 8.2 of labeling.

RECOMMENDATIONS

DPMH revised sections 8.1, 8.2 and 17 of Dyanavel XR (amphetamine) labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling. (See Appendix A for the applicant's proposed pregnancy and lactation labeling.)

DPMH Proposed Dyanavel XR (amphetamine) PLLR labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause fetal harm (8.1).
- Lactation: (b) (4) (8.2).

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are limited published data on the use of amphetamines in pregnant women. These data are insufficient to determine 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. 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 1.5 and 8 times, respectively, the maximum recommended human dose (MRHD). However, long-term neurochemical and behavioral effects have been reported in published animal developmental studies using clinically relevant doses of amphetamine (*d*- or *d, l*-) *[see Data]*.

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 DYANAVEL XR, may cause vasoconstriction, including vasoconstriction of placental blood vessels, and may increase the risk for intrauterine growth restriction. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. Premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers. Monitor infants born to mothers taking amphetamines for symptoms of withdrawal, such as feeding difficulties, irritability, agitation, and excessive drowsiness.

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[36] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

Data

Animal Data

Amphetamine 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 1.5 and (b) (4) times, respectively, the maximum recommended human dose (MRHD) for adolescent of 20 mg/day, on a mg/m^2 body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately (b) (4) times the MRHD for adolescents on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

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 and no effects on milk production. However, long-term neurodevelopmental effects on infants from stimulant exposure are unknown. Because of the potential for serious adverse reactions in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with DYANAVEL XR.

17 Patient Counseling Information

Pregnancy

Advise patients to notify their healthcare providers if they become pregnant or intend to become pregnant during treatment with DYANAVEL XR. Advise patients of the potential fetal effects from the use of DYANAVEL XR during pregnancy *[(see Use in Specific Populations (8.1)]*.

Lactation

Patients should be advised not to breastfeed if they are taking DYANAVEL XR *[(see Use in Specific Populations (8.2)]*.

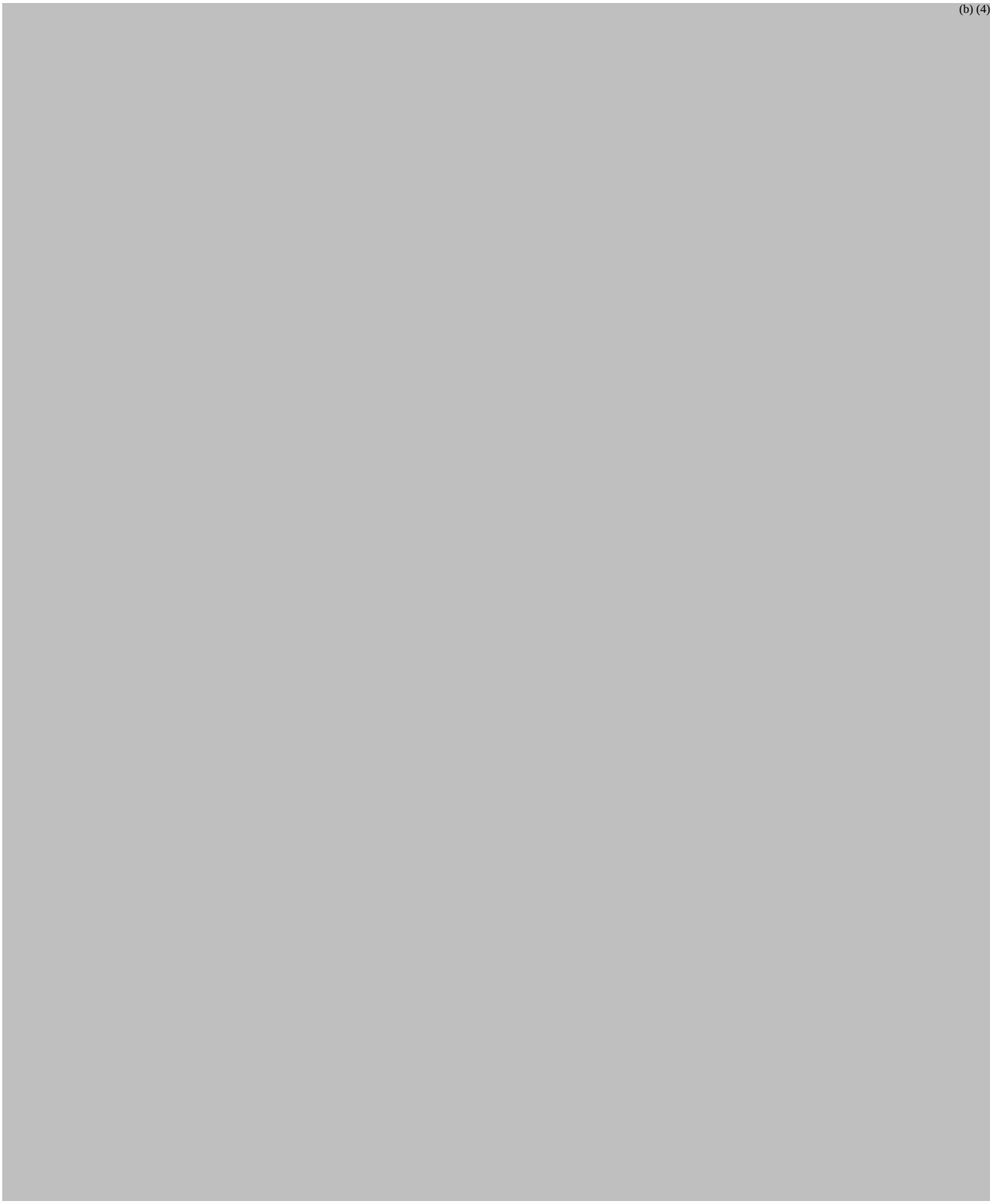
Medication Guide

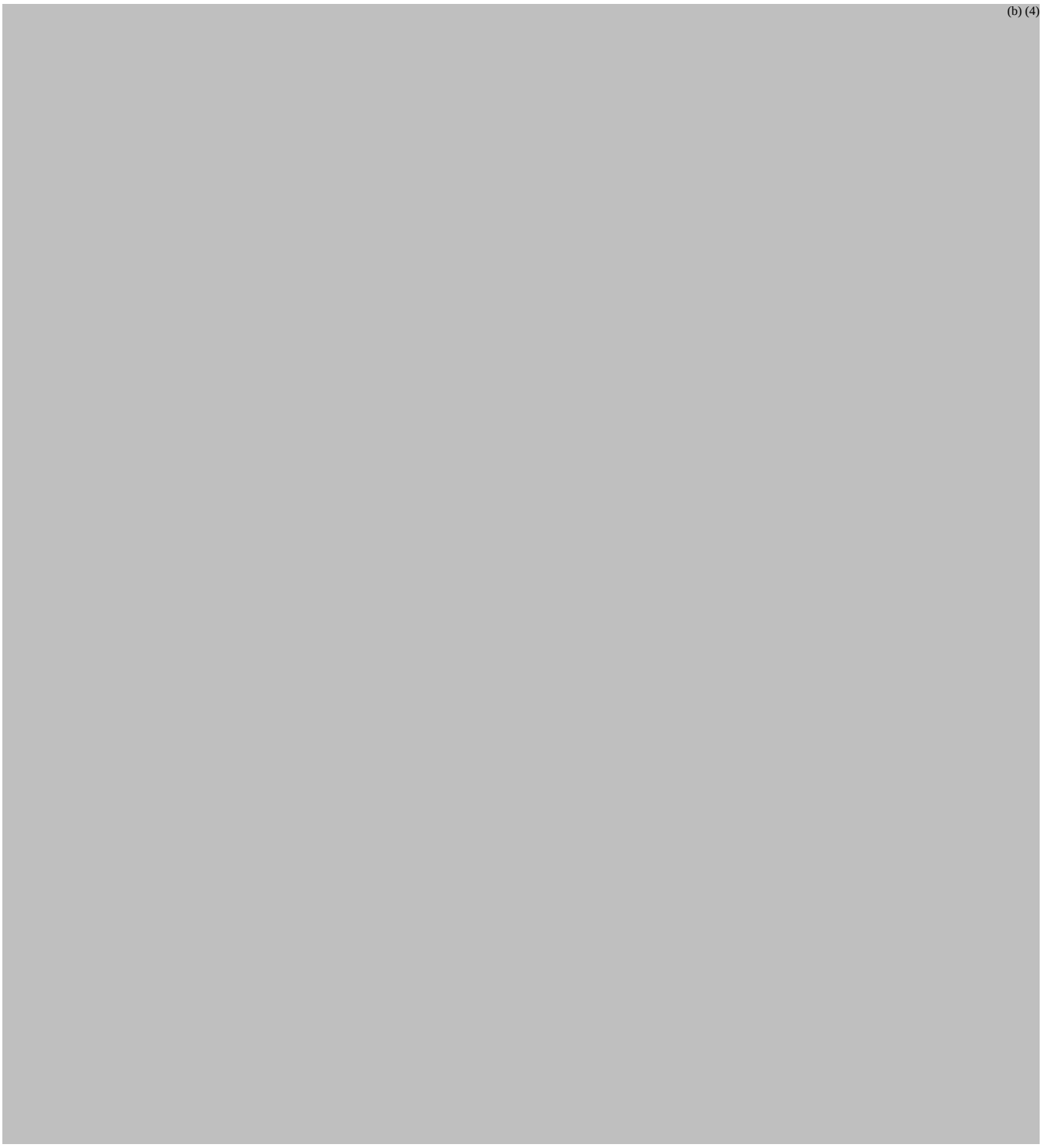
DYANAVEL XR may not be right for you or your child. Before starting DYANAVEL XR, tell your or your child's doctor about all health conditions (or a family history of) including:

- if you or your child are pregnant, (b) (4) to become pregnant. It is not known if DYANAVEL XR will harm your unborn baby.
- If you or your child is breastfeeding or plan to breastfeed. DYANAVEL XR passes into breast milk. (b) (4).

APPENDIX A – Applicant's Proposed Dyanavel XR (amphetamine) Extended-Release Oral Suspension Pregnancy and Nursing Mothers Labeling

(b) (4)




(b) (4)

Appendix B: Strengths and Weaknesses of the Papers on the Karolinska Institute Cohort of Amphetamine-Exposed Children reviewed by the NTP-expert panel

Study	*Strengths*	*Weaknesses*
Eriksson et al., 1978 *(98)*	Trimester data presented (negative consequences appeared only when amphetamine use was throughout pregnancy).	Risk factors other than amphetamine addiction were not mentioned; differences between women who stopped and women who continued amphetamines during pregnancy were not indicated; there was no reference to general population rates of the negative outcomes seen in the sample.
Larsson et al, 1979 *(99)*	Had access to social data; recognized that addicted pregnant women come from "problem families;" differences recognized between women who did and did not stop amphetamine use during pregnancy.	Role (or absence) of father not considered; ethanol use identified as differentiating women who did and did not stop amphetamines, but patterns of drinking not described.
Eriksson et al., 1981 *(100)*	Lists outcomes found in neonates of amphetamine-using women; mentions possible effects of maternal-child separation.	No detail on other risk factors, making a causal link with amphetamines problematic; inadequate attention to tobacco use and clinic attendance.

Study	*Strengths*	*Weaknesses*
Billing et al, 1980 *(101)*	Considered pre- and postnatal amphetamine use; blinded evaluations; contrasting of fostered and non-fostered children; recognized the effects of multiple separations; included data on parent/partner and other people in the home.	Lassitude may have been due to problems with foster homes or problems encountered prior to fostering, even during the first 2 months of life; the hospitalization rate in fostered children may depend on unreported factors such as how many other children are in the home and who provides transportation for the child; the determinants used to diagnose "emotional" problems are an odd mixture, raising questions about their reliability.
Billing et al., 1985 and 1988 *(102, 103)*	Blinded evaluations; data from 4-year-olds; prenatal ethanol identified as an important contributor to outcomes; identification of father criminality as important is in agreement with other studies.	Not clear how fostered children differed from non-fostered children; determination of alcohol as a contributing factor was not clear; pattern of alcohol use (e.g., binging, chronic) not explored; collection of prenatal data may have been retrospective and unreliable; the general assessment of the children's emotional well-being appears subjective and unverifiable.
Eriksson et al., 1985, 1989, 1994 *(104-106)*	Presentation of outcome by child's sex; useful outcome measures (growth, cognitive, behavioral).	Comparison of exposed children with 25-year-old general population statistics; pre- and postnatal risk factors other than amphetamines were not mentioned; it is not clear how fostered children (13/69 at birth and 70% by age 10) were treated analytically; the timing of being placed in foster care was likely to be a surrogate for continued amphetamine use and therefore important; an index describing the mothers' emotional and abuse problems was not explained; the implication that longer amphetamine exposures were causally associated with aggression was not appropriate because there are too many intervening psychosocial variables by age 8.
Eriksson et al., 1994, 2000 Cernerud, 1996 *(107-109)*	Comparison of amphetamine cohort to a similar-age population; evaluation by child's sex; introduces the concept of exposure possibly leading to vulnerability to psychosocial problems.	Although the authors reported that 80% of the cohort was in foster care by age 14, there was no apparent consideration of fostering in the analysis or interpretation of the data. It must be assumed that 52 of the 65 children were removed from their homes because of continuing maternal drug addiction, which would have an important impact on the outcomes considered (performance in school, growth); school performance was evaluated using grades from different teachers; no investigation was reported of the children's possible substance abuse.

Appendix C: Case-Control Studies on Human Pregnancy Outcome after Maternal Exposure to Amphetamines

Cases and Controls	*Exposure Assessment*	*Risk Estimate*	*Reference*
Cases: 184 children with congenital heart disease. *Controls:* 108 children without congenital heart disease.	Mothers asked within a year of the birth about *d*-amphetamine use.	18% of case mothers and 9% of control mothers were exposed ($P < 0.05$) **[OR 2.40, 95% CI 1.06–5.95]**.	*(119)**
Cases: 458 mothers of children with congenital malformations. *Control 1:* 500 mothers of normal children born immediately after each case. *Control 2:* Mothers of 411 mothers of normal children matched to cases on maternal age and parity and infant sex.	Mothers were asked about *d*-amphetamine use, with confirmation of use by general practitioner, hospital records, or prescription records.	For total malformations, exposure during all of pregnancy occurred in 13/458 cases and 10/911 controls **[OR 2.63, 95% CI 1.07–6.52]**, exposure in the first trimester occurred in 11/458 pregnancies and 8/911 controls **[OR 2.78, 95% CI 1.03–2.61]**, exposure during the first 56 days occurred in 10/458 pregnancies and 5/911 controls **[OR 4.04, 95% CI 1.27–13.65]**, and exposure during the first 14 days occurred in 8/458 pregnancies and 2/911 controls **[OR 8.08, 95% CI 1.59–55.25]**.	*(121)*
Cases: 11 infants with biliary atresia. *Controls:* 50 normal infants of the same age.	Drug use histories were solicited from mothers for amphetamines.	4/11 case mothers used amphetamines during the first trimester and 3/50 control mothers used amphetamines in pregnancy **[OR 8.95, 95% CI 1.20–70.92]**.	*(122)**

ORs and 95% CIs were calculated by CERHR using the CDC SABER program.

*This report was judged not to be useful in the evaluation process due to methodologic problems or lack of detail, and is presented here for completeness only.

References

[119] Nora, et al. Dexamphetamine: a possible environmental trigger in cardiovascular malformations. Lancet 1970; 1: 1290-1.

[121] Nelson, M. M. and Forfar, J. O. Associations between drugs administered during pregnancy and congenital abnormalities of the fetus. Br. Med. J. 1971; 1: 523-527.

[122] Levin, J. N. Amphetamine ingestion with biliary atresia. J Pediatr 1971; 79: 130-1.

Appendix D: Cohort Studies on Human Pregnancy Outcome after Maternal Exposure to Amphetamines

Exposed and Unexposed	*Outcome Assessment*	*Risk Estimate/Comparisons*	*Reference*
Therapeutic Use			
50,282 mother-child pairs, retrospective and prospective record of pregnancy exposures; exposures in first 4 lunar months: *d*-Amphetamine: n=367 "Amphetamines": n=215 Methamphetamine: n=89.	Physical examination of children up to 1 year of age in 91% of the sample.	Comparison of children with specific exposure of interest to all children without exposure of interest during first 4 lunar months: *d*-Amphetamine crude RR 1.23 **[95% CI 0.82–1.82]**; standardized RR for any malformation 1.08 (95% CI 0.65–1.68), for major malformation 1.29 (95% CI 0.73–2.10), for minor malformation 1.46 (95% CI 0.59–2.98). Amphetamines crude RR 1.23 **[95% CI 0.72–2.05]**. Methamphetamine crude RR 0.87 **[95% CI 0.21–2.22]**.	*(123)*
		In a separate analysis, birth weight was 100–400 g lower among *d*-amphetamine-exposed non-malformed babies if the mother took the medication after 28 weeks of gestation and gained >12 kg during pregnancy or had a prepregnancy weight ≥45 kg.	*(124)*
White women insured by Kaiser Health Plan who delivered in the San Francisco East Bay area; 1694 used amphetamines for weight loss, 10,213 did not use anorectant drugs.	Diagnosis of a congenital malformation at birth or at a Kaiser clinic through 61 months of age.	For exposures during pregnancy, "severe congenital anomaly" in 3.4% of each exposure group **[crude RR 1.01 95% CI 0.76–1.32]**. Also, cleft palate in 5/1694 exposed, 21/10,213 unexposed **[crude RR 1.43, 95% CI 0.54–3.8]**. For exposures during the first 56 days of pregnancy: Cleft palate 3/175 exposed.	*(125)*
Illicit Use **(Evaluated by the Expert Panel as not useful in the evaluation process due to uncertainty about the constituents of the drug being used, and, for some studies, other methodologic problems.)**			
46 infants exposed antenatally to cocaine or methamphetamine identified by maternal or infant toxicology screens compared to 45 infants not exposed to tested illicit drugs.	Gestational age, birth weight, length, head circumference, perinatal complications. **[SD assumed in interpreting errors.]** Cocaine and amphetamine exposure not separated.	*Parameter* / *Exposed** / *Unexposed* Gestational age (weeks): 37.9±3.0 / 39.4±1.4 Birth weight (g): 2901±711 / 3246±552 Length (cm): 48.0±5.1 / 50.7±2.8 Head circumference (cm): 33.2±2.7 / 34.4±1.5 Perinatal complications (%): 28 / 9 *Differences all statistically significant	*(126)*

References

[123] Heinonen, O. P. Birth defects and drugs in pregnancy. ed. Littleton, MA: Publishing Sciences Group Inc; 1977.

[124] Naeye, R. L. Maternal use of dextroamphetamine and growth of the fetus. Pharmacology 1983; 26: 117-20.

[125] Milkovich, L. and van den Berg, B. J. Effects of antenatal exposure to anorectic drugs. Am. J. Obstet. Gynecol. 1977; 129: 637-642.

[126] Oro, A. S. and Dixon, S. D. Perinatal cocaine and methamphetamine exposure: maternal and neonatal correlates. J Pediatr 1987; 111: 571-8.

<table>
<tr><th>Exposed and Unexposed</th><th>Outcome Assessment</th><th>Risk Estimate/Comparisons</th><th>Reference</th></tr>
<tr><td>81 stimulant-exposed infants (27 infants exposed to methamphetamine) based on infant urine toxicology screening, 87 drug-free infants suspected of having hypoxic-ischemic encephalopathy (HIE), 19 normal drug-free infants. All born at term.</td><td>Presumably record review.
Cocaine and amphetamine exposure not separated. [SD assumed in interpreting errors].</td><td><table><tr><th>Parameter</th><th>Exposed</th><th>HIE</th><th>Unexposed</th></tr><tr><td>Birth weight (g)</td><td>2904±475[a]</td><td>3346±687[b]</td><td>3351±420[b]</td></tr><tr><td>Length (cm)</td><td>48.9±3.1[a]</td><td>50.5±4.8[b]</td><td>51.8±2.5[ab]</td></tr><tr><td>Head circumference (cm)</td><td>33.4±1.5[a]</td><td>34.4±1.8[b]</td><td>34.3±1.1[b]</td></tr><tr><td>Abnormal Cranial Ultrasound (%)</td><td>37.5[a]</td><td>27.6[a]</td><td>5.3[b]</td></tr><tr><td>Gestational Age (weeks)</td><td>38.9±1.3[a]</td><td>39.6±1.3[b]</td><td>39.4±0.7[b]</td></tr><tr><td>Intrauterine Growth Restriction (%)</td><td>19.8[a]</td><td>8.0[b]</td><td>5.3[b]</td></tr></table>* Differences all statistically significant
[ab] Within row, different superscripts are significantly different $P<0.05$.</td><td>(127)</td></tr>
<tr><td>52 methamphetamine-abusing pregnant women compared using record review with 52 women not known to have abused drugs whose babies were born next in the delivery unit.</td><td>Record review.</td><td>No difference between groups in rate of pregnancy complications or congenital anomalies.<table><tr><th>Parameter</th><th>Exposed*</th><th>Unexposed</th></tr><tr><td>Gestational age (weeks)</td><td>39.1±1.5</td><td>39.3±2.0</td></tr><tr><td>Birth weight (g)</td><td>2957.0±574.0</td><td>3295.8±433.3</td></tr><tr><td>Length (cm)</td><td>48.1±2.0</td><td>49.8±2.3</td></tr><tr><td>Head circumference (cm)</td><td>33.2±1.0</td><td>33.9±1.2</td></tr></table>All comparisons except gestational age were significant at $P<0.001$.</td><td>(128)</td></tr>
<tr><td>135 methamphetamine-exposed infants identified by maternal urine toxicology or history, 160 matched controls, all ≥ 37 weeks gestation.</td><td>Record review.</td><td>Gestational age reduced a mean 2.2 weeks ($P<0.001$) in methamphetamine group.
Small for gestational age increased in methamphetamine group to 13/135 compared to 2/160 ($P<0.001$) [crude RR 7.70, 95% CI 2.08–46.20].</td><td>(130)</td></tr>
<tr><td>8 infants with history of maternal methamphetamine use during pregnancy, 8 unexposed infants matched for ethnicity.</td><td>Fagan Test of Infant Intelligence, visual-evoked potentials.</td><td>Birth weight 500 g lower in exposed group. Visual-evoked potentials not affected by exposure status. Fagan performance poorer in exposed infants with 4/8 “at risk” based on their scores, compared to 0/8 unexposed infants.</td><td>(131)</td></tr>
</table>

References

[127] Dixon, S. D. and Bejar, R. Echoencephalographic findings in neonates associated with maternal cocaine and methamphetamine use: incidence and clinical correlates. J Pediatr 1989; 115: 770-8.

[128] Little, B. B., Snell, L. M. and Gilstrap, L. C., 3rd. Methamphetamine abuse during pregnancy: outcome and fetal effects. Obstet Gynecol 1988; 72: 541-4.

[130] Smith, L., Yonekura, M. L., Wallace, T., Berman, N., Kuo, J. and Berkowitz, C. Effects of prenatal methamphetamine exposure on fetal growth and drug withdrawal symptoms in infants born at term. J Dev Behav Pediatr 2003; 24: 17-23.

[131] Hansen, R. L., Struthers, J. M. and Gospe, S. M., Jr. Visual evoked potentials and visual processing in stimulant drug-exposed infants. Dev Med Child Neurol 1993; 35: 798-805.

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/s/

MIRIAM C DINATALE
10/14/2015

TAMARA N JOHNSON
10/19/2015

LYNNE P YAO
10/19/2015

MEMORANDUM

REVIEW OF REVISED LABEL

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 16, 2015
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 208147
Product Name and Strength:	Dyanavel XR (amphetamine) Extended-release Oral Suspension 2.5 mg amphetamine base per mL
Submission Date:	October 15, 2015
Applicant/Sponsor Name:	Tris Pharma Inc.
OSE RCM #:	2015-112-2
DMEPA Primary Reviewer:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Psychiatry Products (DPP) requested that we review the revised Dyanavel XR container label (Appendix A) to determine if it is acceptable from a medication error perspective. The Division of Psychiatry Products recommended removal of the (b) (4) from the label. In addition to removing (b) (4), Tris Pharma made additional revisions to the label since our previous review.[1]

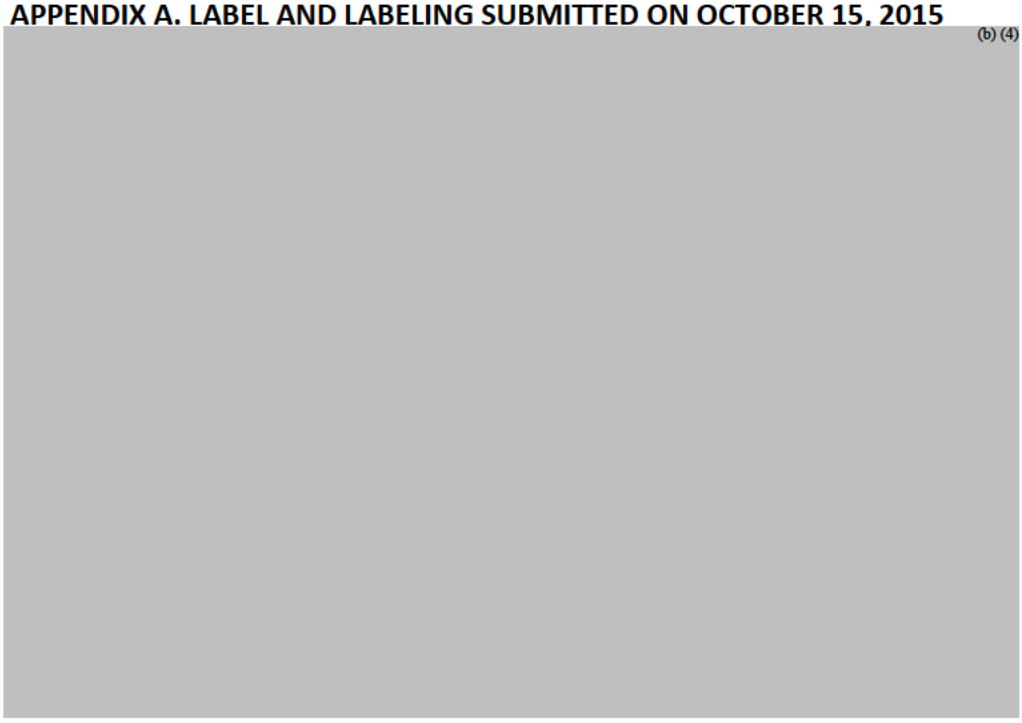
2 CONCLUSIONS

The revised container label is acceptable from a medication error perspective.

[1] Holmes L. Label Review Memorandum for Dyanavel XR (NDA 208147). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Sep 09. 2 p. OSE RCM No.: 2015-112.

APPENDIX A. LABEL AND LABELING SUBMITTED ON OCTOBER 15, 2015

(b) (4)



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/s/

LORETTA HOLMES
10/16/2015

DANIELLE M HARRIS
10/16/2015

505(b)(2) ASSESSMENT

Application Information		
NDA # 208147	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Amphetamine Extended ReleaseOral Suspension Dosage Form: Oral Suspension Strengths: 2.5 mg amphetamine base/ml		
Applicant: Tris Pharma		
Date of Receipt: December 19, 2014		
PDUFA Goal Date: October 19, 2015	Action Goal Date (if different):	
RPM: Renmeet Grewal, Pharm.D., RAC		
Proposed Indication(s): Treatment of Attention Deficit Hyperactivity Disorder		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 011522 Adderall IR	

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

The link has been established between the Amphetmine ER Oral Suspension and amphetamine IR tablet through the relative bioavailability study.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Adderall	*NDA 011522*	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: NDA 011522 Adderall

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new dosage form (tablet to oral suspension)

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

Adderall XR	amphetamine, dextroamphetamine mixed salts
Adderall (RLD in OGD)*	amphetamine, dextroamphetamine mixed salts
Dexedrine Spansule	dextroamphetamine
Vyvanse	lisdexamfetamine dimesylate
Desoxyn	methamphetamine HCl

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): NDA 11522/ patent: 6,384,020

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s): NDA 11522/ patent: 6,384,020

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): *6,384,020*
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *March 24,2015*

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

RENMEET GREWAL
10/15/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 2, 2015
To:	Mitchell Mathis, MD Acting Director **Division of Psychiatry Products (DPP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Susannah O'Donnell, MPH, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	DYANAVEL XR (amphetamine)
Dosage Form and Route:	Extended-Release (ER) Oral Suspension
Application Type/Number:	NDA 208147
Applicant:	Tris Pharma, Inc.

1 INTRODUCTION

On December 18, 2014, Tris Pharma, Inc. submitted for the Agency's review an original New Drug Application (NDA) for amphetamine ER Oral Suspension as a treatment for Attention Deficit Hyperactivity Disorder (ADHD). On March 9, 2015, the Agency granted the sponsor's request for approval of the proprietary name, DYANAVEL XR (amphetamine) Extended-Release Oral Suspension.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on February 27, 2015 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for DYANAVEL XR (amphetamine) Extended-Release Oral Suspension.

2 MATERIAL REVIEWED

- Draft DYANAVEL (amphetamine) Extended-Release Oral Suspension MG received on December 18, 2014, and received by DMPP on September 23, 2015.
- Draft DYANAVEL (amphetamine) Extended-Release Oral Suspension MG received on December 18, 2014, and received by OPDP on September 23, 2015.
- Draft DYANAVEL (amphetamine) Extended-Release Oral Suspension Prescribing Information (PI) received on December 18, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on September 23, 2015.
- Draft DYANAVEL (amphetamine) Extended-Release Oral Suspension Prescribing Information (PI) received on December 18, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on September 23, 2015.
- Approved APTENSIO XR (methylphenidate hydrochloride) comparator labeling dated April 17, 2015.
- Approved VYVANSE (lisdexamfetamine dimesylate) comparator labeling dated April 17, 2015.

3 REVIEW METHODS

In 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG is consistent with the approved comparator labeling where applicable.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHARON W WILLIAMS
10/02/2015

SUSANNAH O'DONNELL
10/02/2015

MARCIA B WILLIAMS
10/02/2015

LASHAWN M GRIFFITHS
10/02/2015

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 30, 2015

To: Mitchell Mathis, M.D., Director
Division of Psychiatry Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff (CDER/OCD/CSS)

From: Edward Hawkins, Ph.D., Pharmacologist
Controlled Substance Staff (CDER/OCD/CSS)

Subject: **Trade Name, dosages, formulations, routes: Dyanavel XR, 2.5mg/ml, Amphetamine suspension, oral**
NDA Number: 208147
Indication(s): Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor: Tris Pharmaceuticals, Inc.
PDUFA Goal Date: 10/19/2015

Materials reviewed: 1. NDA 208147 section 1.11.4

Background:
The Agency sent an information request (IR) to Tris Pharma on September 24, 2015 regarding NDA 208147. The PDUFA date is October 19, 2015. The request conveyed the following:

> Comment to convey to sponsor:
> This product is appropriately listed in Schedule II under the CSA, as stated in your proposed label. However, as stated in the Pre-NDA meeting minutes dated November 19, 2014, for IND 116985, you should provide a rationale and proposal for scheduling, as outlined in 21 CFR 314.50(d)(5)(vii). You should submit this information as an amendment to the NDA in Module 1.11.4, Multiple Module Information Amendment, along with your rationale and summary of the abuse potential of the product. We request your amendment by c.o.b. Oct. 1, 2015, and we may, after reviewing your amendment, propose further revision of Section 9 of the labeling currently under consideration.

The Sponsor replied with section 1.11.4 Multiple Module Information Amendment on September 29, 2015. The reply contains a proposal for Schedule II under the CSA which is in the

draft label submitted to the Sponsor on September 28, 2015. The Sponsor makes two justifications for Schedule II:

1. As a 505(b)(2) application amphetamine is a non-new molecular entity which is already a schedule II compound.
2. Extended release formulations of amphetamine have a long history of being in Schedule II. The Sponsor states that they assume the Amphetamine ER Oral suspension has similar abuse liability as other extended release amphetamine products.
3. The Sponsor makes reference to an alcohol dissolution study
4. The Sponsor also notes: [redacted (b) (4)]."

Conclusions:

- The Sponsor proposes that Amphetamine ER Oral Suspension is a Schedule II product citing that the amphetamine substances contained in their product are currently in Schedule II under 21 CFR Part 1308.12 (d).
- No abuse liability studies have been conducted on the Amphetamine ER Oral Suspension product
    - A summary of the abuse potential of the product was not submitted by the Sponsor
- In Vitro dissolution testing of the release of amphetamine from Amphetamine ER oral Suspension is not significantly different from control in 20% ethanol for 120 minutes
    - For 40% ethanol, there is a [redacted (b) (4)]% increase of release by 15 minutes, which is maintained for 120 minutes.
- The Sponsor does not [redacted (b) (4)].

CSS determines that this review is sufficient for approval.

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/s/

EDWARD G HAWKINS
09/30/2015

MICHAEL KLEIN
09/30/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **September 16, 2015**

To: Renmeet Grewal, PharmD, RAC
Team Leader, Senior Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Susannah K. O'Donnell, MPH, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 208147**
DYANAVEL™ XR (amphetamine) extended-release oral suspension, CII

OPDP has reviewed the draft product labeling (PI), Medication Guide (MG), and carton/container labeling for DYANAVEL™ XR (amphetamine) extended-release oral suspension, CII (Dyanavel XR) as requested in the consult from DPP dated February 27, 2015.

OPDP's comments on the draft PI for Dyanavel XR are based on the version in Sharepoint dated September 10, 2015 (File: Amphetamine Oral Solution Draft PI). Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed MG will be provided to DPP under separate cover.

Carton and Container Labeling

OPDP has reviewed the proposed carton/container labeling, obtained from the EDR (\\CDSESUB1\evsprod\NDA208147\208147.enx) on September 14, 2015, and has the following comment:

The carton includes a (b) (4)

[redacted] We also note that references to [redacted] have already been removed from the draft PI for Dyanavel XR.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials. Thank you!

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/s/

SUSANNAH O'DONNELL
09/16/2015

MEMORANDUM

REVIEW OF REVISED LABEL

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 9, 2015
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 208147
Product Name and Strength:	Dyanavel XR (amphetamine) Extended-release Oral Suspension 2.5 mg amphetamine base per mL
Submission Date:	September 2, 2015
Applicant/Sponsor Name:	Tris Pharma Inc.
OSE RCM #:	2015-112
DMEPA Primary Reviewer:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Psychiatry Products (DPP) requested that we review the revised Dyanavel XR container label (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised container label is acceptable from a medication error perspective.

[1]Holmes L. Label and Labeling Review for Dyanavel XR (NDA 208147). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 May 20. 6 p. OSE RCM No.: 2015-112.

APPENDIX A. LABEL AND LABELING SUBMITTED ON SEPTEMBER 2, 2015

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/s/

LORETTA HOLMES
09/09/2015

DANIELLE M HARRIS
09/09/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 208147 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Animal Rule Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Pediatric
Proprietary Name: Established/Proper Name: Amphetamine Extended Release Dosage Form: Oral Suspension Strengths: 2.5mg amphetamine base per ML		
Applicant: Tris Pharma Agent for Applicant (if applicable):		
Date of Application: 12/18/14 Date of Receipt: 12/19/14 Date clock started after UN:		
PDUFA/BsUFA Goal Date: October 19, 2015	Action Goal Date (if different):	
Filing Date: 2/17/15	Date of Filing Meeting: 1/29/15	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): New dosage form (oral suspension) for ADHD		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 116985	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** *http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm* ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** *http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm*	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf*	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** *http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm* **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it;*	☒	☐	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☐	☒	☐	Sent an email to sponsor to resubmit correctly worded Debarment Certification Statement.
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☒	☐	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*: 2/27/15	☒	☐	☐	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to*	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

[4]

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	☒		

http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

If yes, distribute minutes before filing meeting				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** November 6, 2014 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 29, 2015

BACKGROUND: This is a 505b2 NDA for submission of Amphetamine ER Oral Suspension

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Renmeet Grewal, Pharm.D., RAC	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)			
Division Director/Deputy	Mitchell Mathis, MD Tiffany Farchione, MD		Y
Office Director/Deputy			
Clinical	Reviewer:	Ripi Kohli	Y
	TL:	Lucas Kempf	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Andre Jackson	Y (phone)
	TL:	Hao Zhu	Y
Biostatistics	Reviewer:	Eiji Ishida Semhar Ogbagaber	Y
	TL:	Peiling Yang	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ikram Elayan	Y
	TL:	Linda Fossom	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:		
	TL:		
Product Quality (CMC)	PM:	Dahlia Woody	Y
	TL:	Wendy Wilson	Y
Biopharmaceutics	Reviewer	Sandra Suarez	Y
	TL:		
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Loretta Holmes	Y
	TL:	Irene Chan	U
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☐ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☐ ☐ NO ☒ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: AN Information request was sent to the sponsor for missing information and the sponsor responded with the dates they would submit the information.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☐ YES ☐ NO ☒ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization? **Comments**:	☐ Not Applicable ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Renmeet Grewal, Pharm.D., RAC

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60

☐	If priority review: • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

RENMEET GREWAL
08/26/2015

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 21, 2015

To: Mitchell Mathis, M.D., Director
Division of Psychiatry Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Edward Hawkins, Ph.D., Pharmacologist
Controlled Substance Staff

James Hunter, BPharm., MPH, Pharmacist Reviewer
Controlled Substance Staff

Subject:

Trade Name, dosages, formulations, routes: Dyanavel XR, 2.5mg/ml, Amphetamine suspension, oral
NDA Number: 208147
Indication(s): Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor: Tris Pharmaceuticals, Inc.
PDUFA Goal Date: 10/19/2015

Materials Reviewed: Abuse-related labeling and clinical trial data in NDA 208147; a (505(b)(2) type NDA submitted in eCTD format and dated 12/19/2014.

Table of Contents

I. Summary

1. Background

This memorandum responds to a consult request by the Division of Psychiatry Products (ODEI/DPP) dated February 25, 2015, to evaluate from the CSS perspective, NDA 208147 submitted by Tris Pharmaceuticals, Inc., for Dyanavel XR (amphetamine) oral suspension. This consult is CSS's initial opportunity to assess this proposed drug product, therefore CSS did not have the opportunity to provide input to the review division or Sponsor at the pre-NDA stage nor to assess the fileability of this NDA. This NDA does not contain an overview of the abuse potential of the proposed formulation, including a literature review on the abuse potential of amphetamine. Also, the Sponsor has provided draft labeling (Section 9.1, 9.2 and 9.3) in which the drug is listed in Schedule II of the Controlled Substances Act (CSA).

This proposed oral suspension contains (b) (4) Amphetamine is the primary active pharmaceutical ingredient (API) in this product containing a 3:1 ratio of d- to l-amphetamine resulting in a concentration of 2.5mg/ml of amphetamine base. The product is an extended-release (ER) liquid formulation (b) (4)

The Sponsor proposed indication for Dyanavel XR is treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older. The recommended dose is 2.5 to 5mg once daily in the morning and may be increased incrementally by 2.5mg up to 10 mg/day or until an optimal response is achieved. The Sponsor indicates that doses above 20mg/day have not been tested and are not recommended. The Sponsor is marketing this ER oral suspension for patients who have a difficult time swallowing and

therefore have difficulties taking their ADHD medication in tablet form. The Sponsor also states that the product is designed (b) (4)

Additionally, while there are already multiple ER solid dosage formulations approved by the Agency, such as Adderall XR® and Vyvanse®, there is no ER liquid amphetamine formulation available in the market.

Amphetamine ER Oral Suspension NDA 208147 was submitted as a 505(b)(2) NDA application which relies on safety and efficacy information previously reviewed and approved by FDA for the reference listed drug (RLD) Adderall® tablets (NDA 011522, Teva Women's Health). Since this RLD is listed as discontinued, the Sponsor utilized a product available on the market as a generic, Dextroamphetamine saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate and Amphetamine Sulfate Tablets, Barr Laboratories, Inc. as the reference product. In addition, the Sponsor generated data on safety and efficacy in a phase 3 study conducted by the Sponsor, Tris Pharma, and relative bioavailability data in healthy adult subjects comparing Amphetamine ER Oral Suspension and the reference product. No nonclinical studies were submitted in this NDA; however, the submission includes an overview of publically available information on the nonclinical pharmacology and toxicology of amphetamine salts and inactive ingredients.

2. Conclusions (to be conveyed to the Sponsor)

We have reviewed the nonclinical and clinical abuse-related data and proposed product labeling submitted in NDA 208147 for this oral ER suspension drug product containing amphetamine. Since an evaluation of drug abuse liability, section 1.11.4, was not submitted with the NDA the reviewed data included Section 2.0 Clinical and Non-clinical overviews, Section 3.0 on Drug substance and Drug product and Section 5.0 covering 5 different clinical studies. The Agency concludes:

1. Amphetamine and its salts have a high abuse potential.
2. We concur with the Schedule II status of product as proposed in the submitted draft labeling.
3. The Sponsor's statement (b) (4) [1]

3. Recommendations (to be conveyed to the Sponsor)

Based on our findings as captured in the Conclusions section, we recommend the following:

1. This product is appropriately listed in Schedule II under the CSA, as stated in the proposed label; however, the Sponsor should update the NDA to include an

[1] In Module 2.5 (pg. 32) of the NDA describing the clinical overview the Sponsor states that, (b) (4) "

overview of the abuse potential of the formulation, including a rationale and proposal for scheduling under the CSA, and a literature review on the abuse potential of amphetamine. This information should be included in the NDA ((Module 1.11.4, Multiple Module Information Amendment) as a summary.

2. Suggested changes to draft Labeling
    a. CSS recommends the following changes to the proposed labeling at the time the application is considered for approval: Strike-through sections are to be deleted and highlighted sections are to be added.

3. We concur with Section 5.1 (Warnings and Precautions) of the label as stated below:

5.1 Potential for Abuse and Dependence

CNS stimulants (b) (4) products) have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [see *Drug Abuse and Dependence (9.2, 9.3)*].

4. Modify Section 9 of the labeling on *Drug Abuse and Dependence* as follows:

Edited section: **9.1 Controlled Substance**

DYANAVEL XR contains amphetamine, which is a Schedule II controlled substance in the U.S. Controlled Substances Act (CSA).

Edited section: **9.2 Abuse**

(b) (4) <TRADENAME> is a CNS stimulant that contains amphetamines which (b) (4) a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.
Signs and symptoms of (b) (4) amphetamine abuse may include increased heart rate, respiratory rate, blood pressure, ~~and/or~~ sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation (b) (4) ~~have~~ also (b) (4) ~~been~~ (b) (4). Abusers o (b) (4) amphetamines may (b) (4) use other unapproved routes of administration which can result in overdose and death *[see Overdosage (10)]*.
To reduce the abuse o (b) (4) <TRADENAME>, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for <TRADENAME> use.

Edited section: **9.3 DEPENDENCE**

Tolerance
Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) may occur during the chronic therapy of CNS stimulants including <TRADENAME>.
Dependence
Physical dependence ((b) (4) which is manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) may occur in patients treated with CNS stimulants including <TRADENAME>. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include dysphoric mood, (b) (4) fatigue, insomnia, increased appetite, psychomotor agitation, (b) (4) .

5. In Section 16.2 of the labeling on Disposal, existing text should be modified as follows:

Edited section: **16.2 Storage and Handling**

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired DYANAVEL XR (b) (4) an authorized collect (b) (4) If no take-back program or authorized collector is available, mix <Tradename> with an undesirable, nontoxic substance to make it less appealing to children and pets (b) (4) place the mixture in a container such as a sealed plastic bag and discard <Tradename> in the household trash.

II. Discussion

1. Chemistry

Dyanavel XR is an oral suspension that contains (b) (4)

[2] It is not necessary to include reference in label. Shoptaw, S. J., et al. (2009). "Treatment for amphetamine withdrawal." Cochrane Database Syst Rev(2): CD003021.

(b) (4)

(b) (4) therefore the composition of Amphetamine isomers is 3:1 of d:l, (b) (4) . The amount of each isomer of Amphetamine in a daily dose of 8mLs of API is indicated in Table 1, below.

(b) (4)

(b) (4)

2. Nonclinical Pharmacology

Dyanavel contains both the d and l isomers of Amphetamine (b) (4) Amphetamine resulting in a final ratio of Dyanavel of 3:1 of the d:l racemic amphetamine. This ratio is the same as the previously accepted drug (NDA 021303) Adderall XR 30mg tablets. Amphetamine belongs to the class of substituted amphetamines which have a wide range of behavioral pharmacological effects. Many of these compounds are classified as stimulants, or psychedelics.

The Sponsor referred to the previously accepted NDA for Adderall (for the treatment of ADHD) in reference to the pharmacokinetic profiles (b) (4) .

Amphetamine has been shown to localize in the liver, lung, kidney, and brain in rats dosed intraperitoneally (i.p.) with 1mg/kg amphetamine per day over 5 or 14 days (Liang et al., 2012). Ninety percent of the orally administered amphetamine is excreted in the urine in humans, rhesus monkeys and in greyhound dogs. Rabbits excreted mainly benzoic acid (25%) and benzyl methyl ketone (22%) whereas rats excreted 4-hydroxyamphetamine (Dring et al., 1970). This data indicates species differences in the metabolites of amphetamine; however humans, monkeys and dogs all had similar excretion profiles.

Amphetamine is metabolized through two major pathways. It either goes through a hydroxylation of the aromatic ring to yield p-hydroxy-amphetamine or it goes through a deamination yielding benzyl methyl ketone which degrades to benzoic acid. In the liver, amphetamine is degraded by the P450 2D6 to yield several metabolites including 4-hydroxyamphetamine, hippuric acid, benzoic acid, and benzyl methyl ketone (Wu et al., 1997; Musshoff, 2000; Maurer et al., 2002). 4-Hydroxyamphetamine is a sympathomimetic stimulant that is used to dilate the pupil and has no known abuse liability. The other compounds have little to no biological activity and are excreted in the urine (Dring et al., 1970).

2.1 Animal behavioral studies

These studies were not conducted by the Sponsor as amphetamine is well known to have a high abuse potential and is a Schedule II substance by the CSA.

3. Clinical Studies

No human abuse potential studies were performed by the Sponsor. According to the draft Guidance for Industry- Assessment of Abuse Potential of Drugs the "Sponsor must submit in the NDA an assessment of studies and other information related to the potential abuse of a drug and include a proposal for scheduling if the drug affects the central nervous system (CNS)…". This includes an assessment if the drug is an already marketed product that is reformulated. Information that should be considered for the abuse potential submission is outlined in the Guidance.

To prevent diversion of the drug in clinical studies to determine PK and efficacy, accountability guidelines were distributed and explained to each subject. Each subject was provided 90mLs of drug at a time and bottles were to be returned at the end of the study. All the bottles were weighed before and after dispensing of the drug to the subject's guardian to maintain records of the amount of drug administered. If there was a spill photo documentation of the spill was to be provided by the subject (guardian) for drug accountability. There was no evidence of abuse or misuse in the clinical trials.

4. Regulatory issues and assessment

Vyvanse and Adderall drug labels are similar as they are also amphetamine-containing Schedule II products with labeled indications for the treatment of ADHD.

III. References

Dring LG, Smith RL and Williams RT (1970) The metabolic fate of amphetamine in man and other species. *Biochem J* **116**:425-435.

Liang M, Liu Y, Zheng N, Ananda S and Liu L (2012) Distribution of methamphetamine and its metabolite amphetamine in acute and subacute ethanol-methamphetamine combination abuse model rats. *J Anal Toxicol* **36**:30-35.

Maurer HH, Kraemer T, Kratzsch C, Peters FT and Weber AA (2002) Negative ion chemical ionization gas chromatography-mass spectrometry and atmospheric pressure chemical ionization liquid chromatography-mass spectrometry of low-dosed and/or polar drugs in plasma. *Ther Drug Monit* **24**:117-124.

Musshoff F (2000) Illegal or legitimate use? Precursor compounds to amphetamine and methamphetamine. *Drug Metab Rev* **32**:15-44.

Wu D, Otton SV, Inaba T, Kalow W and Sellers EM (1997) Interactions of amphetamine analogs with human liver CYP2D6. *Biochem Pharmacol* **53**:1605-1612.

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

/s/

EDWARD G HAWKINS
08/21/2015

JAMES R HUNTER
08/21/2015

MICHAEL KLEIN
08/21/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 05/29/2015

TO: Renmeet Grewal, Regulatory Project Manager
Kavneet Kohli-Chhabra M.D., Medical Officer and Clinical Reviewer
Lucas Kempf, M.D., Acting Team Leader
Division of Psychiatry Products (DPP)

FROM: Jenn W. Sellers, M.D., Ph.D. F.A.A.P.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.,
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 208147

APPLICANT: Tris Pharma, Inc.

DRUG: Amphetamine ER Oral Suspension

NME: No

REVIEW: Standard Review

INDICATION: Attention deficit hyperactivity disorder (ADHD)

CONSULTATION REQUEST DATE: March 4, 2015

INSPECTION SUMMARY GOAL DATE: August 19, 2015

DIVISION ACTION GOAL DATES: October 19, 2015

PDUFA DATES: October 19, 2015

I. BACKGROUND

Tris Pharma, Inc., is seeking approval of amphetamine extended-release oral suspension (TRI102) for the treatment of Attention deficit hyperactivity disorder (ADHD). The reference listed drug of this 505(b) (2) application is Adderall tablets approved by FDA on January 19, 1960.

ADHD is a disorder of inattention and/or impulsivity and hyperactivity that affects many aspects of behavior and performance of children, both at school and at home. The main treatments for ADHD are the stimulant drugs methylphenidate and amphetamines. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

This 505(b) (2) application included a randomized, double-blind, placebo-controlled and dose-optimized clinical trial evaluating the efficacy and safety of TRI102 in pediatric ADHD patients aged 6 to 12 years in a laboratory classroom setting. The study design of this trial was briefly described as follows: After Screening and Baseline evaluations were completed; eligible enrolled subjects took open-label TRI102 orally once daily for 5 weeks (Dose Optimization Period). Subjects who achieved a stable dose of TRI102 during the Dose Optimization Period were randomized to take either TRI102 or placebo orally once daily for 1 week (Double-blind Treatment Period). At the end of the 1-week Double-blind Treatment Period, subjects were evaluated for ADHD symptoms and signs using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) assessment in a laboratory classroom setting at multiple time points (at 1, 2, 6, 8, 10, 12, and 13 hours post-dose) during the laboratory school day (Visit 8).

The primary efficacy endpoint for study TRI102-ADD-001 was the assessment of change from pre-dose SKAMP-Combined scores at 4 hours post-dose measured during the laboratory school day. The key secondary efficacy endpoints were change from pre-dose in SKAMP-Combined scores at 1, 2, 6, 8, 10, 12, and 13 hours post-dose during the laboratory school day (Visit 8) that indicated the onset and duration of clinical effects. According to the sponsor, TRI102 demonstrated statistically significant treatment effects in pediatric patients with ADHD.

The Division of Psychiatry Products (DPP) requested inspections of the following clinical investigator sites based primarily on large subject enrollment. Most likely no inspections were conducted in 1960 for Adderall since Bioresearch Monitoring (BIMO) inspections was first introduced in 1977.

II. RESULTS (by Site):

Name of Clinical Investigator Location	Protocol Study Site Number of Subjects Enrolled (n)	Inspection Date	Classification*
John Turnbow, M.D. Westex Clinical Investigations 3315 81st Street, Suite A, Lubbock, TX 79423	TRI102-ADD-001 Site #04 N = 34	05/18/2015 to 05/20/2015	Preliminary NAI
Ann Childress, M.D. Center for Psychiatry and Behavioral Medicine, Inc. 7351 Prairie Falcon Road, Suites 150 and 160, Las Vegas, NV 89128	TRI102-ADD-001 Site #02 N = 30	04/10/2015 to 04/13/2015	Preliminary NAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Deviation(s) from regulations. Data acceptable
OAI = Significant deviations from regulations. Data unreliable
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

CLINICAL INVESTIGATOR (CI)

1. **John Turnbow, M.D.**
3315 81st Street, Suite A, Lubbock, TX 79423

   a. What was inspected: At this site, 39 subjects were screened, 34 were enrolled, and 34 completed the study. A complete review of 23 subject records and an audit of an additional 11 subject records were conducted.

   b. General observations/commentary: The data listing of all subjects reviewed were verified at the clinical site. The primary efficacy endpoint and the key secondary efficacy endpoint data were verifiable. There was no evidence of under-reporting of AEs. No significant regulatory violations were noted and no Form FDA 483 was issued.

   c. Assessment of data integrity: The study appears to have been conducted adequately, and data generated by this site appear acceptable in support of the respective indication.

2. **Ann Childress, M.D.**
7351 Prairie Falcon Road, Suites 150 and 160, Las Vegas, NV 89128

a. What was inspected: At this site, 30 subjects were screened, 30 were enrolled and 25 completed the study. A complete review of 10 subject records and an audit of other subject records were conducted.

b. **General observations/commentary:** The data listing of all subjects reviewed were verified at the clinical site. The primary efficacy endpoint and the key secondary efficacy endpoint data were verifiable. There was no evidence of under-reporting of AEs. No significant regulatory violations were noted and no Form FDA 483 was issued.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator sites (Drs. Turnbow and Childress) were inspected in support of this NDA and no significant regulatory violations were noted at these sites. Based on results of these inspections, it appears that the data submitted by the Applicant in support of the requested indication are acceptable and the studies appear to have been conducted adequately.

The findings above are based on preliminary communications with the FDA field investigators. An addendum to this clinical inspection summary will be forwarded to DPP should there be a change in the final results of the inspection.

{See appended electronic signature page}
Jenn W. Sellers, M.D., Ph.D., F.A.A.P.
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CONCURRENCE: *{See appended electronic signature page}*

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/s/

JENN W SELLERS
06/01/2015

SUSAN D THOMPSON
06/01/2015

KASSA AYALEW
06/01/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 20, 2015
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 208147
Product Name and Strength:	Dyanavel XR (amphetamine) Extended-release Oral Suspension 2.5 mg amphetamine base per mL
Product Type:	Multi-Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Tris Pharma Inc.
Submission Date:	December 19, 2015
OSE RCM #:	2015-112
DMEPA Primary Reviewer:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

The Division of Psychiatry Products (DPP) asked the Division of Medication Error Prevention and Analysis (DMEPA) to review the proposed label and labeling for Dyanavel XR (amphetamine) Extended-release Oral Suspension (NDA 208147) to determine if they are at risk for medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed label and labeling (Prescribing Information and Medication Guide) identified the following areas of needed improvement.

- Container label: the statement of strength lacks adequate visibility, the CII symbol is in too close proximity to the proprietary name, the Medication Guide statement does not state how it is provided, and the label lacks a barcode.

- Insert Labeling: There are areas in the Dosage and Administration section of Highlights of Prescribing Information and Full Prescribing Information where the numerical dose is not followed by "mg" (e.g., 2.5).

4 CONCLUSION & RECOMMENDATIONS

We identified areas where information on the container label and labeling (Prescribing Information) needs to be more prominent, revised, repositioned, or added in order to help ensure the safe use of the product. We provide recommendations in Section 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Dosage and Administration, Highlights of Full Prescribing Information and Full Prescribing Information

There are areas where the numerical dose is not followed by its corresponding unit of measure. For clarity, please add the unit of measure in those instances where it has been omitted (e.g., revise "2.5 to 10 mg" to read "2.5 mg to 10 mg").

4.2 RECOMMENDATIONS FOR TRIS PHARMA

We recommend the following be implemented prior to approval of this NDA:

A. General Comment
It is not clear how the Medication Guides (MG) will be supplied or how many will be supplied with each bottle. Please provide us with this information.

B. Container Label

1. The established name and a portion of the dosage form have a different font and size. Revise the established name and dosage form statement so that they are the same font and size.

2. The statement of strength lacks adequate visibility due to the (b) (4) . Consider the use of a lighter background color, a different color or other means to increase the visibility of the statement of strength.

3. The CII symbol is in too close proximity to the proprietary name and interferes with its readability. Reposition the CII symbol so that it is not in too close proximity to the proprietary name.

4. The MG statement does not state how it is provided. Revise the statement to read as follows (or use similar language) dependent upon how the MG is provided:

"**Attention Pharmacist: Dispense the accompanying Medication Guide to each patient.**"

5. The label lacks a barcode. Add a barcode to the container label (see 21 CFR 201.25).

6. The Usual Dosage statement contains the term [redacted]. To minimize confusion we recommend you consider revising the term [redacted]" to read "prescribing information".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Dyanavel XR that Tris Pharma submitted on December 19, 2014.

Table 2. Relevant Product Information for Dyanavel XR	
Initial Approval Date	N/A
Active Ingredients	dextroamphetamine and amphetamine
Indication	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
Route of Administration	Oral
Dosage Form	Extended-release oral suspension
Strength	2.5 mg amphetamine base per mL
Dose and Frequency	Start with 2.5 mg or 5 mg once daily in the morning. The dose may be increased in increments of 2.5 mg to 10 mg per day every 4 to 7 days until an optimal response is obtained. Daily doses above 20 mg have not been studied and are not recommended.
How Supplied	464 mL bottles
Storage	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F)
Container Closure	Child-resistant Closure

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Dyanavel XR label and labeling submitted by Tris Pharma on December 19, 2014.

- Container label
- Prescribing Information and Medication Guide (no image)

G.2 Label Image

Container Label (not to scale)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LORETTA HOLMES
05/20/2015

DANIELLE M HARRIS
05/20/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 208147
Application Type: New NDA

Name of Drug/Dosage Form: Amphetamine ER Oral Suspension

Applicant: Tris Pharma Inc.

Receipt Date: December 19, 2014

Goal Date: October 19, 2015

1. Regulatory History and Applicant's Main Proposals

This is a 505b2 application

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES"

in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.
   Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

Selected Requirements of Prescribing Information

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

Selected Requirements of Prescribing Information

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or "[*see Warnings and Precautions (5.2)*]".

Comment:

Selected Requirements of Prescribing Information

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

RENMEET GREWAL
02/24/2015