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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208147
Supporting document/s:	000
Applicant's letter date:	12/18/2014
CDER stamp date:	12/19/2014
Product:	Amphetamine ER oral suspension
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Applicant:	Tris Pharma Inc.
Review Division:	DPP
Reviewer:	Ikram Elayan, Ph.D.
Supervisor/Team Leader:	Linda Fossom, Ph.D.
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1 Executive Summary

1.1 Introduction

Tris Pharma submitted this NDA as a 505(b)(2) application (submission date 12-19-2014) referencing immediate release Adderall tablets (Teva Women's Health Inc.) as the Reference Listed Drug (RLD) (NDA 011522). However the sponsor indicated that in agreement with the Division, and due to the fact that this drug is discontinued, and the fact that the labeling for the generic RLD for Adderall tablets has not been updated to meet current Physician Labeling Rule (PLR), they used the following sources during the development of the labeling content for Amphetamine ER oral suspension:

1. Amphetamine ER Oral Suspension pharmaceutical development information provided in this NDA file
2. Clinical Efficacy and Pharmacokinetic data available for Amphetamine ER Oral Suspension and provided in this NDA file
3. Approved labeling for Adderall and currently listed as an RLD, generic for Adderall tablets
4. Approved labeling for Vyvanse® as the most recently updated, representative class labelling.

1.2 Brief Discussion of Nonclinical Findings

Tris Pharma has developed this product, Amphetamine Extended Release (ER) Oral Suspension, for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The product contains 2.5 mg amphetamine base per ml and is intended for use in children 6 years of age and older. The maximum recommended daily dose is 20 mg amphetamine base (8 ml). There were no new non-clinical data submitted with this application and no outstanding chemistry issues regarding impurities or new excipients were identified by the chemistry team.

The sponsor included safety data for the qualification of one inactive ingredient in their submission; sodium polystyrene sulfonate USP (b) (4) resin) which is present at a concentration of (b) (4) The maximum dose of sodium polystyrene sulfonate USP is about (b) (4) . This compound is used as an active ingredient in the treatment of hyperkalemia at an average daily dose of 15-60 g/day, (b) (4) In addition, (b) (4) this compound ((b) (4) were used as an inactive ingredient in a previously approved application (see NDA 202100).

The safety margins calculated in the labeling for the RLD were based on a maximum recommended daily dose of 30 mg amphetamine **salt** while the maximum recommended daily dose for the product in this application is 20 mg amphetamine **base**. The following table was provided by the sponsor summarizing the content of the drug in amphetamine base and comparing it to the RLD (Adderall, as amphetamine salt).

Table 1. Amphetamine Base Content in Amphetamine Formulations

Dosing volume	1 mL	2 mL	3 mL	4 mL	6 mL	8 mL
Amphetamine Base Content in Amphetamine ER Oral Suspension	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	20 mg
Amphetamine Salt Content Equivalent in Mixed Amphetamine Product	4 mg	8 mg	12 mg	16 mg	24 mg	32 mg

1.3 Recommendations

1.3.1 Approvability

From a Pharm/Tox point of view this application is considered approvable pending labeling agreement.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

General comments:

The maximum recommended daily dose for this drug is 20 mg amphetamine base. This is essentially equivalent to (i.e., only 6% higher than) the maximum daily dose of 30 mg amphetamine salt (equivalent to18.8 mg amphetamine base) that is used for the RLD. Therefore, to avoid confusion, we will not adjust the safety margins in the label for this product for the small difference in MRHD compared with the RLD.

Note: In this review, safety margins for the reproductive and fertility studies were calculated based on the conversion factors for an adolescent and those for the carcinogenicity studies were calculated for a child.

For Section 8.1 the sponsor calculated the safety margins for a dose of 20 mg/day using (b) (4), the animal data in that section are based on the salt. Therefore the safety margins calculated by the sponsor (b) (4)) are not accurate, and we propose that these margins should be the same as those described in the RLD label (i.e., 1.5 and 8). However, we note a minor error in the RLD labeling: the safety margins were described as based on the child, whereas the calculated margins

are clearly and appropriately based on adolescents. Therefore, the term “child” should be replaced by “adolescent.”

Labeling proposed by this reviewer for non-clinical sections:

8.1 Pregnancy

Risk Summary

There are limited published data on the use of amphetamines in pregnant women (b) (4) (b) (4) 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, can cause vasoconstriction (b) (4) . 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.

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 8 times, respectively, the MRHD of 20 mg/day (as base), on a mg/m^2 body surface area basis for an adolescent. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times the MRHD) 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.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenicity was found in studies in which d,l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 20 mg/day (as base), on a mg/m^2 body surface area basis for a child.

Mutagenesis

Amphetamine, in the enantiomer ratio present in DYANAVEL XR (d- to l- ratio of (b) (4):1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the E. coli component of the Ames test *in vitro*. d, l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Impairment of Fertility

Amphetamine, in the enantiomer ratio present in DYANAVEL XR (d- to l- ratio of approximately (b) (4):1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day [approximately 5 times the maximum recommended human dose of 20mg/day (as base), on a mg/m^2 body surface area basis for an adolescent].

13.2 Animal Toxicology and/or Pharmacology

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

Note 1: For Adderall XR, section 13.2 of the label has a statement about the neurotoxic effect of amphetamine (see above). This statement appears to have been added based on publicly available literature data about this well-known effect of amphetamines. In addition, this statement is also found in other amphetamine products (i.e. Vyvanse), The reviewer believes that such a statement should be added to the label of this product, even though it is not found in the label of the RLD, for consistency.

Note 2: No juvenile animal studies were conducted with Adderall immediate release (IR) tablets. Since this submission is a 505(b)(2) application, we have been advised that we cannot ask for a juvenile animal study for this product, since the RLD (Adderall IR) did not have a study. It should be mentioned that the Adderall XR label has data from such a study.

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/s/

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09/25/2015

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