NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	505(b)(2) NDA
Application Number(s)	210526
Priority or Standard	Standard
Submit Date(s)	September 25, 2017
Received Date(s)	September 25, 2017
PDUFA Goal Date	July 25, 2018
Division/Office	Division of Psychiatry Products/Office of Drug Evaluation I
Review Completion Date	July 23, 2018
Established Name	Amphetamine Extended-Release Tablets
(Proposed) Trade Name	Dyanavel XR
Pharmacologic Class	CNS Stimulant
Code name	N06BA02
Applicant	Tris Pharma, Inc.
Formulation(s)	Extended-Release Tablets
Dosing Regimen	Starting dose of 2.5 mg or 5 mg once daily in the morning. 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. A daily dose above 20 mg is not recommended.
Applicant Proposed Indication(s)/Population(s)	Children age 6 years and older with Attention Deficit Hyperactivity Disorder (ADHD)
Recommendation on Regulatory Action	Complete Response.
Recommended Indication(s)/Population(s) (if applicable)	As proposed above.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSIS=Office of Study Integrity and Surveillance
OSE= Office of Surveillance and Epidemiology
DPV1= Division of Pharmacovigilance 1
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

This glossary should include all acronyms used in your review. The sample list below includes commonly used acronyms and may be used as a starting point.

AC	advisory committee
ADHD	attention deficit/hyperactivity disorder
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
ER	extended release
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

ITT	intent to treat
LD	listed drug
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OS	oral suspension
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

Tris Pharma is seeking approval of amphetamine extended-release tablets (Dyanavel XR tablet) for the treatment of Attention Deficit Hyperactive Disorder (ADHD) in patients aged 6 years and older, with the intention to demonstrate similar exposures (i.e., meeting bioequivalence criteria) between the new extended-release tablets and Dyavavel XR oral suspension, a marketed product.

Overall, the review team recommends a complete response action due to an outstanding compliance issue at the product manufacturing site. If the product can be considered for approval after the compliance issue at the manufacturing site is resolved, additional clinical development program in pediatric patients 4-5 years of age will be needed as part of post-marketing requirement (PMR) studies. This program should include a PK trial, a randomized, double-blind, placebo-controlled safety and efficacy trial, and an open-label safety trial in 4- to 5-year-old children. (b) (4)

This unireview document includes primary reviews from pharmacology/toxicology, medical, and clinical pharmacology. The primary reviews from other disciplines were recorded separately (Table 1).

Table 1: Other Primary Reviews for NDA 210526

Review Discipline	Finalized Dates
OPQ Review	6/15/2018
OPDP Review	6/28/2018
DMPP Review	6/28/2018
CSS Review	6/20/2018
DMEPA Review	7/3/2018

The executive summary summarizes the findings from all review disciplines. The key findings are listed below:

- Per OPQ, the manufacturing facility has outstanding compliance issues. The facility was inspected in 2017 and was classified OAI (official action indicated). In March 2018, the FDA issued an additional warning letter (CMS#534537). As of now, the identified deficiencies have not been resolved. Besides the issues with manufacturing site, no additional issue has been identified. The manufacturing process description and in-process control were found acceptable. The product release specifications include typical test for an extended release tablet. Data support the proposed (b) (4)-month drug product expiry period and the functional score of 5 mg dosage strength. The biopharmaceutical team found that the proposed dissolution method and acceptance criteria acceptable. Forty percent alcohol induces dose dumping based on dissolution

test. In addition, OPQ recommends that amphetamine aspartate and dextroamphetamine sulfate are mentioned in Section 11 of the package insert.

- Per OCP, the efficacy and safety profiles of the Dyanavel XR tablet in general population are expected to be similar to those for the Dyanavel XR oral suspension, the marketed product, because the average exposures of the active moieties have been demonstrated to be similar (within bioequivalence limits for Cmax, AUCinf, AUC0-5, and AUC5-t). The XR tablet can be swallowed whole or chewed, once daily, without regard to food.
- Per DPP, the safety data derived from the studies in this development program revealed no new, clinically significant safety signals that require further study or a major labeling revision.
- Per pharmacology/toxicology team, the product is approvable. However, there is a concern of using sodium polystyrene sulfonate (SPS) and mannitol together as excipients for a product intended for chronic administration and especially in patients at risk for constipation/fecal impaction, in children or elderly, in populations susceptible to bowel disease, because both excipients are osmotic laxatives. Therefore, the team recommends enhanced pharmacovigilance surveillance strategies associated with the concomitant use of SPS and mannitol in the proposed drug product formulation.

In addition, DMEPA indicated that the proprietary name and established name are acceptable. CSS agreed that the new formulation is a schedule II product. CSS, DMEPA, DMPP, and OPDP provided relevant recommendations to the label.

1.1. Product Introduction

Amphetamine extended-release (ER) tablets, with the proposed tradename of Dyanavel XR, have been developed by Tris Pharma for the treatment of children age 6 years and older with Attention Deficit/Hyperactivity Disorder (ADHD). Amphetamine is a non-catecholamine sympathomimetic amine with central nervous system (CNS) stimulant activity. Amphetamine is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and to increase the release of monoamine into the synapse. However, the mechanism of therapeutic action in treating patients with ADHD is unknown. Amphetamine exists as two optical isomers: dextroamphetamine (d) and levoamphetamine (l). The d-enantiomer is approximately 4 times as potent as the l-enantiomer in releasing dopamine in the brain. Amphetamine ER tablets have a 3.2:1 ratio of the d- and l-isomers.

Several amphetamine salt products have been approved and used in the treatment of patients with ADHD for over five decades. Tris Pharma had also developed amphetamine ER oral suspension (OS) for the treatment of children age 6 years and older with ADHD. This product, with the tradename Dyanavel XR, was approved on October 19, 2015, under NDA 208147. The amphetamine ER tablet was developed as a line extension and alternate dosage form for Dyanavel XR oral suspension. This application was submitted as a 505(b)(2) NDA with Dyanavel OS as the listed drug (LD).

The amphetamine ER tablets may be taken with or without food and may be swallowed whole

or chewed. The recommended starting dose is 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 four to seven days until an optimal response is obtained. A daily dose above 20 mg is not recommended. Patients taking Dyanavel XR OS may be switched to Dyanavel XR tablets at an equivalent daily dose.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The efficacy of amphetamine ER tablets relies on the established efficacy for the LD, Dyanavel XR OS, in the treatment of children age 6 years and older with ADHD and the scientific bridge to the LD demonstrated in Study 2016-4171, a single dose bioequivalence study. Other clinical studies of efficacy were neither conducted nor necessary.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment
This product will provide a new dosage form of a safe and effective treatment for patients with ADHD. The benefits of having another efficacious treatment option that can be taken once daily and may be either chewed or swallowed whole outweigh the established risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Attention Deficit/Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder of childhood, with a lifetime prevalence in the pediatric population of about 11%. It typically presents in early school years and is characterized by difficulty paying attention, hyperactivity, and impulsive behavior. These symptoms cause significant impairment in academic and social functioning during critical years of development unless treated.	ADHD is a very prevalent condition in children and adolescents. ADHD symptoms can substantially compromise childhood academic and social development without treatment.
Current Treatment Options	There are several products that have demonstrated safety and effectiveness in the treatment of ADHD over the past several decades. Most of these products contain amphetamine salts or methylphenidate. More recently approved products contain atomoxetine or guanfacine. These products display some differences in time to therapeutic onset and/or duration of action because of different pharmacokinetic profiles. Thus, some require more than one dose per day because of a short duration of action. Also, products have been developed as different formulations (tablets, capsules, or oral suspensions) which allow for different modes of oral administration (sprinkling on food, chewing, swallowing whole pills).	There are several approved products for the treatment of ADHD. These are available as solid or liquid formulations, have different dosing regimens, and allow for different methods of oral administration to accommodate the needs of the individual pediatric patient.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Amphetamine ER tablets were developed to either be chewed or swallowed whole and provide clinical efficacy from one hour to 13 hours after dosing.	Amphetamine ER tablets allow flexibility in administration (chewing or swallowing whole) and the convenience of once daily dosing.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

					Section where discussed, if applicable
X	The patient experience data that was submitted as part of the application, include:				
	□	Clinical outcome assessment (COA) data, such as			
			□	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			

	X	Other: (Please specify) Palatability Questionnaire.	Report for Study 2016-4171: Sections 9.5.5, 9.7.1.1, 11.4.4.2, and 14.3.6.
□	Patient experience data that was not submitted in the application, but was considered in this review. None.		

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Attention Deficit/Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder of childhood, with a lifetime prevalence in the pediatric population of about 11%. It typically presents in early school years and is characterized by difficulty paying attention, hyperactivity, and impulsive behavior. The clinical presentation may be primarily inattentive, hyperactive/ impulsive, or combined. These symptoms cause significant impairment in academic and social functioning during critical years of development unless treated. Although symptoms often attenuate during adolescence and early adulthood, some patients continue to experience the full disorder or some symptoms of the disorder into mid-adulthood, when symptoms can cause substantial impairment in occupational functioning. Pharmacologic treatments for ADHD have had a significant impact on the well-being and functioning of patients with this disorder.

2.2. Analysis of Current Treatment Options

There are several products that have demonstrated safety and effectiveness in the treatment of ADHD over the past several decades. Most of these products contain amphetamine salts or methylphenidate. More recently approved products contain atomoxetine or guanfacine. These products display some differences in time to therapeutic onset and/or duration of action because of different pharmacokinetic profiles. Thus, some require more than one dose per day because of a short duration of action. Also, products have been developed as different formulations (tablets, capsules, or oral suspensions) which allow for different modes of oral administration (sprinkling on food, chewing, swallowing whole pills) to meet the needs of individual patients.

Amphetamine ER tablets were developed to either be chewed or swallowed whole while providing clinical efficacy from one hour to 13 hours after dosing. Thus, this tablet formulation allows for flexibility in administration (chewing or swallowing whole) and the convenience of once daily dosing.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Amphetamine salt products have been used in the U.S. to treat ADHD for over five decades and have a well-established safety profile. There are several known risks of this drug class, including the potential for abuse and dependence, linear growth suppression, nausea, reduced appetite and weight loss, elevated heart rate and blood pressure, insomnia, emergence of psychotic or

manic symptoms, peripheral vasculopathy (such as Raynaud's phenomenon), hypertensive crisis when used with monoamine oxidase inhibitors, and serotonin syndrome when used with serotonergic drugs. These risks are currently labeled for the LD (Dyanavel XR oral suspension), which will share labeling with this product.

3.2. Summary of Presubmission/Submission Regulatory Activity

A face-to-face pre-IND meeting was held on March 3, 2016, during which the Applicant presented their plan to submit a 505(b)(2) NDA for a chewable, (b) (4) tablet formulation of amphetamine using Dyanavel XR OS, also developed by the Applicant, as the LD. The tablet would be bridged to Dyanavel XR OS with a single-dose bioequivalence (BE) study in adults. The meeting discussion included the following topics:

- acceptability of Dyanavel XR OS as the LD.
- acceptability of the BE study design.
- the requirement to demonstrate BE on selected partial AUCs.
- if BE to Dyanavel XR OS is demonstrated, the Division agreed that clinical studies in patients with ADHD age 6 years and older would not be necessary. Also, pediatric studies in children ages 4 and 5 years conducted with Dyanavel XR OS would suffice for meeting PREA requirements for this product in this age range.
- no requirement for a steady state pharmacokinetic study. But, the Division stated that submission of simulated PK profiles with multiple dosing would be helpful to support their extended-release claim.
- proposed Dosing and Administration labeling language to permit chewing (b) (4) or swallowing whole would be a matter for review.
- unacceptability of the proposed established name of "Amphetamine Extended-Release (b) (4) Tablets."
- the need to develop a 2.5 mg strength for consistency with Dyanavel XR recommendations for initiating treatment.

An application for IND 129044 was submitted on November 1, 2016, and included the protocol for the BE study (Study 2016-4171) as well as Abbreviated Study Reports for two prototype studies (Studies 2016-4009 and 2016-4124). The BE study was allowed to proceed. The May Proceed letter, dated December 22, 2016, requested that the Sponsor conduct an *in vitro* alcohol dissolution study using 40% alcohol.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Study Integrity and Surveillance (OSIS)

An OSIS report was completed on February 20, 2018, by Shila S. Nkah, of the Division of New Drug Bioequivalence Evaluation. Dr. Nkah recommended that the submitted data be accepted without an on-site inspection because both clinical and analytical facilities of (b) (4) were recently inspected, with inspectional outcomes of No Action Indicated.

4.2. Product Quality

The drug product is an extended release oral tablet containing amphetamine in a 3.2:1 enantiomeric ratio. It is designed to be administered in the morning, either chewed or swallowed whole. Marketing of four dosage strengths is proposed (5 mg, 10 mg, 15 mg, and 20 mg). The 5 mg strength has a functional score to give a 2.5 mg dose. Amphetamine is present as dextroamphetamine sulfate, amphetamine sulfate, and amphetamine (b) (4) polystyrene sulfonate (b) (4) This product shares a general design, manufacturing line and most of the major excipients with the Dyanavel XR Oral Suspension reference product. However, the amount of IR and ER components are very different. The oral suspension has (b) (4) whereas this product has a (b) (4) ratio. Despite the proposed product having (b) (4) extended release character, it appears to have the same PK as the reference product of similar formulation with (b) (4) extended release components.

The formulation contains amphetamine (b) (4) sodium polystyrene sulfonate (b) (4) The excipients were found acceptable (generally USP/NF). The product will be packaged in 30-count 60 ml white HDPE bottles with 2g desiccant canister with induction liner and PDT closure.

Long term stability data through 12 months support the proposed (b) (4)-month drug product expiry period. Data, including dissolution data, supported the functional score on the 5 mg dosage strength. A three-stage dissolution method was developed by the applicant and accepted by the biopharmaceutics review team. They also found that the in vitro studies with 40% alcohol induced dose dumping and that the results support the revised label language. The extended release claim was found to be acceptable based on the superimposable PK profiles compared to the reference Dyanavel XR Oral Suspension product. Dissolution data of drug product milled for 5 seconds in a coffee grinder showed that its dissolution characteristics were not immediately impacted by mechanical stress (e.g. chewing). The to-be-marketed formulation of amphetamine was used in the pivotal BA study so no bridging studies were required.

The manufacturing and testing facilities were found to be acceptable by OPQ except for the Tris Pharma drug product manufacturing site for which a withhold recommendation was made due to its current OAI status and March 2018 Warning Letter. Therefore, OPQ has recommended a CR action until the compliance issues at the Tris Pharma site are resolved.

4.3. Clinical Microbiology

There are no clinically important microbiological issues.

4.4. Devices and Companion Diagnostic Issues

There are no clinically important device or companion diagnostic issues.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

NDA 210526 is a 505(b)(2) application filed by Tris Pharma Inc., towards seeking approval for their new amphetamine formulation under the tradename Dyanavel™ XR (amphetamine) Extended Release *tablets* (5, 10, 15, and 20 mg). The active ingredient in this new formulation contains three mixed amphetamine salts (MAS), namely, amphetamine sulfate, dextroamphetamine sulfate, and amphetamine aspartate (b) (4). The proposed indication is for treatment in patients ≥ 6 years old diagnosed with Attention Deficit Hyperactivity Disorder (ADHD). Dyanavel® XR (amphetamine) Extended Release tablets is similar with another of the applicant's drug product, namely, Dyanavel® XR (Extended Release *oral suspension*) that was approved by the FDA on October 19, 2015.

From a nonclinical perspective, Dyanavel™ XR appears to be reasonably safe for approval.

No nonclinical studies have been submitted with this application.

Safety information for nonclinical studies is based on findings from published literature (for excipients), information under the RLDs - Dyanavel® XR Extended Release oral suspension (under NDA 208147 owned by the applicant), and Adderall® IR Immediate Release tablets (under NDA 011522) owned by Teva Womens Health Inc.),

There are no safety concerns with the active ingredient.

There are no new novel excipients although two issues involving excipients were identified.

One excipient, namely, sodium polystyrene sulfonate (SPS) is present in amounts higher than FDA-approved products for the same oral route of administration as listed in FDA's IID (as

updated on June 8, 2018 per reviewer evaluation). However, compared to the applicant's approved oral suspension drug product formulation (Dyanavel® XR Extended Release under NDA 208147) which contains (b) (4) mg of SPS (b) (4)), the current extended release *tablet* formulation contains (b) (4) mg of SPS (b) (4) (base) tablets). Given that the difference in amounts between the two formulations is minimal, and that SPS is a high molecular weight polymer with negligible bioavailability (resulting from low systemic absorption from the gastrointestinal tract), the use of SPS in the proposed amounts in the applicant's tablet formulation is considered reasonably safe for approval.

An additional excipient issue is the *concomitant* use of SPS and mannitol in this drug product formulation. Although the amount of mannitol in the applicant's drug product ((b) (4) mg in a (b) (4) (base) tablet) is less than in other FDA-approved products for the same oral route of administration, the *concomitant* use of SPS with sorbitol (which is another sugar comparable to mannitol) is known to result in adverse gastrointestinal effects. This is based on clinical case reports, reports in the Adverse Event Reporting System (AERS), and published literature in animal studies (Ayub et al, 2015; Lillemoe et al, 1987; McGowan et al, 2009; Romolo and Williams, 1979; and Thomas et al, 2009) and epidemiology studies, FDA safety reviews of other drug products (Adzenys ER™ under NDA 204325; (b) (4), and a previous clinical safety evaluation conducted by the Division of Cardiovascular and Renal Products (see TSI # 518 dated July 25, 2010).

Given that sorbitol and mannitol are both naturally occurring sugars with similar chemical structure and physiological behavior in-vivo (both are osmotic laxatives), safety evaluation on the concomitant use of SPS and mannitol is considered relevant for the applicant's drug product formulation. The mode of action is uncertain, and the pathology includes detection of SPS crystals in ulcerated tissue (animal studies).

Based on individual excipients, the lowest reported dose of (b) (4) g/day of SPS associated with gastrointestinal necrosis in adults/children, and a mannitol dose of (b) (4) g/day ((b) (4) mL of a (b) (4)% solution), the margins of safety based on the highest strength tablet (20 mg/day) of the applicant's tablet given to a 20-kg child was calculated to be (b) (4) times for SPS, and (b) (4) times for mannitol. Although reasonable and adequate safety margins exist for individual excipients, the data is insufficient to definitively conclude on the safe *concomitant* use of low dose SPS and mannitol over chronic administration dosing regimens, *particularly* in patients at risk for constipation/fecal impaction, in children or elderly, or in populations susceptible to bowel disease. Following discussion with the clinical team, enhanced pharmacovigilance strategies associated with the concomitant use of SPS and mannitol in the proposed drug product formulation have been included (please see Section 8.2.5).

All other listed excipients are lower than that used in other FDA-approved products and/or lower than the maximum potency per unit dose for the same oral route of administration as listed in FDA's IID (as updated on June 8, 2018 per reviewer evaluation).

The new proposed draft label (titled "Draft Package Insert Text" in Module 1.14.1.3) from the applicant is a joint Prescribing Information label with the applicant's approved drug product Dyanavel® XR (amphetamine) extended-release oral suspension (NDA 208147). Labeling changes include revisions to dose multiples based on the maximum recommended human dose of 20 mg/day for the applicant's product for the most sensitive and appropriate population (as opposed to (b) (4) mg/day based on Dyanavel® XR under NDA 208147 – see Dr.Elayan's review in DARRTS dated October 25, 2015), comparisons of amphetamine (base to base) strengths between the dose stated in the label and the animal toxicology studies, and formatting consistency (where applicable) based on the most recently approved MAS label (Adzenys ER under NDA 204325).

Given the long history of clinical use of the active ingredient, safety information available from the RLD, Adderall® IR Immediate Release tablets (under NDA 011522 owned by Teva Womens Health Inc.), and the recent approval of the RLD Dyanavel® XR Extended Release oral suspension (under NDA 208147 owned by the applicant Tris Pharma, Inc.), the lack of novel excipients, and the use of excipients in reasonable amounts (compared to FDA's IID and/or use in other FDA approved drug products), Dyanavel-XR™ appears to be reasonably safe for approval from a nonclinical perspective.

Please see Section 8.2.5 for enhanced pharmacovigilance strategies on the concomitant use of SPS and mannitol in Dyanavel-XR™.

5.2. Referenced NDAs, BLAs, DMFs

IND 129044
Product Name: TRI108
Applicant:Tris Pharma, Inc
Indication: ADHD
Status: Active

NDA 011522
Product Name: Adderall® IR Immediate Release tablets
Applicant: Teva Womens Health Inc
Indication: Obesity
Status: Approved on January 19, 1960

NDA 208147
Product Name: Dyanavel® XR Extended Release oral suspension
Applicant: Tris Pharma, Inc
Indication: ADHD
Status: Approved on October 19, 2015

5.3. Pharmacology

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

5.4. ADME/PK

This is 505(b)(2) application. See label for details.

5.5. Toxicology

5.5.1. General Toxicology

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.

5.5.2. Genetic Toxicology

Amphetamine, in the enantiomer ratio (d- to l- ratio of 3:1), 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.

5.5.3. Carcinogenicity

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 4, 2, and 1 (equivalent) times, respectively, the maximum recommended human dose of 20 mg/day (as base) given to children, on a mg/m2 basis.

5.5.4. Reproductive and Developmental Toxicology

Amphetamine, (d- to l- ratio of approximately 3 to 1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day [approximately 8 times the

maximum recommended human dose of 20 mg/day (as base) given to adolescents on a mg/m2 basis].
Amphetamine (d- to l- enantiomer ratio of 3:1) had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 2 and 12 times, respectively, the MRHD of 20 mg/day (as base) given to adolescents, on a mg/m2 basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 10 times the MRHD given to adolescents on a mg/m2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A 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.

Juvenile animal studies remain unincluded in the current proposed label as addressed in Dr.Elayan's review (under NDA 204325).

5.5.5. Other Toxicology Studies

Excipients:
There are no new novel excipients although two issues involving excipients were identified.

Except SPS, all listed excipients are lower than that used in other FDA-approved products and/or lower than the maximum potency per unit dose for the same oral route of administration as listed in FDA's IID (as updated on June 8, 2018 per reviewer evaluation).

SPS is present in amounts ((b) (4) mg (b) (4)) higher than FDA-approved products for the same oral route of administration as listed in FDA's IID (as updated on June 8, 2018 per reviewer evaluation). The maximum amount of SPS noted in FDA's IID at this time is 18 mg. Compared to the applicant's approved *oral suspension* drug product formulation (Dyanavel® XR Extended Release under NDA 208147) which contains (b) (4) **mg** of SPS (b) (4) of drug product oral suspension, the current extended release *tablet* formulation contains (b) (4) of SPS (b) (4) (base) tablets]. Given that the *difference in amounts between the two formulations is minimal*, and that SPS is a high molecular weight polymer with negligible bioavailability (resulting from *low systemic absorption from the gastrointestinal tract*), the use of SPS in the applicant's tablet formulation is considered reasonably safe for approval.

Impurities:

No nonclinical studies on impurities were conducted.

One degradant impurity of the drug substance process, namely (b) (4) was identified. The proposed specification limit in the drug product was set by the applicant at NMT (b) (4)% (or (b) (4) µg which is at the acceptable threshold for degradation products (per Q3B(R2) at the MRHD of 20 mg/day). The limit of this impurity for the drug substance remains 0.25% (same as the USP monograph for dexamphetamine sulfate). At release, none of the batches contained any detectable levels of benzaldehyde impurities.

For a complete review, refer to the Quality review for this NDA.

Labeling:

Sections 8, 12.1, 12.2, and 13 (relevant to nonclinical information) have been excerpted from the applicant's submission (word file titled "Draft Package Insert Text" dated 09/25/2017 under Module 1.14.1.3). Proposed changes are italicized in blue below. The proposed changes shown below have been included into the most updated version of the label [version in Sharepoint titled "PI_draft (03-21-18)"] and may not reflect the finalized label (pending) accurately. It should be noted that the following label changes documented in this review are work-in-progress.

The new proposed draft label (titled "Draft Package Insert Text" in Module 1.14.1.3) from the applicant is a joint Prescribing Information label with the applicant's approved drug product Dyanavel® XR (amphetamine) extended-release oral suspension (NDA 208147).

Text in blue highlighting changes include revisions to dose multiples based on the maximum recommended human dose of 20 mg/day for the applicant's product for the most sensitive and appropriate population (as opposed to (b) (4) mg/day based on Dyanavel® XR (amphetamine) extended-release oral suspension under NDA 208147 – Dr.Elayan's review in DARRTS dated October 25, 2015), comparisons of amphetamine (base to base) strengths between the dose stated in the label and the animal toxicology studies, and formatting consistency (where applicable) based on the most recently approved MAS label (Adzenys ER under NDA 204325).

For reference, safety margins for the reproductive and fertility studies were calculated based on the conversion factors for an adolescent, and those for carcinogenicity were calculated for a child. Juvenile animal studies remain unincluded in the current proposed label as addressed in Dr.Elayan's review (under NDA 204325).

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DYANAVEL XR during pregnancy. Healthcare providers are encouraged to register patients by calling t6he National Pregnancy Registry for Psychostimulants at 1-866-961-2388.

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 (b) (4) times, respectively, the maximum recommended human dose (MRHD) of 20 mg/day (as base) given to adolescents, on a mg/m^2 basis. However, long-term neurochemical and behavioral effects have been reported in published animal developmental studies using clinically relevant doses of amphetamine (b) (4) [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.

Data

Animal Data

Amphetamine (d- to l- enantiomer ratio of 3:1) had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately (b) (4) times, respectively, the MRHD of 20 mg/day (as base) given to adolescents, on a mg/m^2 (b) (4) basis (b) (4). 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~~)~~ given to 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.

8.4 Pediatric Use

Safety and effectiveness have been established in pediatric patients with ADHD ages 6-17 years [see *Adverse Reactions (6.1), Clinical Pharmacology (12),* and *Clinical Studies (14)*]. Safety and efficacy in pediatric patients younger than 6 years with ADHD have not been established.

Long-Term Growth Suppression

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

8.5 Geriatric Use

AMPHETAMINE XR(b) (4) has not been studied in the geriatric population.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Amphetamines 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.

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 (b) (4) (equivalent) times, respectively, the

maximum recommended human dose of 20 mg/day (as base) given to children, on a mg/m^2 (b) (4) (b) (4) basis (b) (4).

Mutagenesis
Amphetamine, in the enantiomer ratio (b) (4) (*d*- to *l*- ratio of 3:1), 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, (b) (4) ~~(~~*d*- to *l*- ratio of approximately 3 to 1~~)~~, did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day [approximately (b) (4) times the maximum recommended human dose of 20 mg/day (as base) given to adolescents on a mg/m^2 (b) basis (b) (4)].

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

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

X	X

Primary Reviewer Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

Tris Pharma is seeking approval of amphetamine (AMP) Extended-Release Tablets (proposed brand name Dyanavel XR tablet) for the treatment of Attention Deficit Hyperactive Disorder (ADHD) in patients aged 6 years and older, via 505b(2) approach. The listed drug for this application is Dyanavel XR extended-release oral suspension, NDA 208,147, also owned by Tris Pharma.

The drug product is an extended-release tablet formulation of AMP. (b) (4) . The tablets contain (b) (4) resulting in a formulation with immediate and extended-release components containing a 3.2:1 ratio of *d*- to *l*-AMP. The ratio for the immediate-release component and the extended-release component is (b) (4)

In this submission, one pivotal relative bioavailability study (Study 2016-4171) was conducted in healthy adult volunteers. The effect of food or chewing on the PK of the commercial formulation was also evaluated. In addition, two pilot studies with prototype formulations were conducted.

In this review, the term of "Dyanavel XR tablet" is used interchangeably with "Dyanavel XR chewable tablet", and "AMP ER tablet".

6.1.1 Recommendations

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval of Dyanavel XR tablet. Per the recommendation (Appendix 4.1) from the Office of Study Integrity and Surveillance (OSIS), the data from the pivotal relative bioavailability study is considered acceptable. No inspection of the clinical or analytical site for the pivotal study 2016-4171 was deemed necessary, because those sites were recently inspected and no issues were identified. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP?	Comment
Overall	☒ Yes ☐ No ☐ NA	Pending labeling agreements with the sponsor
Evidence of effectiveness	☒ Yes ☐ No ☐ NA	Clinical efficacy and safety information is extended from the listed drug (LD) based on PK similarity of amphetamine.

Proposed dose for general patients	☒ Yes ☐ No ☐ NA	Same as for the LD
Labeling	☐ Yes ☒ No ☐ NA	Pending satisfactory agreement with the sponsor

6.1.2 Post-Marketing Requirements and Commitments

PMC* or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☐ PMC ☒ PMR	What are the PK properties of Dyanavel XR chewable tablet in male or female children (4 to 5 years of age) with ADHD?	Concentration time profile of amphetamine determines the onset and duration of the clinical response. It is valuable to assess the PK profiles in patients 4-5 years old with ADHD and ensure its similarity to that in older patients. This information can help inform dose selection for the clinical efficacy and safety trial.	Study population: patients 4-5 years old with ADHD Study design: single dose, open label Sample size: (b) (4) Dose(s): a relevant dose Endpoints: AUC, C_{max} Submit protocol by: June, 2019 Start study by: Dec, 2019

Note: * The sponsor is conducting clinical trials in pediatric patients 4-5 years of age with Dyanavel XR oral suspension, the listed product, to fulfil the (b) (4) PREA requirement. The same PMR trials will be required for Dyanavel XR tablet. Dyanavel XR tablet demonstrates similar exposure to Dyanavel XR oral suspension. (b) (4)

6.2. Summary of Clinical Pharmacology Assessment

- An adequate link has been established between Dyanavel XR tablet and Dyanavel ER suspension (LD) through the relative bioavailability study.
- The average exposure of *d*-AMP and *l*-AMP has been demonstrated to be similar (within bioequivalence limits for C_{max}, AUC_{inf}, AUC_{0-5}, and AUC_{5-t}). Hence, the efficacy and safety profiles of the Dyanavel XR tablet in general population are expected to be similar to those for the LD.

- The pharmacokinetic profile of Dyanavel XR tablet is consistent with the expectation for an extended-release formulation and is sufficient to support a once daily dosing regimen.
- Dyanavel XR tablet can be administered without regard to food.
- Dayanavel XR tablet can be swallowed whole or chewed.

6.2.1. Pharmacology and Clinical Pharmacokinetics

The only pivotal study submitted in this application is a relative bioavailability study which was to demonstrate the exposure similarity between Dyanavel XR tablet and Dyanavel XR oral suspension. The study results showed that the average exposures of *d*-AMP and *l*-AMP were similar (within bioequivalence limits for C_{max}, AUC_{inf}, AUC_{0-5}, and AUC_{5-t}) between the two formulations. The average pharmacokinetic profiles from the two formulations are almost superimposable. Hence, similar pharmacodynamic profiles (i.e., efficacy and safety) are expected between the two Dyanavel XR formulations. ADME properties of AMP after administration of Dyanavel XR tablet are expected to be the same as those after administration of Dyanavel XR oral suspension.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Dosing recommendation will be the same as the listed drug, Dyanavel XR oral suspension. The recommended starting dose is 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 four to seven days until an optimal response is obtained. A daily dose above 20 mg is not recommended. Patients taking Dyanavel XR oral suspension may be switched to Dyanavel XR tablets at an equivalent daily dose.

Therapeutic Individualization

Dyanavel XR tablet can be administered without regards to food, and may be swallowed whole or chewed. Dosing instructions are expected to the same as LD based on intrinsic factors or extrinsic factors such as drug interactions. The most recent label approved for Dyanavel XR oral suspension can be found here.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Refer to section 6.2.1.

6.3.2. Clinical Pharmacology Questions

Are similar average efficacy and safety profiles expected for Dyanavel XR chewable tablet and oral suspension?
Yes. Similar average efficacy and safety profiles are expected for Dyanavel XR chewable tablet and Dyanavel XR oral suspension.

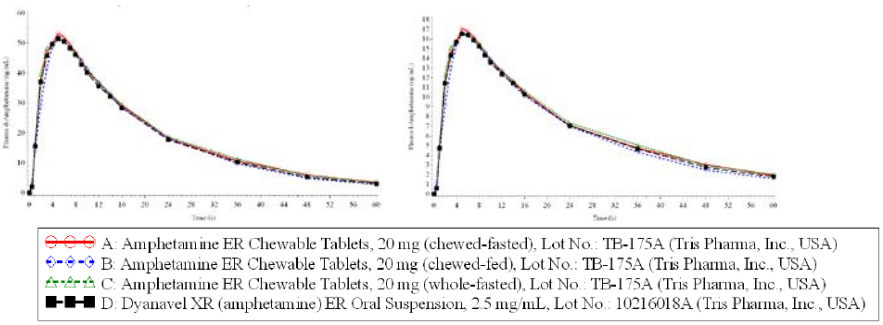
The LD, Dyanavel XR oral suspension, was shown to be safe and efficacious in the treatment of ADHD in patients 6 years and older. For Dyanavel XR chewable tablet, there are no clinical trials conducted to evaluate its efficacy and safety. However, the efficacy and safety data of Dyanavel XR chewable tablet can be extended from its LD, Dyanavel XR oral suspension, based on the exposure similarity (i.e., C_{max}, AUC_{0-5}, AUC_{5-t}, and $AUCi_{nf}$) demonstrated for *d*- and *l*-AMP between the two formulations (Table 1 and Figure 1). The mean pharmacokinetic profiles of *d*- and *l*-AMP are almost superimposable between the two formulations (Figure 1).

Table 1: Plasma *d*- and *l*-AMP PK Parameters After Dyanavel Administration as Chewable Tablet or Suspension under Fasted Conditions

Parameters	Chewable Tablet (T, n=31)	Suspension (R, n=32)	Geomean ratio (T/R, 90% CI, n=31)
d-AMP			
C_{max} (ng/mL)	54.7 (17)	53.1 (17)	102.5 (99.9, 105.1)
AUC_{0-5} (hr*ng/mL)	173 (24)	170 (26)	100.9 (95.4, 106.7)
AUC_{5-t}(hr*ng/mL)	959 (24)	921 (24)	103.2 (98.99, 107.6)
AUC_{inf} (hr*ng/mL)	1206 (25)	1156 (24)	103.5 (99.6, 107.6)
l-AMP			
C_{max} (ng/mL)	17.5 (18)	17.0 (18)	102.1 (99.5, 104.8)
AUC_{0-5} (hr*ng/mL)	54 (25)	54 (27)	100.7 (95.2, 106.5)
AUC_{5-t}(hr*ng/mL)	365 (26)	354(27)	102.4 (97.9, 107.1)
AUC_{inf} (hr*ng/mL)	473 (28)	457 (31)	103.2 (98.4, 108.1)

Data are presented as arithmetic mean (%CV); Tmax: median (range); Source: Tables 11-2, 11-3, 14-2, and 14-5 of CSR

Figure 1: Mean Plasma Concentration vs. Time Profiles: *d*-AMP (right); *l*-AMP (right)



-Source: Figures 11-1 and 11-3 of CSR

What are the PK properties of d- and l-AMP after single dose administration of Dyanavel XR chewable tablet?

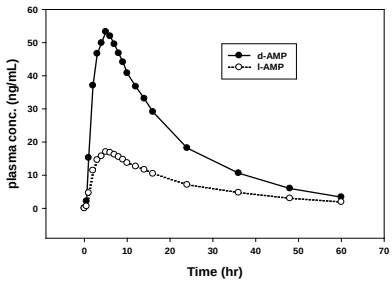
Following a single dose administration (chewed) of 20mg Dyanavel XR chewable tablet to healthy volunteers under fasting conditions, both enantiomers of AMP reached C_{max} in about 5 hours post dose (Table 2, Figure 2), with an estimated half life of about 13.9 hours and 17.8 hours for *d*- and *l*-AMP, respectively. With a once daily dosing regimen for Dyanavel XR chewable tablet, about 40% and 60% accumulation of *d*-AMP and *l*-AMP is expected after multiple dosing. The overall exposure to *d*-AMP was about 2.5-fold of that to *l*-AMP after a single dose administration of 20mg Dyanavel XR chewable tablet.

Table 2: Plasma *d*- and *l*-AMP PK Parameters after A Single Dose Administration of 20mg Dyanavel XR Tablet Under Fasted Conditions, Chewed

Parameters	*d*-AMP	*l*-AMP
C_{max} (ng/mL)	54.7 (17)	17.5 (18)
T_{max} (hr)	5.0 (3.0-7.0)	5.0 (3.0-7.0)
AUC_{inf} (hr*ng/mL)	1206 (25)	473 (28)
$T_{1/2}$ (hr)	13.9 (22)	17.8 (25)

Data are presented as arithmetic mean (%CV); Tmax: median (range); Source: Tables 11-2, 11-3, 14-2 and 14-5 of CSR

Figure 2: Mean Plasma Concentration vs. Time Profiles after A Single Dose Administration of 20mg Dyanavel XR Tablet Under Fasted Conditions, Chewed



Does food affect the bioavailability of Dyanavel XR chewable tablet?

Food has no meaningful effect on the bioavailability of either *d*- or *l*-AMP (Table 3). The magnitude of change in exposure is expected to have a minimal effect on the efficacy or safety profile of the product. Dyanavel XR chewable tablet can be administered without regard to food.

Table 3: Plasma *d*-and *l*-AMP PK Parameters After Administration of 20mg Dyanavel XR Tablet Under Fasted Or Fed Conditions, Chewed

Parameters	Fed (T, n=31)	Fasted (R, n=31)	Geomean ratio (T/R, 90% CI, n=31)
d-AMP			
C_{max} (ng/mL)	52.8 (16)	54.7 (17)	96.7 (94.2, 99.2)
T_{max} (hr)	5.0 (3.0-7.05)	5.0 (3.0-7.0)	-
AUC_{0-5} (hr*ng/mL)	158 (18)	173 (24)	92.2 (87.2, 97.6)
AUC_{5-t}(hr*ng/mL)	923 (23)	959 (24)	96.6 (92.7, 100.8)
AUC_{inf} (hr*ng/mL)	1136 (22)	1206 (25)	94.7 (91.1, 98.5)
l-AMP			
C_{max} (ng/mL)	16.9 (17)	17.5 (18)	97.0 (94.5, 99.5)
T_{max} (hr)	5.0 (3.0-9.0)	5.0 (3.0-7.0)	-
AUC_{0-5} (hr*ng/mL)	49.7 (19)	54 (25)	92.9 (87.8, 98.4)
AUC_{5-t}(hr*ng/mL)	346 (25)	365 (26)	95.3 (91.1, 99.7)
AUC_{inf} (hr*ng/mL)	436 (28)	473 (28)	92.7 (88.4, 97.2)

Data are presented as arithmetic mean (%CV); Tmax: median (range); Source: Tables 11-2, 11-3, 14-2 and 14-5 of CSR

Does chewing affect the bioavailability of Dyanavel XR tablet?

Chewing had minimal effect on the bioavailability of either *d*- or *l*-AMP (Table 4). The bioavailability of *d*- and *l*-AMP was considered comparable (i.e., met bioequivalence criteria). Therefore, Dyanavel XR tablet can be chewed or swallowed whole.

Table 4: Plasma *d*- and *l*-AMP PK Parameters After 20 mg Dyanavel XR Tablet Administration Either Swallowed Whole Or Chewed Under Fasted Conditions

Parameters	Chewed (T, n=31)	Swallowed Whole (R, n=32)	Geomean ratio (T/R, 90% CI, n=31)
d-AMP			
C_{max} (ng/mL)	54.7 (17)	53.4 (17)	101.9 (99.3, 104.5)
T_{max} (hr)	5.0 (3.0-7.0)	5.0 (2.0-9.0)	-
AUC_{0-5} (hr*ng/mL)	173 (24)	176 (21)	96.9 (91.6, 102.5)
AUC_{5-t}(hr*ng/mL)	959 (24)	960 (22)	98.8 (94.8, 103.1)
AUC_{inf} (hr*ng/mL)	1206 (25)	1215 (23)	98.2 (94.5, 102.1)
l-AMP			
C_{max} (ng/mL)	17.5 (18)	17.2 (18)	101.3 (98.8, 103.9)
T_{max} (hr)	5.0 (3.0-7.0)	5.0 (2.0-9.0)	-
AUC_{0-5} (hr*ng/mL)	54 (25)	55 (23)	96.6 (91.3, 102.2)
AUC_{5-t}(hr*ng/mL)	365 (26)	367 (22)	98.0 (93.7, 102.6)

AUC_{inf} (hr*ng/mL)	473 (28)	481 (22)	97.3 (92.8, 101.9)
Data are presented as arithmetic mean (%CV); Tmax: median (range); Source: Tables 11-2, 11-3, 14-2, and 14-5 of CSR			

Is there any conclusive evidence to suggest change in dosage for Dyanavel XR tablet when gastric pH modulators are coadministered?

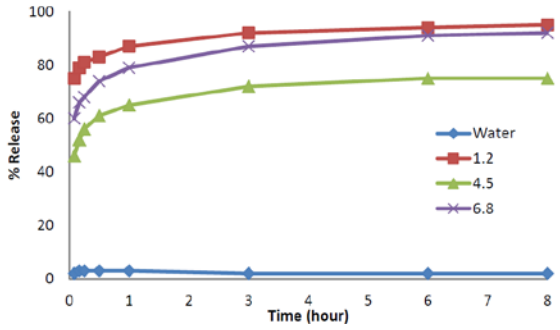
No. No conclusive data are available to suggest any change in dosage recommendation for Dyanavel XR tablet when gastric pH modulators (e.g., proton pump inhibitors) are coadministered.

Gastric pH modulators (e.g., proton pump inhibitors or H2 blockers) increase gastric pH. Subsequently, drug release may be altered for a formulation coated with pH-sensitive polymers, when this formulation is taken concomitantly with a gastric pH modulator. However, the following findings do not support a consistent change in drug release from Dyanavel XR tablet when gastric pH is elevated.

Per the sponsor, the ER component of Dyanavel XR tablet (b) (4) More importantly, the ER component (b) (4) of the total dose. A significant change in drug release from the ER component is not anticipated even if this component (b) (4)

Specifically, no consistent pattern has been identified from an *in vitro* dissolution study at different pH levels. To evaluate the drug release as a function of pH, dissolution studies were conducted with the highest strength (20mg) of the clinical lot (TB-175A). The results showed that the *in vitro* drug release of AMP from the Dyanavel XR tablet was the highest and fastest at pH1.2. As pH increased to 4.5, the rate and extent of drug release were decreased (Figure 3). Then the rate and extent of drug release were increased, when pH was further increased to 6.8. Per the Sponsor, the drug release from (b) (4) amphetamine (b) (4) does not have ions so the drug release is slow as compared to the different pH buffer media (Figure 3).

Figure 3: Dissolution Profiles of Dyanavel XR Tablet (20mg) in Media with Different pH



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Primary Reviewer	Team Leader

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Data to support this NDA were derived from three clinical trials: two pilot studies conducted with prototypes of amphetamine ER tablets and one pivotal bioequivalence trial with the to-be-marketed formulation. These trials are summarized in the table below.

Table 1: Table of Clinical Studies

Trial ID	Trial Description
Pilot Studies	
2016-4009	Randomized, open label, single dose, four-period, four-treatment, four-sequence, crossover study to compare the bioavailability of a prototype formulation of amphetamine ER chewable tablets 20 mg (chewed, orally disintegrated in the mouth, or swallowed whole) to amphetamine ER oral suspension 20 mg under fasted conditions in 16 healthy adults. Concentrations of d-amphetamine and l-amphetamine were measured over 48 hours after dosing.
2016-4124	Randomized, open label, single dose, three-period, three-treatment, three-sequence, crossover study to compare the bioavailability of two prototype formulations of amphetamine ER chewable tablets 20 mg (chewed) to Dyanavel XR oral suspension 20 mg under fasted conditions in 12 healthy adults. Concentrations of d-amphetamine and l-amphetamine were measured over 48 hours after dosing.
Pivotal Study	
2016-4171	Randomized, open label, single dose, four-period, four-treatment, four-sequence, crossover study to compare the relative bioavailability and food effect of amphetamine ER chewable tablets 20 mg to amphetamine ER oral suspension 20 mg in 36 healthy adults. Four treatments were administered: • Treatment A: Amphetamine ER tablet chewed under fasted conditions. • Treatment B: Amphetamine ER tablet chewed 30 minutes after starting a high-fat, high-calorie meal. • Treatment C: Amphetamine ER tablet swallowed whole under fasted conditions. • Treatment D: Dyanavel XR oral suspension under fasted conditions. Concentrations of d-amphetamine and l-amphetamine were measured over 60 hours after dosing.

7.2. Review Strategy

Efficacy in the treatment of children age 6 years and older with ADHD was inferred from the established efficacy of the LD, Dyanavel XR oral suspension. Therefore, no clinical efficacy data were presented in this application.

Clinical studies were not pooled for the safety review because of differences in formulations and study designs across the three trials. I reviewed serious adverse events and premature discontinuations due to adverse events from all three studies to identify any major, new safety concerns associated with amphetamine administration in these trials. I also reviewed the incidence of all adverse events, changes in blood pressure and pulse, and changes in ECG parameters across the four treatment groups in Study 2016-4171 to determine if the to-be-marketed tablet formulation, administered under various conditions, was associated with any substantial difference in relevant safety measures compared to the LD. I did not examine other standard safety parameters (such as laboratory tests, suicidal ideation/behavior, and weight change) because this was a single dose study in which those measures were unlikely to reveal any substantial effects.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Not applicable because no clinical efficacy trials were conducted to support this application.

8.2. Review of Safety

8.2.1. Safety Review Approach

See Section 7.2.

8.2.2. Review of the Safety Database

Only Abbreviated Study Reports (ASRs) for the pilot studies 2016-4009 and 2016-4124 were submitted. These ASRs were reviewed for deaths, other serious adverse events, and dropouts secondary to adverse experiences. No safety datasets were available for these two studies.

A full Clinical Study Report (CSR) and safety datasets for the pivotal BE study 2016-4171 were submitted. These were reviewed as described in Section 7.2.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Governor of Missouri issued a State of Emergency for the southern half of Missouri due to an ice storm on January 12, 2017. Out of concern for subject safety, the 60-hour post-dose blood draw in Period 4 of Study 2016-4171 was collected up to five hours earlier than scheduled and the end-of-study safety evaluations were rescheduled and performed when subjects returned to the study site to collect payment for study participation. These actions are not expected to significantly impact the safety conclusions from this study. Otherwise, there were no issues regarding data integrity and submission quality from a clinical safety perspective.

Categorization of Adverse Events

The coding of reported adverse events to MedDRA (version 19.1) Preferred Terms for Study 2016-4171 was reviewed and found to be satisfactory.

Routine Clinical Tests

In Study 2016-4171, adverse events were documented and other safety monitoring consisted of the following:

- blood pressure and pulse were measured pre-dose and at 1, 2, 3.5, 6, 8, 12, and 23 hours post-dose.
- electrocardiograms were recorded pre-dose and at 4, 12, and 23 hours post-dose.

Laboratory tests were assessed only at screening and at the end-of-study safety evaluation.

Given the known safety profile of amphetamine salts and the single-dose administration of study drug in this trial, this safety monitoring is felt to be adequate.

8.2.4. Safety Results

Deaths

No deaths occurred in any of the three studies of this development program.

Serious Adverse Events

Only one serious adverse event (atrial fibrillation) was reported in this development program: Subject # (b) (6) in the pilot Study 2016-4009 was a 23 year old male with elevated blood pressure readings during screening which normalized on repeat testing and allowed study entry. The subject reported no significant medical history. Screening and pre-dose ECGs were read as normal. The subject received amphetamine ER oral suspension during Period 1. After dosing, the subject had several elevated blood pressure readings between one hour and 24 hours post-dose, with readings as high as 166/104 (at 3.5 hours post-dose). ECGs at 4 and 12 hours post-dose were read as normal but at 24 hours tachycardia (119 bpm), atrial fibrillation, and a questionable atrioventricular block were found. The subject had been asymptomatic up to that

point but reported some dyspnea and nervousness at that time. The subject was sent to the emergency department by ambulance for evaluation, where an ECG was found to be normal and the subject was discharged with a diagnosis of palpitations and paroxysmal atrial fibrillation. Three days later, an evaluation at the site revealed a normal ECG and slightly elevated blood pressure (145/89). Study participation was terminated. Post-study evaluations were done five days later and revealed no significant abnormalities. The subject was to be evaluated by a cardiologist but the site staff were unable to reach him for further information.

Reviewer's Comment: It is not known whether this subject had previous episodes of atrial fibrillation. Nonetheless, I cannot rule out amphetamine as a potential etiology or precipitating factor for this adverse event. However, it is notable that this occurred with the marketed oral suspension formulation of Dyanavel XR and not the tablet.

Dropouts and/or Discontinuations Due to Adverse Effects

Two other subjects dropped out of the pilot Study 2016-4009 due to adverse events:

- Subject # (b) (6) was terminated by the investigator in Period 4 because of nausea and vomiting after taking the amphetamine ER tablet by swallowing it whole.
- Subject # (b) (6) was terminated by the investigator because of a prolonged QTc interval (463 msec) noted prior to dosing in Period 3. The Period 2 dose was administered seven days earlier. Previous ECGs were unremarkable.

One subject dropped out of the pivotal BE Study 2016-4171 because of an adverse event (chest discomfort): During Period 2, Subject # (b) (6) chewed the amphetamine ER tablet within 30 minutes after starting a high-calorie, high-fat breakfast. At 27.5 hours post-dose, the subject experienced chest discomfort which was reported at the 36-hour visit. Vital signs and ECG were normal. The chest discomfort resolved about one hour after she reported it. Nonetheless, the subject was referred to the emergency department where labs, ECG, and a physical examination were normal. A follow-up evaluation with a cardiologist included an echocardiogram and exercise tolerance test, which revealed no remarkable findings.

Reviewer's Comments: Nausea and, in some cases, vomiting have been reported after taking an amphetamine product and, thus, are not unexpected. It seems unlikely that the case of QTc prolongation was related to amphetamine administration given that the last dose was a week earlier. Because the upper limit of the range of Tmax for both d- and l-amphetamine is about nine hours, it seems unlikely that the onset of chest discomfort at 27 hours post-dose was caused by amphetamine.

Significant Adverse Events

The only unexpected adverse events were:

- blepharospasm (in one subject after the chewing tablet in the fed condition in Period 4).

This was described as left eye twitching, occurred four days after dosing, and lasted for about ten days.

- platelet count increased (in one subject after swallowing the tablet whole under fasted conditions in Period 4). This was a 48 year old female taking no concomitant medications. A count of 542K/µL was noted two days following dosing and was confirmed by a repeat count (screening count=405K/ µL; normal range=140 to 400K/ µL). There were no associated symptoms reported. The investigator considered this finding resolved 34 days later.
- paresthesia (in one subject after chewing the tablet in the fed condition in Period 4). This was described as a tingling sensation in the fingertips of her left hand about 2 hours after dosing and following a blood pressure measurement. It spontaneously resolved after two days.
- rash (in one subject after the oral suspension in Period 4). The rash occurred two days after dosing and lasted for about 13 days.

All of these events were rated as mild in severity.

Treatment Emergent Adverse Events and Adverse Reactions

In Study 2016-4171, there was a higher incidence of any adverse event in two of the amphetamine ER tablets treatment periods compared to the oral suspension: 18%, 24%, 27%, and 15% of subjects who received Treatments A, B, C, and D, respectively.[1]

The most common adverse event was tachycardia, which was reported by a slightly higher percentage of patients in the amphetamine tablet treatment periods: 6%, 9%, 6%, and 3% of subjects who received Treatments A, B, C, and D, respectively.

Dizziness was reported following administration of the tablet under fasted conditions but not under fed conditions or after the oral suspension: 3%, 0%, 6%, and 0% of subjects who received Treatments A, B, C, and D, respectively.

Reviewer's Comments: Considering the small numbers of subjects reporting adverse events, the crossover design of this study, the lack of major differences in event rates across treatment periods, and similarity of the PK profiles for d- and l-amphetamine over time across treatments, I do not consider the above findings, to include the unexpected adverse events, to represent any new safety signals associated with amphetamine or any substantial safety profile differences across the four treatments administered in this trial.

[1] Treatment A=Amphetamine ER tablet chewed under fasted conditions, Treatment B= Amphetamine ER tablet chewed 30 minutes after starting a high-fat, high-calorie meal, Treatment C=Amphetamine ER tablet swallowed whole under fasted conditions, and Treatment D=Dyanavel XR oral suspension under fasted conditions.

Vital Signs

Mean systolic blood pressure, diastolic blood pressure, and pulse rate measurements over time were comparable across the four treatments in Study 2016-4171. No pulse rates were higher than 120 bpm.

Electrocardiograms (ECGs)

The mean heart rate, PR interval, and QRS interval values over time were similar across the four dose administrations in Study 2016-4171.

QT

Mean QTcB intervals by each ECG assessment were comparable across the four treatments in Study 2016-4171. No subject had a QTcB value over 480 msec at any time point.

8.2.5. Analysis of Submission-Specific Safety Issues

This product contains sodium polystyrene sulfonate (SPS) and mannitol as excipients. There are several previous reports of intestinal necrosis and other serious gastrointestinal adverse events associated with the use of SPS (especially Kayexalate) and sorbitol, including cases with a fatal outcome. The causal mechanism for intestinal necrosis is uncertain, but detection of SPS crystals in the ulcerated tissue was frequently observed. The estimated incidence of these events among SPS-treated patients was in the range of 0.1% to 0.4%. Therefore, a warning was added to Kayexalate labeling to 1) advise against concomitant use of sorbitol, 2) use only in patients with normal bowel function, 3) avoid use in patients at risk for constipation or impaction, and 4) stop use in patients who develop constipation. The Pharmacology-Toxicology reviewer, Dr. Deepa Rao, raised the question of whether a similar risk could be associated with this product in compromised populations given that both SPS and mannitol are excipients in this product and based on the similarity between mannitol and sorbitol in chemical structure, molecular weight, and physiological properties to serve as osmotic laxatives in the gastrointestinal tract.

Accordingly, Dr. Rao requested that the Applicant evaluate the safety of the combination of SPS and mannitol with respect to serious gastrointestinal adverse events. The Applicant submitted a report of their evaluation on March 14, 2018, as Serial #0009 under this NDA. I reviewed this report and noted the following:

- some reports of bowel necrosis occurred after administration of SPS alone, either orally or by enema per rectum. Others occurred with sorbitol but there were no reports with SPS and mannitol. The amount of sorbitol administered in cases of intestinal necrosis was ≥20 grams.
- with one exception, all reports involved the administration of very large amounts of SPS (≥15 grams per day). The exception was the administration of 850 mg of SPS per rectum

to a premature infant with hyperkalemia due to kidney failure who weighed two pounds and had multiple acute medical problems, including sepsis.

The amount of SPS (b) (4) of this product is (b) (4) mg and the amount of mannitol is (b) (4) mg. (It is noted that sorbitol and mannitol are both naturally occurring sugars (b) (4) osmotic laxatives and have the same molecular weight.) The differences between the amounts of SPS and sorbitol in cases of intestinal necrosis and the amounts present in the highest strength of this product are huge (approximately (b) (4), respectively).

Reviewer comment: *For this reason, I do not believe there is any appreciable risk of serious intestinal adverse events with this product. Nonetheless, I do recommend that we request that the Applicant forward expedited reports of any serious gastrointestinal adverse events to the Agency after launch of this product and that we alert the Division of Pharmacovigilance 1 (DPV1) to inform us as soon as possible of any such reports to the FDA Adverse Event Reporting System (FAERS). If such serious events are reported in the postmarketing phase, this issue should be revisited.*

The NDA review team met on June 14, 2018, with DPP leadership to discuss this issue and there was agreement with the above plan for enhanced pharmacovigilance as opposed to any other measures, such as a warning in labeling or a REMS.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There were no clinical outcome assessment analyses that would inform safety or tolerability.

8.2.7. Safety Analyses by Demographic Subgroups

No safety subgroup analyses were conducted or required because of the small sample size in Study 2016-4171.

8.2.8. Specific Safety Studies/Clinical Trials

No specific safety studies were conducted as part of this development program.

8.2.9. Additional Safety Explorations

No additional safety explorations were indicated or performed.

8.2.10. Safety in the Postmarket Setting

This product has not yet been marketed.

Expectations on Safety in the Postmarket Setting

At this time, there are no outstanding postmarketing safety issues with amphetamine products under evaluation by the Division Safety Team.

From a clinical point of view, this product is expected to be reasonably safe in the postmarketing environment.

Nevertheless, as discussed in Section 8.2.5, we should request enhanced pharmacovigilance for serious gastrointestinal adverse events with this product after launch, specifically, that the Applicant submit any such reports to the Agency on an expedited basis. In addition, DPV1 should be requested to notify DPP as soon as possible of any serious gastrointestinal events associated with this product that are reported to FAERS.

8.2.11. Integrated Assessment of Safety

The safety data derived from the studies in this development program revealed no new, clinically significant safety signals that require further study or a major labeling revision vis-à-vis other amphetamine products. Most of the safety data are consistent with the known safety profile of amphetamine products. Although these studies involved the administration of only single doses of drug to healthy adults and are incapable alone of providing adequate safety data to support clinical use, the established bioequivalence to a marketed product and extensive clinical experience with amphetamine products over the past several decades do support its safety.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

No statistical issues were identified in this application. No statistical review was performed.

8.4. Conclusions and Recommendations

Clinically, I expect this product to be reasonably safe and recommend approval.

X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting or other external consultations were deemed necessary for this application.

10 Pediatrics

(b) (4)

The Applicant requested a partial waiver for children under age 4 years, a deferral for ages 4 and 5 years pending completion of studies with the oral suspension in this age range, and a pediatric assessment for children and adolescents ages 6 to 17 years. These requests were discussed by the FDA Pediatric Review Committee (PeRC) on June 13, 2018. The PeRC concurred with these requests.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

This table should include only high-level changes to the labeling submitted by the Applicant. Your recommendations for major changes (additions, deletions, or modifications) to the clinically-relevant aspects of the Applicant's proposed prescribing information, based on your assessment of the evidence at the time your review is completed, are important to inform these ongoing deliberations. This table provides a concise summary of those recommendations and your rationale.

Table 2: Significant Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
6.2	This section requires inclusion of additional adverse events consistent with the labeling of other amphetamine products.	Adverse events have been added as appropriate.

Other Prescription Drug Labeling

Provide a high-level summary of the recommendations and rationale for critical changes to other labeling proposed by the Applicant (if applicable):

- Patient labeling (i.e., Medication Guide, Patient Information, Instructions for Use)
- Carton and container labeling

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS is required for this product.

13 Postmarketing Requirements and Commitment

Pediatric assessment of safety and efficacy in the 4 to 5 year age range is required and is expected to be fulfilled by clinical studies with Dyanavel (b) (4) the Agreed iPSP does provide for a PK study, a randomized, double-blind, placebo-controlled safety and efficacy trial, and an open label safety trial in 4 and 5 year old children if safety and efficacy (b) (4) These studies will be PMRs with the approval of this application (b) (4)

14 Division Director (OCP)

X

APPEARS THIS WAY ON ORIGINAL

15 Division Director (DPP)

X

APPEARS THIS WAY ON ORIGINAL

16 Appendices

16.1. References

[Insert text here.]

16.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study 2016-4171

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation

		from Applicant)

16.3. Nonclinical Pharmacology/Toxicology

16.4. OCP Appendices (Technical documents supporting OCP recommendations)

16.5. Additional Clinical Outcome Assessment Analyses

Palatability Assessment

Subjects in Study 2016-4171 rated the palatability of the amphetamine ER chewable tablets using a 5-item palatability questionnaire after administration of Treatment A or Treatment B (chewing under fasted conditions or chewing under fed conditions, respectively). The following questions comprised the questionnaire:

1. Rate the oral sensation/mouth feel of the drug product.
2. Rate the taste of the product.
3. How strong is the taste?
4. Rate the aftertaste of the product.
5. How strong is the aftertaste?

Questions 1, 2, and 4 (on palatability) were rated on the following scale:

- 1=very unpleasant.
- 2=unpleasant.
- 3=no sensation/mouth feel.
- 4=pleasant.
- 5=very pleasant.

Questions 3 and 5 (on strength) were rated as follows:

- 1=very strong.
- 2=strong.
- 3=moderate.
- 4=mild.
- 5=no (after)taste.

Scores of 1 or 2 were considered negative in terms of acceptability. A score of 3 was considered neutral. Scores of 4 or 5 were considered positive with respect to acceptability. The distribution of scores by question is displayed below.

Table 3: Palatability Assessment Results

			Evaluation Score (%)				
Question	**Trt**	**N**	**1**	**2**	**3**	**4**	**5**
1. Rate the oral sensation/mouth feel of the drug product	A	33	4 (12.1%)	3 (9.1%)	5 (15.2%)	18 (54.5%)	3 (9.1%)
	B	34	3 (8.8%)	0 (0.0%)	5 (14.7%)	19 (55.9%)	7 (20.6%)
		Overall	10.4%	4.5%	14.9%	55.2%	14.9%
2. Rate the taste of the drug product	A	33	3 (9.1%)	2 (6.1%)	1 (3.0%)	24 (72.7%)	3 (9.1%)
	B	34	3 (8.8%)	1 (2.9%)	1 (2.9%)	22 (64.7%)	7 (20.6%)
		Overall	9.0%	4.5%	3.0%	68.7%	14.9%
3. How strong is the taste?	A	33	1 (3.0%)	4 (12.1%)	15 (45.5%)	12 (36.4%)	1 (3.0%)
	B	34	2 (5.9%)	2 (5.9%)	14 (41.2%)	15 (44.1%)	1 (2.9%)
		Overall	4.5%	9.0%	43.3%	40.3%	3.0%
4. Rate the aftertaste of the drug product	A	33	2 (6.1%)	0 (0.0%)	4 (12.1%)	25 (75.8%)	2 (6.1%)
	B	34	1 (2.9%)	0 (0.0%)	6 (17.6%)	24 (70.6%)	3 (8.8%)
		Overall	4.5%	0.0%	14.9%	73.1%	7.5%
5. How strong is the aftertaste?	A	33	2 (6.1%)	0 (0.0%)	17 (51.5%)	12 (36.4%)	2 (6.1%)
	B	34	2 (5.9%)	1 (2.9%)	10 (29.4%)	18 (52.9%)	3 (8.8%)
		Overall	6.0%	1.5%	40.3%	44.8%	7.5%

Most subjects rated the mouth sensation, taste, and aftertaste as positive. The strength of the taste and aftertaste was most commonly rated as mild or moderate. There were no clear differences between administration after fasting compared to with food.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KOFI B ANSAH
07/23/2018

DEEPA B RAO
07/23/2018

IKRAM M ELAYAN
07/23/2018

GREGORY M DUBITSKY
07/23/2018

JASMINE C GATTI
07/23/2018

HAO ZHU on behalf of HUIXIA ZHANG
07/23/2018

HAO ZHU
07/23/2018

MEHUL U MEHTA
07/23/2018

MITCHELL V Mathis
07/23/2018