CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211230Orig1s000
211230Orig2s000

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date:	December 17, 2018
To:	Mitchell Mathis, MD Director **Division of Psychiatry Products (DPP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Christine Bradshaw, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	SUNOSI (solriamfetol)
Dosage Form and Route:	tablets, for oral use, C-XX
Application Type/Number:	NDA 211230
Applicant:	Jazz Pharmaceuticals

1 INTRODUCTION

On December 20, 2017, Jazz Pharmaceuticals, submitted for the Agency's review an original New Drug Application (NDA) for SUNOSI (solriamfetol) tablets, for oral use, C-XX, for the proposed indication of use to improve wakefulness and reduce excessive sleepiness in adults with narcolepsy or obstructive sleep apnea (OSA).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on August 14, 2017 and February 6, 2017, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SUNOSI (solriamfetol) tablets, for oral use, C-XX.

2 MATERIAL REVIEWED

- Draft SUNOSI (solriamfetol) MG received on December 20, 2017 and received by DMPP and OPDP on December 14, 2018.
- Draft SUNOSI (solriamfetol) Prescribing Information (PI) received on December 20, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 14, 2018.

3 REVIEW METHODS

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

In our collaborative review of the MG we:

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

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
12/17/2018

CHRISTINE J BRADSHAW
12/17/2018

LASHAWN M GRIFFITHS
12/17/2018

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

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

Memorandum

Date: December 14, 2018

To: Sarah Seung, Regulatory Project Manager
Division of Psychiatry Products (DPP)

Kimberly Updegraff, Associate Director for Labeling, DPP

From: Christine Bradshaw, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for SUNOSI (solriamfetol) tablets, for oral use, C-XX

NDA: 211230/O1 & O-2

In response to DPP's consult request dated February 6, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Sunosi.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPP (Sarah Seung) and downloaded from Share Point on December 10, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 7, 2018, and our comments are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Christine Bradshaw at (301) 796-6796 or Christine.Bradshaw@fda.hhs.gov.

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/s/

CHRISTINE J BRADSHAW
12/14/2018

M E M O R A N D U M

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

Date: December11, 2018

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

Through: Dominic Chiapperino, Ph.D., Director
Silvia Calderon, Ph.D., Senior Pharmacologist
Martin S. Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff

From: Shalini Bansil, M.D., Medical Officer
Edward Hawkins, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: **Product name:** JZP-110 ([R]-2-amino-3-phenylpropylcarbamate hydrochloride) Solriamfetol.
NDA: 211230
Trade Name, dosages, formulations, routes: Sunosi tablets (b) (4) mg oral once daily
IND Number: 107203 (Narcolepsy), 122590 (Obstructive Sleep Apnea)
Indication(s):

1. To improve wakefulness and reduce excessive sleepiness (ES) in adult patients with narcolepsy
2. To improve wakefulness and reduce excessive sleepiness (ES) in adult patients with obstructive sleep apnea (OSA).

. **Sponsor:** Jazz Pharmaceuticals, Inc.
PDUFA Goal Date: December 20, 2018

Materials Reviewed:

- 1.11.4 Proposal for Scheduling and Rationale
- 1.14 Labeling
- 2.6 Nonclinical Written and Tabulated Summaries
- 2.7.4 Summary of Clinical safety
- 3.2.S Drug Substance
- 3.2.P Drug Product
- 4.2.1, 4.2.2, 4.2.3 Nonclinical Study Reports
- 5.3.1., 5.3.3., 5.3.4., 5.3.5. Clinical study reports

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I. SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Psychiatry Products (DPP) dated January 10, 2018 to the Controlled Substance Staff (CSS) to evaluate abuse related preclinical and clinical data submitted by Jazz Pharmaceuticals, Inc. in NDA 211230 [INDs 107203 (Narcolepsy), 122590 (Obstructive Sleep Apnea)] for Sunosi (Solriamfetol; JZP-110). The drug product is indicated for improved wakefulness and to reduce excessive sleepiness (ES) in adult patients with narcolepsy or obstructive sleep apnea (OSA). The recommended dose is (b) (4) mg oral tablets once daily. JZP-110 was previously known as ADX-N05, (b) (4) and YKP-10A.

JZP-110 ([R]-2-amino-3-phenylpropylcarbamate hydrochloride), a new molecular entity (NME), is a selective dopamine and norepinephrine reuptake inhibitor (DNRI). The Sponsor states that dopamine and norepinephrine are wake-promoting neurotransmitters, and dysfunction of the dopaminergic and norepinephrine pathways originating from the brainstem have been observed in animal models of sleep apnea and narcolepsy. Through the blockade of the dopamine and norepinephrine transporters, JZP-110 enhances dopamine and norepinephrine signaling in the brainstem arousal systems. JZP-110 is a derivative of the amino acid phenylalanine. The Sponsor also asserts that, clinically, JZP-110 produces robust wake-promoting effects without rebound hypersomnia, and the pharmacological effects of JZP-110, as a selective DNRI, are presumed to be responsible for its claimed low abuse potential. The formulation does not include any abuse deterrent properties,

JZP-110 is a NME that has not been approved for marketing in the U.S. or any other country.

The Sponsor asserts that the scientific and medical evidence do not support a Controlled Substance Act (CSA) level of control that is more restrictive than Schedule IV for JZP-110.

2. Conclusions

- The receptor binding and activity data indicate that JZP-110 is a low potency dopamine and norepinephrine reuptake inhibitor (DNRI).

- In general, the nonclinical in vivo abuse potential studies were conducted in a manner such that no concrete conclusions can be drawn. The data provided by the Sponsor indicate that rats do not self-administer JZP-110; however, these studies have several problems in their design and implementation. The Sponsor also used drug discrimination assays indicating that, at very high doses, JZP-110 produced discriminative stimulus cues similar to cocaine and only partially to d-amphetamine.

- The data from the human abuse potential (HAP) study show that for all primary and key secondary end points JZP-110 has similar or lower abuse potential compared to the active control drug phentermine (a Schedule IV drug).

- In clinical trials, although abuse related adverse events (AEs) occurred in JZP-110 treated subjects, they occurred at a low rate, usually less than 5%. Anxiety, insomnia, and agitation occurred with JZP-110, consistent with the stimulant activity of the drug.

- There was no signal in the clinical trials suggesting drug diversion, abuse, or misuse.

- No consistent pattern of withdrawal symptoms occurred upon abrupt discontinuation of JZP-110.

3. Recommendations

Based on the findings of the HAP study, low rate of abuse-related AEs in clinical trials, absence of withdrawal symptoms, and lack of evidence of drug abuse and diversion during the clinical trials, we concur with the Sponsor that Solriamfetol should be placed in Schedule IV of the CSA.

Drug label: CSS recommends the following changes to the Sponsor's label, where additions are indicated in bold underlined text and deletions have been stricken through.

9. DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

SUNOSI contains solriamfetol~~,~~ (b) (4) **(Controlled substance schedule to be determined after DEA review)**

9.2 Abuse

SUNOSI has potential for abuse. **Abuse is the intentional non- therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. The abuse potential of** SUNOSI (**300** (b) (4) mg, **600** (b) (4) mg, and **1200** (b) (4) mg) was assessed relative to phentermine, ~~(~~45 mg and 90 mg~~)~~, **(a Schedule IV controlled substance)** in a human abuse potential study in individuals experienced with **the recreational use** (b) (4) of **stimulants.** (b) (4) Results from this clinical study demonstrated that SUNOSI produced **Drug Liking Scores** (b) (4) similar to or (b) (4) **lower** than phentermine**.** (b) (4) **In this study, elevated mood was reported by 2.4% of placebo treated subjects, 8-24% of SUNOSI treated subjects, and 10-18% of phentermine treated subjects. A 'feeling of relaxation' was reported in 5% of placebo treated subjects, 5-19% of SUNOSI treated subjects and 15-20% of phentermine treated subjects**

(b) (4)

Physicians should carefully evaluate patients for a recent history of drug **abuse, especially those with a history of stimulant (e.g., methylphenidate, amphetamine, or cocaine),** or alcohol abuse, and follow

such patients closely, observing them for signs of misuse or abuse of SUNOSI (e.g., **incrementation of doses,** drug-seeking behavior).

9.3 Dependence

(b) (4)

In a long-term safety and maintenance of efficacy study, the effects of abrupt discontinuation of SUNOSI were evaluated following at least 6 months of SUNOSI use in patients with narcolepsy or OSA. **Phase 3 clinical trials included an evaluation of effects that occurred after abrupt discontinuation of SUNOSI.** There was no evidence that abrupt discontinuation of SUNOSI resulted in (b) (4) **or a consistent pattern** (b) (4) of adverse events suggestive of physical dependence or withdrawal.

(b) (4)

II. DISCUSSION

1. Chemistry

The chemical properties of a substance impact the assessment of abuse potential because they determine possible synthetic pathways and methods of administration. An understanding of the chemical properties of a substance may help to determine if an individual with a basic knowledge of chemistry could synthesize the substance based upon the availability of the starting materials and complexity of the synthetic path. Furthermore, an understanding of the physicochemical properties of a substance can help to predict if a person can produce a solution for injection upon extraction of the active pharmaceutical ingredient, or if the drug could be easily vaporized to be smoked or inhaled. An evaluation of the chemical properties of JZP-110 and its known active metabolites is given below.

1.1 Substance and product Information

Drug Substance

Solriamfetol is a new molecular entity, also known by the Sponsor codes ADX-N05, (b) (4) YKP10A, (b) (4) 10A000-301, (b) (4) 31,872, and (b) (4) 16253887- (b) (4) and identified by the CAS registry number 17829-65-7. Solriamfetol is the non-proprietary name of (*R*)-2-amino-3-phenylpropylcarbamate hydrochloride and it has a molecular formula of $C_{10}H_{15}N_2O_2Cl$ and a molecular weight of 194.23 g/mol (as the free base) and 230.69 g/mol (as HCl salt).

Solriamfetol is a white, to off white, solid that has a melting point between 183-189 °C. In a 1% solution of water it produces a pH of 5.4 and it is highly soluble in water over the entire gastric pH range of 1-7 (**Table 1**).

Solriamfetol has a pKa of 8.5 and a Log P at a pH of 11 of 1.2. The dissociation constant (pKa) is defined as the negative logarithm of the equilibrium coefficient of the charged and neutral forms of a substance. The pKa helps to determine the charge of a molecule at any given pH, the Log P measures how a substance partitions between a lipid (octanol) and water.

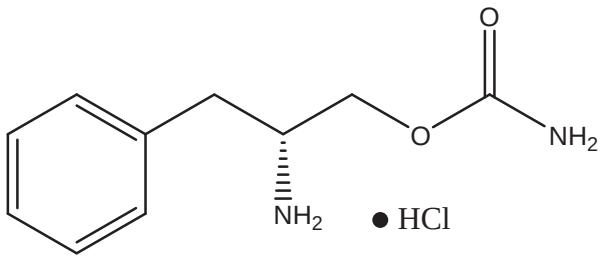
JZP-110 possesses one chiral center at position 2 which is in the "*R*" configuration. It was also found to generate polymorphs in the water:dioxane and water:acetonitrile mixtures of the drug. However, these polymorphs are not present in the crystalline form of the drug. Identification of the different polymorphs can be achieved through differences in the X-ray powder diffraction (XRPD) profile or melting point.

(b) (4)

(b) (4) None of the steps in the manufacturing process produce or utilize substances that have a known potential for abuse, nor can they be easily modified to generate a substance with abuse potential.

Table 1: General Chemical Properties of JZP-110

Nomenclature	
International non-proprietary name (INN)	JZP-110
Chemical Abstract Number (CAS)	178429-65-7
Chemical Name (IUPAC)	(*R*)-2-amino-3-phenylpropylcarbamate hydrochloride
Sponsor codes during development	ADX-N05, (b) (4) YKP10A, (b) (4) 10A000-301, (b) (4) 31,872, and (b) (4) 16253887- (b) (4)
Structure	
Molecular Formula	$C_{10}H_{15}N_2O_2Cl$
Molecular Weight	230.69 daltons (as HCl salt)

Structure	
General Properties	
Appearance	White to off-white solid
pH (1% solution in water)	5-6
pKa	8.5 ± 0.1
Solubility (25°C)	Soluble in water between pH of 1-7
Melting point	183-189 °C

Drug Product

Solriamfetol drug product is a film-coated immediate release tablet [redacted] described by the weight of the free base (conversion ratio of base to salt is 1.1877):

1. 75 mg, equivalent to 89.3 mg of HCl salt
2. 150 mg, equivalent to 178.5 mg of HCl salt

[redacted]

[redacted]. Each tablet contains solriamfetol as the HCl salt, hydroxypropyl cellulose, magnesium stearate, and [redacted] (composed of polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and yellow iron oxide).

No major metabolites have been detected (Section 3.1).

1.2 Potential Drug Isomers

JZP-110 has one stereocenter at the two position on the propyl chain. The formulated drug product is in the (*R*) configuration. One study was conducted to compare the pharmacological effects of JZP-110 and its enantiomer. In study [redacted] 96-6, JZP-110 was known as YKP 10A, and the Sponsor compared its pharmacology to its enantiomer YKP 10B. The study used mice to compare the effects of the two substances in the forced swim test, oxotremorine-induced tremors, and the rotorod test. YKP 10B did not have a significant pharmacological effect in any of the assays measured. YKP 10A produced a significant decrease in the duration of immobility in the forced swim test which is used to measure antidepressant effects. YKP 10A had no effect on oxotremorine-induced tremors indicating that it does

not affect cholinergic signaling and also had no effect on the rotorod test which is usually used to measure motor coordination. As a result, the active enantiomer, JZP-110/YKP 10A, was chosen for development.

1.3 In Vitro Manipulation and Extraction Studies

The Sponsor did not conduct manipulation or extraction studies with this drug product formulation.

2. Nonclinical Pharmacology

Receptor binding and activity assays can give an indication as to whether or not a substance affects a receptor pathway that is known to be associated with abuse potential. For substances that are CNS active the Sponsor is required to determine if their active pharmaceutical ingredient, and any major metabolites, will bind to and have activity at these receptors. The Sponsor provided 15 binding and activity studies to determine the receptor binding and activity profile of JZP-110. The data, summarized below, indicate that JZP-110 is most likely a dopamine and norepinephrine selective reuptake inhibitor that produces increased wakefulness, anorexia, and locomotor activation.

2.1 Receptor Binding and Functional Assays

The Sponsor conducted fifteen in vitro studies to assess the binding and functional activity of JZP-110 in order to determine its mechanism of action (**Table 2**). Many of these studies include the different code names of JZP-110 that were used during the research phase of the drug: ADX-N05, (b) (4) YKP10A, (b) (4) 10A000-301, (b) (4) 31,872, and (b) (4) 16253887-(b) (4)

The receptor binding screens include receptors, transporters, and ion channels associated with abuse as well as many individualized studies conducted to determine JZP-110's mechanism of action. Studies (b) (4) 870189, (b) (4) 10003212, and (b) (4) 16253887-22457057 indicate that JZP-110's major mechanism of action is through the monoamine transporters. This mechanism of action is typical of stimulant substances that are controlled in Schedule II of the CSA. Furthermore, these studies indicate that JZP-110 does not bind to other receptors (e.g. opioid, cannabinoid, GABAergic, and other ion channels) typically associated with abuse.

Table 2: In vitro receptor binding and activity studies conducted for JZP-110

Number	Study Number	Study type	Route	Species or Cell type	Dose	Result
1	(b) (4) 600027	receptor profile	in vitro	Multiple	10 μM	54% inhibtion of control specific binding 5-HT_{1A}

2	(b) (4) 870189	receptor profile	in vitro	Multiple	10 μM	none
3	DD6604	receptor profile	in vitro	H3 receptor	10 μM	K_i > 10,000 nM
4	(b) (4) 100032012	receptor profile	in vitro	Multiple	10 μM	80.2% inhibtion of control specific binding DAT
5	(b) (4) 16253887-22457057	83-GPCRs	in vitro	COS-7 cells	tritiated at 20,000cpm/sample	no significant binding
6	(b) (4) 8470	DAT activity	in vitro	rat brain slices	10 μM	weak binding but no function at 5-HT1A; modulation of DA signaling
7	(b) (4) 9072	hVMAT2	in vitro	HEK cells	250 uM	does not bind to HVMAT2
8	(b) (4) 96-2389	DAT transporter	in vitro	guinea pig striata	10 uM	K_i = 3,410 nM
9	NO1DA-7-8071	Monoamine transporter binding	in vitro	HEK cells	10 uM	Less potent than cocaine at DAT, NET and SERT
10	(b) (4) 870 and 871	receptor profile	in vitro	Bovine cerebral and guinea pig striatal membranes	10 uM	53% inhibtion of control specific binding at alpha 2 adrenoceptor
11	(b) (4) 5318	DA and 5-HT receptors and uptake	in vitro	rat brain and cell lines	10 uM	no effect on DA receptors, but increased DA uptake at high dose
12	(b) (4) Y1-DA-5007-03-B	Transporter binding/activity	in vitro	HEK cells	10 uM	**TABLES 3 & 4**
13	(b) (4) Y1-DA-5007-03-A	Transporter binding/activity	in vitro	HEK cells	10 uM	Does not induce release of monoamines
14	(b) (4) 6605	Orexin receptor 2	in vitro	PRSK-1 cells	10 uM	no activity at OXR2

15	(b) (4) 0893	receptor screen	ex vivo	DA, adrenergic, DAT, NET, SERT	rat - 40 mg/kg, SC	no significant binding

The receptor binding and functional assays indicate that JZP-110 most likely exerts its therapeutic effects as a dopamine and norepinephrine reuptake inhibitor (DNRI). Study (b) (4) Y1-DA-5007-03-B determined the binding affinity of JZP-110 on the human dopamine reuptake transporter (DAT), norepinephrine reuptake transporter (NET), and serotonin reuptake transporter (SERT) transfected into human endothelial kidney (HEK) cells. JZP-110 had a K_i of 14,200 nM, 81,500 nM, and 3,700 nM at DAT, SERT, and NET, respectively. The calculated binding affinity is much lower than cocaine (CII) , which was used as a positive control (**Table 3**). Another binding study, (b) (4) 96-2389, indicated that JZP-110 has a K_i of 3,410 nM at DAT. Although the binding affinities from these studies differ remarkably, they both indicate that JZP-110 has low affinity for DAT.

Furthermore, IC_{50} measurements, which indicate the amount of drug required to inhibit or reduce the maximum response (in this case reuptake of the three different bioamines) by half were 2,900 nM for DAT and 4,400 nM for NET (**Table 4**). Again, the calculated activity of JZP-110 at these transporters is much lower than that of the Schedule II substance, cocaine (**Table 4**).

Table 3: Binding affinity of JZP-110 to monoamine transporters

Drug	Binding affinity, K_i (nM)		
	hDAT	hSERT	hNET
JZP-110	14,200	81,500	3,700
Cocaine	236	361	505

Table 4: Functional activity of JZP-110 at monoamine transporters

Drug	Functional activity, IC_{50} (nM)		
	hDAT	hSERT	hNET
JZP-110	2,900	> 100,000	4,400
Cocaine	385	355	194

The low inhibitory activity (potency) of JZP-110 at the monoamine transporters may not account for the full activity of this drug. As a result, the Sponsor conducted a series of studies to determine if JZP-110 increased the release of monoamines or acted directly on dopaminergic and serotonergic receptors. Study (b) (4) Y1-DA-5007-03-A was conducted to determine if JZP-110 increased the release of the monoamines dopamine, norepinephrine, and serotonin, similar to the Schedule II substance methamphetamine. This study determined that the releasing effect of JPZ-110 at the three monoaminergic sites was minimal. Another mechanism to increase monoamines in the synaptic cleft is through the direct release of cytosolic monoamines. The cytosolic levels of monoamines are determined by the activity of the vesicular monoamine transporter 2 (VMAT2). VMAT2 is responsible for the uptake of cytosolic monoamines into the synaptic vesicles of CNS monoaminergic neurons, thus inhibition of VAMT2 will result in an increase of cytosolic catecholamine levels. Study (b) (4) 9072

determined that JZP-110 did not bind to and had no effect at VMAT2 compared to the positive control reserpine.

Two studies ((b) (4) 5318 and (b) (4) 0893) determined that JZP-110 does not bind to dopamine or serotonin receptors.

As a result, the binding and activity data in **Table 3** and **Table 4** indicate that JZP-110 is a DNRI that doesn't appear to have substantial activity in other mechanisms known to increase monoamines which would be typical of a stimulant drug. It also does not bind to or activate DA or 5-HT receptors, or other receptors or ion channels, typically associated with abuse.

2.2 Safety Pharmacology/Metabolites

Studies conducted to determine the safety of a substance and its metabolites are extremely pertinent to abuse potential. This is because individuals with an abuse related disorder rarely follow dosing guidelines and typically administer the substance through various methods of administration and doses to achieve the desired effects. As a result, the Sponsor conducted study (b) (4) TOX-6188 and determined that an oral dose of 5 mg/kg had no effect on blood pressure, heart rate, or ECG in a 12-hour period in male dogs. However, after a dose of 50 mg/kg there was a significant increase in the diastolic blood pressure, heart rate, and changes in the ECG as well as an increase in the respiratory rate and tidal volume. At this dose, locomotor activity was increased over a period of 10 hours.

No major metabolites for JZP-110 were detected in metabolism studies, therefore, they were not studied for their safety (Section 3.1).

2.3 Findings from Safety Pharmacology and Toxicology Studies

CNS effects

The CNS mediated effects of a drug can help make a determination about how similar a drug is to another substance with known pharmacological effects. The Sponsor conducted several studies to assess the CNS mediated effects of JZP-110.

Study (b) (4) 95-12 – was conducted to determine the effects of JZP-110 (60 mg/kg, IP) on normal body temperature in male CD1 mice. Rectal temperatures were measured at 0, 30, 60, 90, and 120 minutes after administration. The study found a reduction of body temperature by 2.3°C after 30 minutes with full recovery to normal body temperature by 90 minutes. This result is opposite to that of amphetamine which results in an increase in body temperature (Bowyer and Hanig, 2014).

Study (b) (4) 95-6 – was conducted to determine the effects of JZP-110 on apomorphine induced hypothermia in mice. Apomorphine produced hypothermia through stimulation of DA receptors. Several drugs that increase monoamine activity, tricyclic antidepressants, monoamine oxidase inhibitors, and amphetamine can antagonize this effect. Mice were given apomorphine (16 mg/kg, IP) which was followed by a dose of JZP-110 (15 or 30 mg/kg, p.o.) 30 minutes later. In contrast to the above study

([(b) (4)]95-12), and similar to amphetamine, both doses of JZP-110 were able to significantly decrease the apomorphine induced hypothermia.

Study [(b) (4)] 1833 – was conducted to determine the effects of JZP-110 on haloperidol induced catalepsy. Haloperidol is a D2 antagonist that produces catalepsy, therefore, an increase in DA signaling could block this effect. Adult male rats received JZP-110 (30, 60, or 90 mg/kg, IP) or vehicle 30 minutes prior to receiving haloperidol (0.75 mg/kg, IP). JZP-110 was able to block haloperidol induced catalepsy suggesting it increases dopaminergic signaling, however, the positive control, bupropion had minimal effect in the study thereby making the study invalid.

Study [(b) (4)] 96-5 – was conducted to determine the effects of pimozide on JZP-110 in the forced swim test. Pimozide is a D2 receptor antagonist and blocks the effects of bupropion and was preinjected (0.375 mg/kg, IP) into mice 15 minutes before the administration of vehicle or JZP-110 (30 mg/kg, IP). Pimozide significantly increased the duration of immobility of JZP-110 from 72.9 to 121.6 seconds in the forced swim test indicating that the drug functions, at least partly, through increasing activity at the D2 receptor.

Studies conducted to determine the mechanism of action of JZP-110

Study [(b) (4)]8880 was an in vivo micro-dialysis study that measured monoamine levels in the prefrontal cortex and striatum of male Sprague-Dawley rats. The animals were implanted with cannulae (CMA ½) using stereotaxic procedures to confirm localization in specific brain regions. First, three baseline samples were collected, each of 50 minutes duration, then animals were injected with drug and 8 more samples were collected, again, each of 50 minutes duration (total of 400 minutes). The effects on neurotransmitter levels were measured using high-performance liquid chromatography with an electrochemical detector (HPLC/ECD). The comparisons were made between the baseline measurements and JZP-110 injected SC at doses of 10 or 30 mg/kg. The results indicate that the 10 mg/kg dose of JZP-110 did not alter DA levels from baseline, however, the 30 mg/kg dose increased DA levels approximately 350% compared to baseline levels 100 minutes after administration. These levels slowly decreased throughout the course of the experiment but did not return to baseline. Levels of DA in the prefrontal cortex were below the limits of detection for the experiment and could not be measured. Norepinephrine levels in both the striatum and the prefrontal cortex increased in a dose dependent manner, however, variability in the measurements makes the significance of this result difficult to determine. A similar effect was found with 5-HT, where low levels of the neurotransmitter and high variability in the measurement make the data difficult to interpret. Although there is a trend indicating that JZP-110 increased the levels of DA, NE, and 5-HT, these data indicate that the effects of drug most likely through increasing DA and NE levels in the striatum and prefrontal cortex.

[(b) (4)] was a similar study as that conducted above to determine if JZP-110 altered catecholamines and their metabolites in different brain regions. The levels of DA, NE, 5-HT, and their metabolites, DOPAC, HVA, MOPEG, and 5-HIAA were measured in the frontal cortex, hippocampus, striatum, hypothalamus, nucleus accumbens, and brain stem of male Wistar rats. Animals were injected with JZP-110, cocaine, or amphetamine and sacrificed after 1 hour, at which time the brain regions were isolated and flash frozen. The samples were prepared and then analyzed using HPLC/ECD. This study produced a large amount of data, so this overview will focus on the data that is correlated to the abuse potential of the drug. Generally, JZP-110 increased dopaminergic activity similar to cocaine in most of

the brain regions testes. Importantly, it did not increase DA levels in the nucleus accumbens and frontal cortex, a mechanism known to be involved with the positive reinforcing effects of a stimulus (e.g., a drug of abuse) (Volkow et al., 2013). These data also suggest that there is a dose dependent increase in 5-HT levels in the frontal cortex which was not seen in the previous study ((b) (4) 8880).

Study (b) (4) 1783 was conducted to compare the behavioral effects of JZP-110 against currently available antidepressants. The studies were conducted in male Wistar rats or in male NMRI mice and were administered either SC or IP depending on the study. The study consisted of a series of in vivo tests in which antidepressant drugs are known to have a measured effect and included: Ro-4-1284 antagonism, reserpine antagonism, and a general observation battery. Other tests were conducted; however, they are deemed as irrelevant in regard to producing information about the abuse potential of the substance (e.g. comparison to monoamine oxidase inhibitors).

1. Reversal of the effects of Ro-4-1284 indicate that a substance is able to increase CNS monoamine signaling, a mechanism of action typical of stimulant and antidepressant drugs. JZP-110 reversed the hypothermia and ptosis in mice induced by Ro-4-1284 with an ED_{50} of 7.9 and 18 mg/kg, SC respectively. However, unlike d-amphetamine, JZP-110 did not block Ro-4-1284 induced hypomotility, block the tail-pinch response (dopaminergic signaling), or increase 5-hydroxytryptophan (5-HTP) behaviors in rats (serotonergic signaling).

2. A similar study in rats used reserpine (10 mg/kg, SC) to induce ptosis, sedation, and miosis. JZP-110 reversed these effects with an ED_{50} of 32, 32, and 37 mg/kg SC respectively. These first two in vivo studies indicate that JZP-110 increases centrally mediated monoamine neurotransmission.

3. In the general observation battery, JZP-110 closely mimicked the behavioral profile of d-amphetamine by inducing mydriasis (ED_{50}: 21 mg/kg, IP), excitation (ED_{50}: 25 mg/kg, IP), rearing (ED_{50}: 25 mg/kg, IP), and hyperthermia (ED_{50}: 37 mg/kg, IP).

From these studies it can be concluded that JZP-110 increases the signaling of monoamines in the CNS through an unknown mechanism of action. Its inability to affect the tail-pinch response or increase 5-HTP indicates that its major mechanism is to increase noradrenergic and dopaminergic signaling.

Sleep wake cycle

Study (b) (4) 1485 was conducted to test the effects JZP-110 on the sleep-wake cycle in rats using cocaine and amphetamine as positive controls. The effects of JZP-110 (3, 10, and 30 mg/kg, IP), cocaine (1, 3, and 10 mg/kg, IP), and amphetamine (1, 3, and 10 mg/kg, IP) were measured in male Sprague-Dawley rats implanted with electrodes to measure sleep wake cycles. The 10 and 30 mg/kg doses of JZP-110 produced significant increases in wakefulness (16% and 19% respectively) indicated by significant shifts in the time spent in REM sleep to an awake state. A rebound effect was seen after removal of JZP-110 that produced a sleep state of approximately 7 hours. The positive controls, cocaine 10 mg/kg increased wakefulness by 14% and all three doses of amphetamine (1, 3, and 10 mg/kg) increased wakefulness by 27%, 47%, and 66% respectively. These data indicate that JZP-110 (at 10 and 30 mg/kg) has a wakefulness effect that is similar to that of cocaine (10 mg/kg) and amphetamine (all doses) both of which are controlled in Schedule II of the CSA.

Anorexic effects

Study (b) (4) 7006 was conducted to determine the effects of JZP-110 on food intake in mice. Amphetamine like stimulants have long been known to have anorexic effects (Cole, 1978). JZP-110 was tested in food non-deprived and deprived animals in both the light phase and the dark phase of the day/night cycle. Non-deprived animals treated with 60 and 120 mg/kg of JZP-110 in both phases of the light cycle experienced a significant reduction in food intake. The same is true of the deprived animals except that a dose of 120 mg/kg of JZP-110 was required in the light phase group in order to see a significant effect. Significant reductions in body weight were also seen across all of the groups. Although there was no positive control in the study this data indicates that JZP-110 produces anorexic effects expected from a stimulant drug.

Locomotor Activity

Study (b) (4) 2802 was an open field study conducted to determine the effects of JZP-110 on the locomotor activity and anxiety of C57Bl/6 mice. JZP-110 (40 mg/kg, SC), modafinil (40 mg/kg, IP), dexamphetamine (2 mg/kg, SC), and haloperidol (0, 0.0375, 0.075, and 0.15 mg/kg, SC) were used in this study. Haloperidol is a preferential D2 receptor antagonist and has been shown to block the hyperlocomotion effects induced by amphetamine but not that of modafinil (Simon et al., 1995). This suggests that amphetamine and modafinil utilize different mechanisms of action to induce their activating or hyperlocomotion effect. This is relevant for abuse because amphetamine is currently controlled in Schedule II and modafinil is controlled in Schedule IV of the CSA. This study sought to compare the hyperlocomotion effects of JZP-110, modafinil, and dexamphetamine to determine if differences in their inhibition by haloperidol could help determine if JZP-110 has a similar profile to dexamphetamine (CII) or modafinil (CIV). Data on locomotor activity are presented as the mean distance traveled in centimeters ± SEM (**TABLE 5**). Haloperidol, at all doses, significantly decreased modafinil-induced-hyperlocomotion. In JZP-110 and dexamphetamine treated animals, only haloperidol at the highest dose tested (0.15 mg/kg) reduced the distance traveled by the animals in the open field test.

Table 5: Effects of the interaction of JZP-110 ((b) (4) modafinil, and dexamphetamine with haloperidol on locomotion in the open field test (distance traveled in centimeters) (Obtained from NDA 211230, Module 4.2.1.1, study (b) (4) 2802, pg. 17)

	Haloperidol			
Treatment	0 mg/kg	0.0375 mg/kg	0.075 mg/kg	0.15 mg/kg
modafinil 40 mg/kg	10255.0 ± 559.3	7794.8 ± 416.2	7380.3 ± 314.0	6157.2 ± 448.0
R228060 40 mg/kg	5262.1 ± 699.8	4104.3 ± 304.2	4072.7 ± 285.4	2331.5 ± 251.5
dexamphetamine 2 mg/kg	4777.1 ± 550.7	4424.2 ± 280.4	3105.0 ± 347.3	1901.0 ± 207.6

Values represent means ± SEM

This study indicates that JZP-110 may have a mechanism of action more similar to that of dexamphetamine. However, the comparison was made using only a single dose of the activating drugs, therefore, a complete assessment was not made. An isobolographic analysis would compare several doses of the activating agents against several doses of the inhibitor and would give a complete

comparative analysis of the effects of these drugs. However, this type of analysis is time and resource intensive and does not need to be conducted to assess the abuse potential of JZP-110.

Study (b) (4) 3946 was another locomotion study conducted to determine the spontaneous locomotor effects of JZP-110 in DA transporter knockout (KO) mice. These KO mice are hyperactive in the open field test and drugs such as haloperidol or amphetamine reduce their hyperlocomotion when compared to wildtype (WT) mice. Female and male DA transporter KO mice were placed in the open field for 30 minutes to assess their baseline activity. They were then given vehicle, amphetamine (20 mg/kg SC), or JZP-110 (10, 30, or 100 mg/kg, SC) and returned to the open field for an additional 90 minutes. The behaviors measured were locomotor activity, rearing, and stereotypy. The KO mice produced significantly higher baseline (no drug) measurements than WT mice in all of the behaviors. The positive control, amphetamine, significantly increased all behaviors in WT mice and decreased all of the behaviors in the KO mice. On the other hand, JZP-110 did not significantly alter any of the tested behaviors in WT mice, however, the 30 and 100 mg/kg doses significantly decreased locomotor activity, rearing, and stereotypy in the KO mice. These data indicate that JZP-110 does not produce the same stimulant effect as amphetamine in WT mice at doses that have a greater inhibitory effect on movement behaviors in DA transporter KO mice.

Study 7316 was conducted to compare the toxicity of JZP-110 to bupropion because a previous study ((b) (4) 96-5) indicated that they may have a similar pharmacological profile. This study measured a series of motor effects in mice given JZP-110 (200 to 1000 mg/kg, IP) and bupropion (100 to 300 mg/kg, IP). The 200 mg/kg dose of JZP-110 produced ataxia and hypermotility which became less evident at the higher doses as the animals moved in a less coordinated fashion. The high doses of 800 to 1000 mg/kg produced a loss of the righting reflex and death. These data further substantiate the locomotor activating effects of JZP-110 at doses up to 200 mg/kg.

Study (b) (4) 15756 was conducted to evaluate the effects of JZP-110 in rats in the elevated plus maze (EPM) and spontaneous motor effects in the open field. Rats were given 5, 10, or 35 mg/kg, p.o. of JZP-110 and tested 60 minutes later in the EPM to determine the drug produced anxiogenic or anxiolytic properties. Pentylenetetrazol was used as a positive control indicated by a decrease in time spent in the open arms of the maze compared to the closed arms. JZP-110 did not differ from vehicle indicating that it does not produce anxiogenic or anxiolytic properties at the doses tested. In the open field test only the highest dose of 35 mg/kg produced a significant activating effect compared to vehicle.

Further studies conducted to support the stimulation of locomotor activity of JZP-110 were (b) (4) N01DA-7-8076-B and (b) (4) N01DA-7-8076-C. These studies were conducted in mice (Swiss-Webster) and used cocaine as a positive control. In both studies a significant stimulatory effect was measured 50-80 minutes post dosing of 10, 30, and 100 mg/kg, IP of JZP-110. An ED_{50} of 8.5 mg/kg for locomotor activity was calculated in mice. Furthermore, the mouse study indicated that doses ranging from 3 to 100 mg/kg failed to affect the locomotor activity induced by 20 mg/kg cocaine, however, a dose response curve is not presented to indicate if 20 mg/kg cocaine is producing a maximal hyperlocomotion effect that cannot be amplified (ceiling effect).

Study (b) (4) 95-9 was conducted in mice (male, CD-1) and rats (Wistar) to determine the effects of orally administered JZP-110 (100 mg/kg in mice and 30 and 60 mg/kg in rats) on spontaneous locomotor activity. Although there was a trend towards an increase in locomotor activity in mice it did

not reach statistical significance. This correlates to the data obtained in study 7316 in which no significant increase in locomotor activity was found at the doses tested, and doses above 200 mg/kg IP became toxic. However, it is in opposition to studies (b) (4) N01DA-7-8076-B and (b) (4) N01DA-7-8076-C which determined that 10, 30, and 100 mg/kg, IP of JZP-110 significantly increased locomotor activity in mice and rats. The discrepancy between the studies could be the result of the strain of animal used in each study as it is well documented that some strains of mice or rats are more sensitive to particular assays then others (Wiltshire et al., 2015; Roberts et al., 2018).

It should be noted that several studies were conducted that determined that JZP-110 does not produce pharmacological effects similar to that of classical amphetamine like stimulant drugs. For example, Study (b) (4) CPF-33 and (b) (4) CPF-536 determined that it did not alter cardiac effects (e.g. blood pressure, heart rate, and ECG morphology), study (b) (4) 8742 indicated that the drug did not possess proconvulsant effects, and study (b) (4) 2397 indicated that it did not increase attentional performance. With an unidentified mechanism of action and pharmacological and behavioral effects that are similar to and contrary to those of classical stimulants, the decision regarding the abuse liability of JZP-110 should rely directly on the nonclinical and clinical abuse studies.

The Sponsor also conducted several single dose and repeat dose toxicological studies to determine the effects of high doses of JZP-110. Single dose studies were conducted in mice, rats, and beagle dogs and drug was administered PO and IV in rodents and PO in dogs. In general, these studies found that administration of the drug correlated to stimulatory behavior resulting in restlessness, tremor, convulsions, elevated body temperature, and rhythmic head movements. The repeat dose studies were conducted in dogs, mouse, rabbit, and rat and used oral administration for all of the long-term studies. Similar behavioral profiles were observed in the long-term studies as those observed in the short-term studies.

In summary, the Sponsor conducted several animal studies indicating that JZP-110 produces stimulant-like effects. In mice, a subcutaneous dose of 2 mg/kg amphetamine produced similar hyperlocomotion as that of 20 mg/kg SC JZP-110. Furthermore, doses between 10 and 200 mg/kg IP demonstrated significant increases in locomotor behavior whereas higher doses led to ataxia and loss of the writing reflex. This data is further supported by single and multiple dose toxicological studies in multiple species in which further stimulatory behaviors were measured such as restlessness, tremor, convulsions, elevated body temperature, and rhythmic head movements. As a result, although JZP-110 is ~20-fold less potent than amphetamine, and it appears that it can produce similar stimulant effects.

2.4 Animal Behavioral Studies

Abuse liability studies

According to the Sponsor, the behavioral similarities between JZP-110 and other drugs indicate that it could possess reinforcing properties. To test this, the Sponsor conducted conditioned place preference and self-administration studies in a number of different species. These studies were followed by drug discrimination studies that compare the discriminative stimulus cues elicited by different drugs. In combination these studies are used to make a non-clinical assessment of the abuse potential of a particular substance.

Conditioned place preference

Study (b) (4)0794 was a conditioned place preference study that was used to determine if JZP-110 induced place conditioning which can be an indication of positive reinforcement. Male Sprague-Dawley rats were given amphetamine (2 mg/kg, IP), JZP-110 (10, 30, 90 mg/kg, IP), or vehicle and placed in a box, designated by the researcher (unbiased procedure) that is connected to another box through a short passageway. The boxes were differentiated by shapes placed in their walls to which the animals established discriminative stimulus cues which correlated to the drug they were given. The amount of time that an animal spends in a box paired with a particular drug stimulus gives an indication of the animal's liking of that stimulus. The vehicle treated group did not display CPP or have an increase in locomotor activity. The amphetamine positive control group had both an increase in locomotor activity and a significant preference for the animals to spend time in the drug paired box. Animals treated with 90 mg/kg JZP-110 produced a significant locomotor activating effect and a trend towards a preference for the drug paired box which did not reach significance. The two lower doses of JZP-110 did not produce a significant effect in any of the measured parameters. These results are difficult to interpret because the doses used in human study 15-009 (**Table 11**) indicate that the highest therapeutic dose would produce a C_{max} of approximately 1740 ng/mL in humans. However, the PK studies listed in section 3.1, make it difficult to correlate how rat IP administration of drug correlate to this C_{max} and the Sponsor does not support why these doses for JZP-110 were used in this study. Higher doses of the drug may produce a C_{max} that is within two to three-fold of the highest therapeutic C_{max} and might produce a significant preference for the animals to spend time in the drug paired box.

Self-administration studies

A self-administration assay is an experimental paradigm in which animals identify if a substance has positive reinforcing effects. Positive reinforcement occurs when the presentation of a desired stimulus results in an increase in behavior that is associated with the administration of the desired stimulus (Gauvin et al., 2017). For example, for abuse assessment purposes, animals are first trained to press a lever (behavior) resulting in the administration (typically IV) of a training drug (desired stimulus) known to be a drug of abuse (e.g. cocaine). Once properly trained, the animals undergo an extinction test to confirm that the training drug is the stimulus responsible for the reinforcing effects and not some other cue in the assay. Animals then receive test drug, and rates of lever pressing, and rates of injections are measured. If the rates of administered drug are significantly different from placebo and the animals are not motor impaired by the drug, as measured by rates of lever pressing, the drug is said to be self-administered (Gauvin et al., 2017).

Study (b) (4)2029 was a self-administration study conducted to determine the reinforcing effects of JZP-110 in rats. Forty-eight male Sprague-Dawley rats were surgically implanted with jugular catheters to allow for the IV administration of the control drug (cocaine) or the test drug (JZP-110). The animals were then trained in a nose-poke procedure in which a poke at either end of the chamber would be registered by a beam break. This injected drug or saline at a rate of 20 µl/s and was followed by a 40 second time out period during which no drug could be administered. There was no consequence to the animal for an incorrect nose poke. The acquisition session consisted of four separate groups with 12 animals for each group. One group was given cocaine (0.8 mg/kg/injection) and the other 3 groups were given JZP-110 at three different doses (0.25, 0.5, or 1 mg/kg/injection). Animals were trained on a fixed ratio 1 (FR1) level of reinforcement for 1 hour for a total of 9 sessions. Animals were then

progressively increased to an FR8 level of reinforcement. Test sessions were then conducted in which the animals maintained on cocaine (FR8) were given JZP-110 (10, 30, 60, or 100 mg/kg) or vehicle IP 30 minutes before the cocaine self-administration session. Comparisons were also made using amphetamine (2.5 mg/kg) administered IP 20 minutes before the cocaine self-administration session.

According to the Sponsor there are several results that can be drawn from this experiment. First, the number of active nose pokes significantly increased for cocaine as the FR schedule increased to FR8, however, for all doses of JZP-110 the number of nose pokes decreased to below 20 in the acquisition phase (first 9 sessions of FR1) (**Figure 1**). The second point focuses on the effect of the pre-administration of JZP-110 or amphetamine on cocaine self-administration. The 60 and 100 mg/kg doses of JZP-110 significantly decreased the number of active nose pokes and self-injections of cocaine however, this is presumed to be the result of a significant decrease in locomotor activity that was seen at both of these doses. Amphetamine also produced a significant decrease in the number of active nose pokes and self-injections but it did not affect locomotor activity.

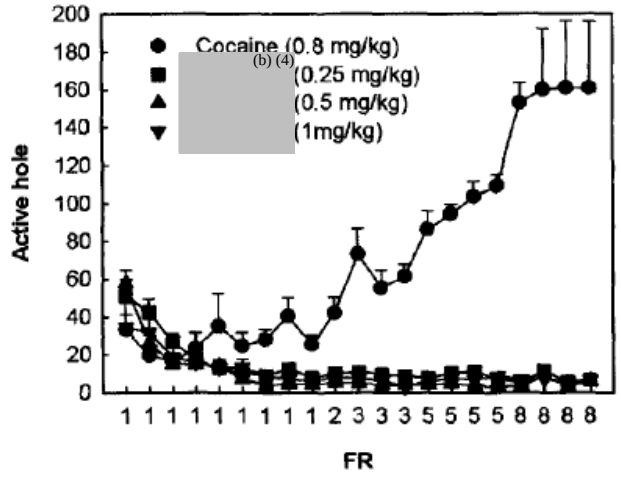


Figure 1: Cocaine and JZP-110 self-administration - acquisition to FR8 (Obtained from NDA 211230, Module 4.2.3.7.4, study (b) (4) 2029, pg. 13)

There are several problems with the design of study (b) (4) 2029 that lead to difficulties in the interpretation of the data. First, it appears as though the study did not train the animals to an FR10 schedule of reinforcement on cocaine and then challenge them with JZP-110 after 3 days with no drug (extinction). This is a standardized study design to determine the binary (yes or no) reinforcing effects of a substance. Without performing an extinction test it cannot be proven that the drug is the positively reinforcing cue, for example, the animal could be responding to a noise or light cue in the box. Secondly, in the study that the Sponsor did perform, it is clear that they were unable to train the animals to respond on the JZP-110 associated cue, however, no mention is made as to why this is the case. One could speculate that it is the result of the doses that were used to train the animals. The doses used in human study 15-009 (**Table 11**) indicate that the highest therapeutic dose would produce a C_{max} of approximately 1740 ng/mL in humans, however, the PK studies listed in section 3.1, make it difficult to correlate how rat IV administration of drug correlate to this C_{max}. Furthermore, the Sponsor does not support why the 0.25, 0.5, or 1 mg/kg/injection doses for JZP-110 were used in the study and how they

correlate to therapeutic and supratherapeutic doses. Thirdly is the effect of the pre-administration of JZP-110 (60 and 100 mg/kg, IP) which significantly decreased the locomotor activity in animals maintained on cocaine. The Sponsor does not have an answer for this decrease which is perplexing considering there are many locomotor studies (Section 2.3) indicating that JZP-110 increases locomotor activity at these doses.

Study DA-7-8073-A was a self-administration study conducted in Rhesus monkeys who were trained to self-administer cocaine (0.032 mg/kg/inj, IV) under a fixed ratio 30 (FR30) schedule of reinforcement. Two types of studies were conducted: 1) a dose ranging study and 2) the effects of the single dose JZP-110 on cocaine self-administration. In the first study, animals were given IM doses of JZP-110 10 – 32 mg/kg 30 minutes before the session. These data indicate that monkeys had a decrease in self-administration of JZP-110 at 18 or 32 mg/kg even though cocaine was able to maintain its reinforcing effects. The second study indicated that administration of 32 mg/kg IM JZP-110 reduced the self-administration of cocaine in two monkeys but had no effect in the other two monkeys. This study does not directly assess the self-administration of JZP-110, instead, it tests the effects of the drug on the self-administration of cocaine. In this study, it could be hypothesized that JZP-110 decreased cocaine self-administration in a manner consistent with a drug that is producing a similar pharmacological effect as the control drug but is less potent, as a result, less of the control drug is required to produce the same effect (e.g. a decrease in cocaine responding).

Both of the self-administration studies conducted by the Sponsor were designed and conducted in a manner that make them inadequate to fully assess the reinforcing effects of JZP-110.

Drug Discrimination

Drug discrimination is an experimental method in which animals identify whether a test drug produces physical or behavioral effects (an interoceptive response) similar to those produced by another drug with known pharmacological properties. If the known drug is one with abuse potential, drug discrimination can be used to predict if a test drug will have abuse potential in humans (Balster and Bigelow, 2003). For abuse assessment purposes, an animal is first trained to press one bar when it receives a known drug of abuse (the training drug) and another bar when it receives placebo. A challenge session with the test drug determines which of the two bars the animal presses more often, as an indicator of whether the test drug is more like the known drug of abuse or more like placebo. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing ≥80% on the bar associated with the training drug (Sannerud and Ator, 1995; Doat et al., 2003). Thus, a test drug that generalizes to a known drug of abuse will likely be abused by humans (Balster and Bigelow, 2003).

Study (b) (4) 4015 was a study that was designed to measure acquisition of a visual discrimination task in rats. Rats were trained to press a lever that was proximal to a signal light. After acquisition of the task, rats were divided into treatment groups that received either JZP-110 (3, 10, or 30 mg/kg), d-amphetamine (1 mg/kg), or vehicle. The acquisition rules were then reversed such that the animals were required to respond to the lever distal to the signal light in order to receive the food reward. Animals that received 3 or 30 mg/kg JZP-110 or amphetamine required fewer trials to reach criterion levels compared to vehicle controls. This study indicates that animals can be trained to a JZP-110 cue at these doses for further drug discrimination testing. No further comparisons can be drawn between JZP-110 and amphetamine in this study.

Study (b) (4) 9868 was a drug discrimination study designed to determine the discriminative stimulus effects of JZP-110 compared to amphetamine. Rats were trained to press a lever in a two-lever food reinforcement procedure to a fixed ratio 10 (FR10) schedule of reinforcement. Six male rats were trained to distinguish d-amphetamine (0.8 mg/kg, SC) from vehicle to an FR10 and were then challenged with JZP-110 (0, 3, 10, and 30 mg/kg, SC) in test sessions. The results indicate that three of the six rats treated with 30 mg/kg JZP-110 selected the d-amphetamine lever 50% of the time. This indicates partial generalization of the JZP-110 and amphetamine cues which indicates that JZP-110 does not have similar discriminative stimulus cues as d-amphetamine at these doses.

A second drug discrimination study ((b) (4) N01DA-7-8076-A) was conducted to determine if JZP-110 could substitute for the discriminative stimulus effects of cocaine (10 mg/kg). Similar to the above study, six male rats were trained to discriminate cocaine (10 mg/kg) from saline under a two-lever choice procedure to an FR10 schedule of reinforcement. Before testing the animals received doses of 2.5-100 mg/kg JZP-110. This dose range produced a typical inverted U-shaped response when responses per second was plotted against dose indicating that high doses of the drug have a detrimental effect on responding. The percent of cocaine-lever appropriate responding was nearly 100% at the highest dose of 100 mg/kg JZP-110, however, the animals appear to be heavily compromised since their rate of responding on the cocaine associated lever dropped by 41% of vehicle. At the highest dose where response rates appear unaffected, 30 mg/kg, JZP-110 does not generalize to cocaine with only 20% responding on the cocaine associated lever. Therefore, JZP-110 at100 mg/kg, a dose that decreases response rates generalizes to the cocaine associated cue, and it does not generalize to cocaine at a dose of 30 mg/kg which appears to have no significant effect on lever responding.

The third drug discrimination study (DA-7-8073-B) was conducted in monkeys trained to distinguish the discriminative stimulus effects of cocaine (0.40 mg/kg) from saline. Once animals met training criteria they were tested with JZP-110 (0.1 -18 mg/kg) using a substitution protocol that was interspersed with continuous training sessions. All doses of JZP-110 completely substituted for the stimulus cue induced by cocaine and produced similar response rates as those produced by cocaine. Specifically, both drugs increased response rates in two animals, did not change response rates in one animal, and decreased response rates in the fourth animal. These results suggest that despite being approximately 20-fold less potent, JZP-110 is able to fully substitute for the discriminative stimulus effects of cocaine. However, the data are variable because of the small n (n = 4) and no significant conclusions can be drawn from the study.

The drug discrimination studies indicate that in rats JZP-110 does not generalize to the amphetamine cue and does generalize to the cocaine associated cue. However, the high dose required to obtain complete generalization with cocaine produces a decrease of ~47% responding to the cocaine associated lever. A drug discrimination study in monkeys trained to discriminate cocaine from saline also produced mixed results. As a result, there is no clear indication that JZP-110 produces discriminative stimulus effects similar to that of amphetamine or cocaine.

2.5 Tolerance and Physical Dependence Studies in Animals

Study (b) (4) 95-4a – was a study that was conducted to determine the physical dependence liability of JZP-110 using codeine as a positive control. Male and female Wistar rats were given JZP-110 (10

mg/g), codeine (0.061 mg/g), or amphetamine (0.639 mg/g) by mixing the drug into their food. The animals were administered drug for seven days, on the eighth day they were weighed and switched to drug free food for 24 hours and weighed again. This process was repeated three times after which all of the animals received naloxone (50 mg/kg) to precipitate withdrawal in the codeine group. This study did not yield interpretable results because JZP-110 was found to be unpalatable by the rats. For example, the rats ate 4.4 g of JZP-110 per day while the control, codeine, and amphetamine groups all ate between 17 and 18 g per day. As a result, no conclusions can be drawn from this study regarding the physical dependence of JZP-110.

Several rat and dog toxicity studies were also conducted by the Sponsor in which chronic dosing of JZP-110 was followed by abrupt discontinuation of the drug (studies (b) (4) TOX-5705 and (b) (4) TOX-5706). Male and female rats received oral doses of 600 or 450 mg/kg of body weight/day for 6 consecutive months followed by a 3-month recovery period (animals given 600 mg were dropped to 450 mg on day 93 because of increased mortality). In the dog study, male and female animals received oral doses of JZP-110 (0, 10, 25, 50 mg/kg/day) for one year followed by a 13-week treatment free period. There was no indication of withdrawal from discontinuation of the drug, a hallmark of physical dependence. Therefore, JZP-110 does not appear to produce physical dependence in rats or dogs at the doses tested. This is consistent with what is known about stimulant products of the amphetamine class which produce psychological dependence but little to no physical dependence (Malenka RC, 2015).

3. Clinical Pharmacology

The clinical pharmacology of a substance is an assessment of how that substance associates with the body and typically includes measurements of PK, pharmacodynamics, toxicology, drug interactions and several other parameters. For abuse purposes, these data are used to determine mechanism of action, whether or not the drug enters and has activity in the CNS, and whether the drug produces psychoactive effects. The data that was submitted appears sufficient to conclude that JZP-110 has high oral bioavailability, is quickly absorbed, is not greatly metabolized, and is excreted in the urine.

3.1 Absorption, Distribution, Metabolism, Elimination (ADME)

This section gives an overview of the nonclinical and clinical data that were submitted as part of NDA 21130 in regard to the multitude of studies that were conducted to assess the pharmacokinetics, absorption, distribution, metabolism, and elimination of JZP-110.

Pharmacokinetics and Absorption

Study 0830XY01-001 was a PK study for JZP-110 using oral and IV administration in rats and mice. As a preliminary study there was an N=1 for each group, therefore the power of the study is not considered strong enough to be significant. The Sponsor then conducted studies to determine the PKs in mice (Study (b) (4) 95-06) and rats (Study 0830XY01-002). The mouse study administered a single oral or IV dose of JZP-110 at 35 mg/kg to male CD-1 mice. The data presented in **Table 6** indicate that there are no real differences between the PK parameters in mice when JZP-110 is administered orally versus IV. The drug is quickly absorbed with a T_{max} of less than 30 minutes and is widely distributed with a large volume of distribution (V_d) (5.98 L/kg) when administered IV.

Table 6: Mean PK of JZP-110 in male mice after oral or IV administration (Obtained from NDA 211230, module 4.2.2.2, study (b) (4) 95-06, pg 6)

Route	Dose	Sex	Cmax (µg/mL)	Tmax (hr)	$AUC_{(0-t)}$ (hr*µg/mL)	T1/2 (hr)	V_d (L/kg)
PO	35	M	7.68	0.25	8.14	0.96	-
IV	35	M	10.2	-	8.04	0.95	5.98

Study 0830XY01-002 consisted of two groups of 15 rats each; one group was orally administered 20 µCi/kg of 14C-loriamfetol and the other group received the same dose administered IV. The data presented in **Table 7** indicate that the PK parameters appear relatively similar between oral and IV administration of the drug, although there were sex differences. Female rats appear to have a higher C_{max} and AUC than their male counterparts. These data also indicate that the drug is quickly absorbed with a T_{max} of 1 hr and that approximately 80% of the drug is excreted in the urine 72 hours after administration.

Table 7: Mean PK and percent recovery of JZP-110 in male and female rats administered PO and IV (Obtained from NDA 211230, module 4.2.2.2, study 0830XY01-002, page 2)

Route	Sex	C_{max} (µg*eq/g)	T_{max} (hr)	AUC_{0-24hr} (µg*eq*hr/mL)	Urine recovery (% of dose)	Feces recovery (% of dose)
PO	M	7.43	1	35.36	76.6	14.4
PO	F	9.03	1	40.26	81	6.7
IV	M	6.88	1	37.75	83.7	11.8
IV	F	10.3	1	50.72	80.4	13.7

A second study ((b) (4)-20082733) was conducted to measure the PKs of JZP-110 in juvenile (postnatal day 28) rats at oral doses of 35, 80, and 200 mg/kg. Blood samples were obtained at 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose. The results of this study are presented in **Table 8** and indicate that there are no significant differences between male and female rats that were present in the adult rats used in study 0830XY01-002. The C_{max}, AUC, and half-life increased dose dependently and the T_{max} of 0.5 hrs indicates that the drug is quickly absorbed.

Table 8: Mean PK of JZP-110 in juvenile rats following oral administration (obtained from NDA 211230; module 4.2.2.2, study (b) (4)-20082733, pages 120-121)

Route	Dose	Sex	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{(0-t)}$ (hr*ng/mL)	$T_{1/2}$ (hr)
PO	35	M	5620	0.5	14200	1.41
PO	80	M	7670	0.5	35900	1.98
PO	200	M	11500	0.5	104000	3.82
PO	35	F	4960	0.5	15600	1.71
PO	80	F	7290	0.5	39800	1.6
PO	200	F	14900	0.5	108000	4.38

After determining the PK of JZP-110 in mice and rats the Sponsor continued measuring the PK of the drug using beagle dogs. The Sponsor used a crossover study design to give 4 male beagle dogs a single oral dose or a single IV dose of 35 mg/kg JZP-110. The data presented in **Table 9** support the previously collected data from mice and rats indicating that JZP-110 is quickly absorbed and distributes extensively into surrounding tissues. The major difference is that the drug had a 4-hour half-life in dogs compared to one hour in mice and rats.

Table 9: Mean PK of JZP-110 in male beagle dogs after oral or IV administration (Obtained from NDA 211230, module 4.2.2.2, study (b) (4) 96-02, pg 6)

Route	Dose	Sex	Cmax (µg/mL)	Tmax (hr)	$AUC_{(0-t)}$ (hr*µg/mL)	T1/2 (hr)	V_d (L/kg)
PO	35	M	11.39	1.33	86.56	3.8	-
IV	35	M	15.95	-	99.67	4.1	2.08

Several studies were conducted by the Sponsor assessing the safety and PK of JZP-110 in humans. Studies (b) (4) 9603-01 (nine subjects per group) and (b) (4) P01-101 (4 subjects per group) determined the PK of single oral doses of the drug between doses of 42 – 1008 mg in healthy adult male subjects. These studies concluded that the C_{max} and AUC of the drug increase in a linear dose-dependent fashion throughout the tested dose range and that the T_{max} varies from 1.64 to 2.5 hours (dose independently) (**Table 10**). JZP-110 also has a dose dependent half-life ranging from 4.99 to 6.67 hours.

Table 10: Mean PK of single oral dose of JZP-110 in male adult human subjects (obtained from NDA 211230, module 5.3.3.1, study (b) (4) 9603-01, pg 65)

Route	Dose (mg)	Sex	Cmax (ng/mL)	Tmax (hr)	$AUC_{(0-t)}$ (hr*ng/mL)	T1/2 (hr)
PO	50	M	205	1.86	1721	4.99
PO	100	M	448	1.64	4358	6.23
PO	200	M	740	2.43	6920	5.24
PO	400	M	1482	2.08	16690	5.97
PO	600	M	2228	2.36	25521	6.67
PO	800	M	3003	2.1	34855	6.49
PO	1000	M	3948	1.93	40348	6.14
PO	1200	M	4578	2.5	49482	6.3

The Sponsor conducted two studies to assess the effects of multiple doses, food, and sex differences in human subjects ((b) (4) NED-1 and 15-009). These studies indicated that there are no significant sex differences and that the fed state has only a slight effect on slowing the C_{max} and the T_{max} of the drug (**Table 11**).

Table 11: Mean PK of single oral dose of JZP-110 in fasted or fed state (obtained from NDA 211230, module 5.3.3.4, study 15-009, pg 145-46)

Route	Dose (mg)	Sex	Fed or Fasted	Cmax (ng/mL)	Tmax (hr)	$AUC_{(0-t)}$ (hr*ng/mL)	T1/2 (hr)
PO	350	M/F	Fasted	1740	2.13	16937	6
PO	350	M/F	Fed	1650	3.14	16626	5.9

The Sponsor also conducted several PK measurements as part of their long-term toxicity studies:

1. Study (b) (4) 96-06 was a 90-day study administering JZP-110 at doses of 9, 18, or 27 mg/kg/day in beagle dogs.
2. Study (b) (4) 96-07 was a 90-day study administering JZP-110 at doses of 35, 110, or 350 mg/kg/day in rats.
3. Study (b) (4) 96-06 was a 52-week study administering JZP-110 at doses of 10, 25, or 50 mg/kg/day in beagle dogs.

The studies concluded that there were no apparent sex differences and that there were no significant differences in PK between the effects of repeated and single dosing of the drug.

Distribution

Study (b) (4) 0833XY01-001 was conducted to compare the plasma binding properties of JZP-110 in different species. In human and mouse plasma the drug was bound 13.6% and 13.3%, respectively; less bound in the rat, rabbit, and dog. This indicates that the drug is 86.7% unbound in human plasma which correlates with its rapid T_{max} and distribution observed in the PK studies.

The direct tissue distribution of the drug was determined in studies (b) (4) FK4423 and (b) (4) FK4424. Both studies used a single oral dose of ^{14}C labeled drug in rats to measure whole-body autoradiography over the course of 14 days. The studies indicated that the amount of radioactivity measured in the kidney and liver were approximately 11 times those in the blood, and levels 3.5-fold of blood levels were measured in the spleen. Levels in the brain were approximately the same as those measured in the blood indicating that the drug does not appear to be restricted by the blood brain barrier.

Metabolism and Excretion

Studies (b) (4) DM99394 and (b) (4) FK3675 were conducted to determine the metabolism of JZP-110. The parent drug (10, 100, or 500 µg/mL) was incubated with rat or human liver microsomes for 90 minutes and analyzed using mass spectrometry. The data supported that of the in vivo mass balance studies indicating that most of the drug is excreted unchanged. The results measured 95% parent drug and three minor metabolites; OH-phenyl-YKP-10A (< 0.5%), O-desamido-YKP-10A (< 0.5%), and desamino-YKP-10A (2%). As a result, JZP-110 does not appear to be extensively hepatically metabolized.

Two in vivo study were conducted to determine the metabolism and excretion of JZP-110; one was conducted in rats ((b) (4) FK4450) and the other was conducted in beagle dogs ((b) (4) 4618). In the rat study, 41% (male) and 54% (female) of the drug was excreted unchanged in the urine after an oral dose

of 100 mg/kg ^{14}C-JZP-110. The most prominent metabolic pathway found in the rat was through aromatic hydroxylation at the para position on the phenyl moiety resulting in the formation of R33023 (M5) which was excreted in the feces. The M5 metabolite produced approximately 14% of the radioactive dose. The M5 metabolite could undergo subsequent glucuronidation to produce M1 which was solely detected in the urine. In beagle dogs, JZP-110 was dosed to 15 mg base-eq./kg and the metabolism, excretion, and plasma PK were measured. In this study the majority of the 70% of the dose was excreted as parent drug in the feces and only 3 minor metabolites could be detected in the urine. M1, M2, and M3 were detected at 1.75%, 0.73%, and 2.83% respectively of the administered dose, and therefore don't fit the criteria of being major metabolites.

The metabolism and excretion of JZP-110 in humans was assessed in study (b) (4) P01-101 entitled: The absorption, metabolism, and excretion of 14C-(b) (4) after a single oral dose in healthy male subjects. A dose of 200 mg was given to four healthy adult male subjects based on the safety and tolerability profile of a single dose that can be administered without titration. Blood, plasma, urine, and feces were collected and analyzed for up to 7 days post administration of the drug which was based on a previously calculated elimination half-life of 5.2 hours. This study concluded that approximately 95% of the radioactivity is excreted in the urine with an additional 1% excreted in the feces. Furthermore, in the mass balance study, the total mean plasma concentration of unchanged drug decreases with time at the same rate as the total radioactivity indicating that the drug is not heavily metabolized or does not place those metabolites into the blood stream.

3.2 Drug-Drug Interactions

The majority of individuals with a drug abuse disorder use multiple drugs in search of the desired high and effect. As a result, the importance of determining drug-drug interactions for the safety of the individual is paramount.

Three studies were conducted to determine if JZP-110 interacts with drug transporters such as P-glycoprotein 1 (P-gp) which can alter drug permeability across the blood brain barrier. In vitro binding studies (b) (4) 8304273, (b) (4) 8335453, and (b) (4) 168124 indicate that JZP-110 is not a substrate for or inhibitor of a panel of drug transporters. Therefore, it is unlikely that JZP-110 will cause drug-drug interactions through this mechanism of action.

An in vivo study (1868), was conducted to determine the effects of JZP-110 on ethanol induced anesthesia. Ethanol has many mechanisms of action, however, it is known to be a positive allosteric modulator of the gamma-aminobutyric acid A channel ($GABA_A$) similar to the benzodiazepines, although binding to a different location on the channel. In this regard, this study may give an indication about the effects of JZP-110 on controlled GABA modulators. Adult male mice were first given an oral dose of JZP-110 (100 mg/kg) followed 60 minutes later by a nonhypnotic dose of ethanol (3 g/kg, IP). The animals in the control group, ethanol only group, and those that received both drugs exhibited perfect scores in the righting reflex test. At the doses tested, JZP-110 appears to have no effect on ethanol, however, a full dose response curve was not conducted to test the effect of multiple, specifically higher doses.

4. Clinical Studies

Of the 17 completed clinical studies in the JZP-110 clinical program, three have been conducted in subjects with narcolepsy, two in subjects with OSA, three in subjects with major depression disorder [(MDD) (b) (4)], six in healthy volunteer subjects (including one study to evaluate the effects of JZP-110 on QT/QTc interval), and three in special populations (two studies in subjects with a history of recreational drug use [polydrug and stimulant] and 1 study in subjects with normal or impaired renal function). Adverse events (AEs) were coded using MedDRA version 18.0 to classify events under primary system organ class (SOC) and preferred term (PT).

4.1 Human Abuse Potential Studies

The Sponsor conducted two human abuse potential studies (HAPs), Study (b) (4) SAB-101 and Study 14-001. In the first Study the relative abuse potential of the study drug was compared to that of methylphenidate (Schedule II), and in the second study it was compared to phentermine (Schedule IV)

The next sections provide a summary of these studies and conclusions.

4.1.1 A 2-Week, Double-Blind, Randomized, Placebo-Controlled, Crossover Study of Single Doses of (b) (4) (400 mg, 800 mg and 1,200) mg and Methylphenidate (45 mg and 90 mg) in Adults (N=18) with Polysubstance Abuse. (b) (4) SAB-101. This was an in-patient study.

The following details of the study design described below is derived from the Sponsor's synopsis:

Primary objective: To characterize the abuse potential of (b) (4) as compared with placebo in 18 subjects with recent histories of illicit drug use.

Secondary objective: To test the hypothesis that (b) (4) at doses up to 3 times the proposed therapeutic dose of 400 mg, could be distinguished from methylphenidate (MPH).

This study was a single center, 2-week, double-blind, randomized, placebo-controlled, crossover, Phase 1 study in which 18 subjects (12 men and 6 women between 21 and 55 years of age, inclusive) were enrolled. The subjects were randomly assigned to 1 of 6 treatment-sequence groups. All subjects received 1 dose of placebo, 2 doses of MPH (45 mg and 90 mg) and 3 doses of (b) (4) (400 mg, 800 mg, and 1,200 mg) in a sequence determined by the group to which they were assigned. They received a single dose of drug ((b) (4) or MPH) or placebo on each of 6 treatment days during the study. Doses were administered at 48-hour intervals. The subjects were sequestered for a total of 14 days.

Number of Subjects: Planned: 18. Analyzed: 18.

Diagnosis and Main Criteria for Inclusion:

Men and women with a documented history of recent substance abuse, including the abuse of at least 1 drug in the stimulant class (e.g., dexamphetamine, amphetamine, MPH, cocaine) were enrolled. Subjects must have demonstrated a historical pattern of regularly abusing stimulants, such as cocaine and/or amphetamines, for a minimum of a 1-month period, and must have used stimulants within the last 30 days.

- The primary abuse liability variables were: Liking score from the Drug Rating Questionnaire-Subject (DRQS). The DRQS includes 3 visual analog scales that increase from 1 on the left ("not at all") to 29 on the right ("an awful lot"). The "liking" score is the subject's response to the question "Do you like the effects you are feeling now?" and was considered the primary abuse potential measurement.
- Morphine benzedrine group (MBG) scale score from the Addiction Research Center Inventory (ARCI).

To test the sensitivity of the study in assessing drug stimulant activity, the results of each MPH dose group was compared with placebo. Neither the 45 mg (mean Drug Liking 4.39±7.04) nor the 90-mg dose (mean Drug Liking 4.89 ±4.97) of MPH produced results that were statistically significantly different from placebo (mean Drug Liking (5.28±7.09). Similarly, for the MBG scale score, differences between both doses of MPH were not significantly different from placebo.

Therefore, since the positive control did not separate from placebo, the study is invalid. According to the results of the DRQS, (b) (4) was most "liked" at its lowest dose (400 mg) although this result was not significantly greater than placebo (mean difference 4±8.19; p= 0.054). None of the treatment arms, including both doses of MPH, was significantly different from placebo on the paired t-test.

(b) (4) 1,200 mg showed a statistically significant difference compared with placebo in euphoria as measured by the ARCI MBG scale.

Conclusions: CSS agrees with the Sponsor, that this study is not valid, however the reasons are unclear. Since there was no Qualification Phase, subjects entered in this study may not have been sensitive to MPH. The DRQS Drug Liking VAS scale scores ranged from 1-29, and this narrow range may not have been sensitive to detect differences between groups.

Euphoria (5-17%) occurred at similar rates in the active treatment groups (MPH and study drug). These findings would suggest that although both drugs did not differentiate from placebo, both drugs displayed euphorigenic properties.

4.1.2. A Randomized Double-Blind, Placebo-Controlled, Crossover, Human Abuse Liability Study of JZP-110 in Recreational Polydrug Users with Recent Histories of Stimulant Use. 14-001.

In this study the relative abuse potential of single doses of JZP-110 (300 mg, 600 mg and 1,200 mg) was studied relative to that of phentermine (45 mg and 90 mg). Thirty-seven out of 43 enrolled subjects completed the study. Unlike the study described above, this study included a Qualification Phase, and the primary Drug Liking endpoint was measured in a bipolar VAS scale with a 0 to100 range. This was an inpatient study.

Primary objective:

- To evaluate the abuse potential of JZP-110 compared to phentermine and placebo in 30 recreational polydrug users with recent histories of stimulant use.

Secondary objective:

- To evaluate the safety and subjective effect profile of JZP-110 compared to phentermine and placebo in 30 recreational polydrug users with recent histories of stimulant use.

This was a randomized, double-blind, placebo-controlled crossover study comparing the abuse potential of JZP-110 to placebo and phentermine (a C-IV stimulant positive control). The study had three phases: A Screening Phase, a Qualification Phase, and a Test Phase.

Inclusion Criteria:

- History of recreational polydrug drug use as determined by self-reported nontherapeutic use of a drug (i.e., to get high) from ≥2 illicit drug classes, including a stimulant drug (i.e., cocaine, amphetamine, methamphetamine, methylphenidate, or phentermine).
- Recreational use of a stimulant drug (i.e., cocaine, amphetamine, methamphetamine, methylphenidate, or phentermine) at least 10 times in the past 5 years and at least once in the past 3 months.

Exclusion Criteria:

- Current diagnosis of substance dependence according to Diagnostic and Statistical Manual of Mental Disorders (DSM) Edition 4, Text Revision (DSM-IV TR) criteria or a severe substance use disorder according to DSM Edition 5 (DSM-5) criteria (except for nicotine or caffeine).
- Current or past treatment (within the past 2 years) for a substance related disorder.
- Seeking treatment for a substance related disorder.
- Daily caffeine use at the Screening Phase >600 mg/day of caffeine or >6 cups of coffee/day.
- Daily cigarette use >20 cigarettes/day or any other daily use of nicotine-containing products.
- Positive urine drug or alcohol screen (except for tetrahydrocannabinolic acid [THCA] and benzodiazepines) on admission to the Qualification Phase (Day -1) or Test Phase (Day T1) visits.

Primary Endpoint

- Peak (Emax) ratings of liking across the first 12 hours of drug effect on a bipolar VAS

Key Secondary Endpoints

- Overall Drug Liking (next-day ratings at 24 hours) on a bipolar VAS
- Overall Take Drug Again, i.e., how much the subject would like to take the drug again (next-day ratings at 24 hours), on a VAS

Qualification Phase: Subjects were randomized in a 1:1 ratio to receive either a sequence of placebo on Day 1 and phentermine 60 mg on Day 4 or a sequence of phentermine 60 mg on Day 1 and placebo on Day 4. Only subjects who tolerated phentermine and reported a greater liking for phentermine versus placebo (peak liking at least 15 points higher on a bipolar liking-disliking visual analog scale [VAS]), time-dependent effects, and neutral liking for placebo (within 40 to 60 points on a bipolar liking-disliking VAS) were eligible for the Test Phase of the study.

Test Phase: Subjects who met eligibility criteria at the end of the Qualification Phase were randomized to one of six treatment sequences in the Test Phase:
placebo; JZP-110 300, 600, and 1200 mg; and phentermine 45 and 90 mg.

Subjects resided in a closed residential research unit during the Qualification and Test Phases, including washout days. Dosing occurred in the morning on experimental session days. Subjects fasted for approximately 8 hours overnight and for at least 2 hours after dosing. On dosing days, cigarette smokers were allowed to smoke 1 cigarette upon rising and remained abstinent until the assessments scheduled for the 6-hour time point were completed. After completion of the 6-hour assessments, cigarette smokers were allowed to smoke ad libitum for the remainder of the day but were not allowed to smoke within 30 minutes prior to the assessments scheduled for 8 and 12 hours after dosing. On washout or non-dosing days, cigarette smokers were allowed to smoke ad libitum (in accordance with the rules of the study site) after vital signs and any scheduled 24-hour assessments were completed. Caffeine use was not allowed during the study.

Phentermine (PTN) was chosen as a positive control because it is a scheduled stimulant drug in C-IV of the CSA, with measurable abuse potential. The two doses of 45 and 90 mg PTN were chosen based on the significant effects that were reported for doses of PTN on measures of abuse potential in previous HAP studies (Jasinski et al. 2008, Schoedel et al. 2012). A 300 mg dose of JZP-110 is the highest planned therapeutic dose. Thus, the range of doses in this study (300 to 1200 mg) includes one dose within the therapeutic dose range and two supra-therapeutic doses up to approximately four times the highest planned therapeutic dose. The high supra-therapeutic dose of 1200 mg JZP-110 is the highest dose that has been studied in humans.

Consecutive experimental dosing days of the Test Phase were separated by 2 days to allow for a washout period between experimental conditions. This washout period of 72 hours roughly corresponds to four times the maximum t1/2 of the longest acting drug in the study (the mean terminal t1/2 of PTN is approximately 20 hours) and is greater than five times the t1/2 of JZP-110 (6 to 7 hours).

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) system, version 17.0, to classify events under primary system organ class (SOC) and preferred term.

Results: Forty-three subjects were randomized into the test phase and all received study drug in that phase. Thirty-seven of the 43 subjects (86.0%) completed the study. Six of the 43 subjects (14.0%) discontinued the study: 4 withdrew due to personal reasons and 2 discontinued due to adverse events. The 43 subjects who entered the test phase (i.e., the safety population) ranged in age from 19 to 52 years (mean= 29.3 years, SD=7.11). The population included 32 males (74.4%) and 11 females (25.6%).

During the qualification phase, in the Per Protocol (PP) population (N=37), the mean Emax on the Liking at the Moment VAS was 85.6 (SD=10.79) for PTN 60 mg and 50.2 (SD=1.01) for placebo.

A statistics consult from the Division of Biometrics VI was obtained for this HAP study (Liu, Wei; DARRTS July 26, 2018)

HAPS VAS and Abuse Related Measurements Test Phase

Primary end point:

The HAP study was validated since both doses of PTN produced statistically significant higher ratings than placebo for Drug Liking at the Moment (with lower bound value of 15 (δ_1= 15); **Table 13**).

There was a dose related increase in Drug Liking at the Moment for JZP-110 which was statistically greater than placebo for all JZP doses (**Tables 12 and 13**) with upper bound values higher than margin of 11 (δ_3= 11), indicating that JZP is liked more than placebo.

As seen in **Table 13**, JZP-110 300 mg had statistically significant Drug Liking smaller mean than both doses of PTN. There was no statistically significant difference in means between JZP-110 600 mg and PTN 45 mg, JZP-110 1,200 mg and PTN 45 mg for the primary endpoint, indicating that JZP-110 at the 600 mg and 1200 mg doses is liked as much as PTN 45 mg.

PTN 90 mg had a statistically significant higher mean than any of the three doses of JZP-110. A margin of 0 was used to test the null hypothesis that the difference of the means between Control and Test drug was lower or equal to 0 (δ_2 = 0)

Table 12 summarizes the mean, standard deviation (SD), minimum (Min), first quartile (Q1), median (Med), third quartile (Q3) and maximum (Max) for the six treatment arms in the study and for the primary endpoint Drug Liking Emax N=37

Table 12: Summary statistics for Drug Liking (N=37)

Treatment	Mean	SD	Min	Q1	Med	Q3	Max
PTN 45 mg	74.9	16.6	50	62	76	86	100
PTN 90 mg	86.3	11.9	60	78	87	99	100
JZP-110 300 mg	65.3	17.0	50	50	57	78	97
JZP-110 600 mg	70.9	14.7	50	58	68	84	98
JZP -110 1200 mg	79.6	15.9	50	69	79	94	100
Placebo	52.7	6.1	50	50	50	53	81

The mean time course profiles by treatment for Drug Liking and High VAS are presented in **Figures 2** and **3**, respectively. These figures show that JZP-110 and PTN have similar onset. The effects of the higher dose of JZP-110 as well as those of both doses of PTN last for approximately 4 hours.

Figure 2: (Liu, Wei; DARRTS July 26, 2018). Time Course of Mean Drug Liking VAS Scores Over Post-Dosing Hour (Completers, N = 37)

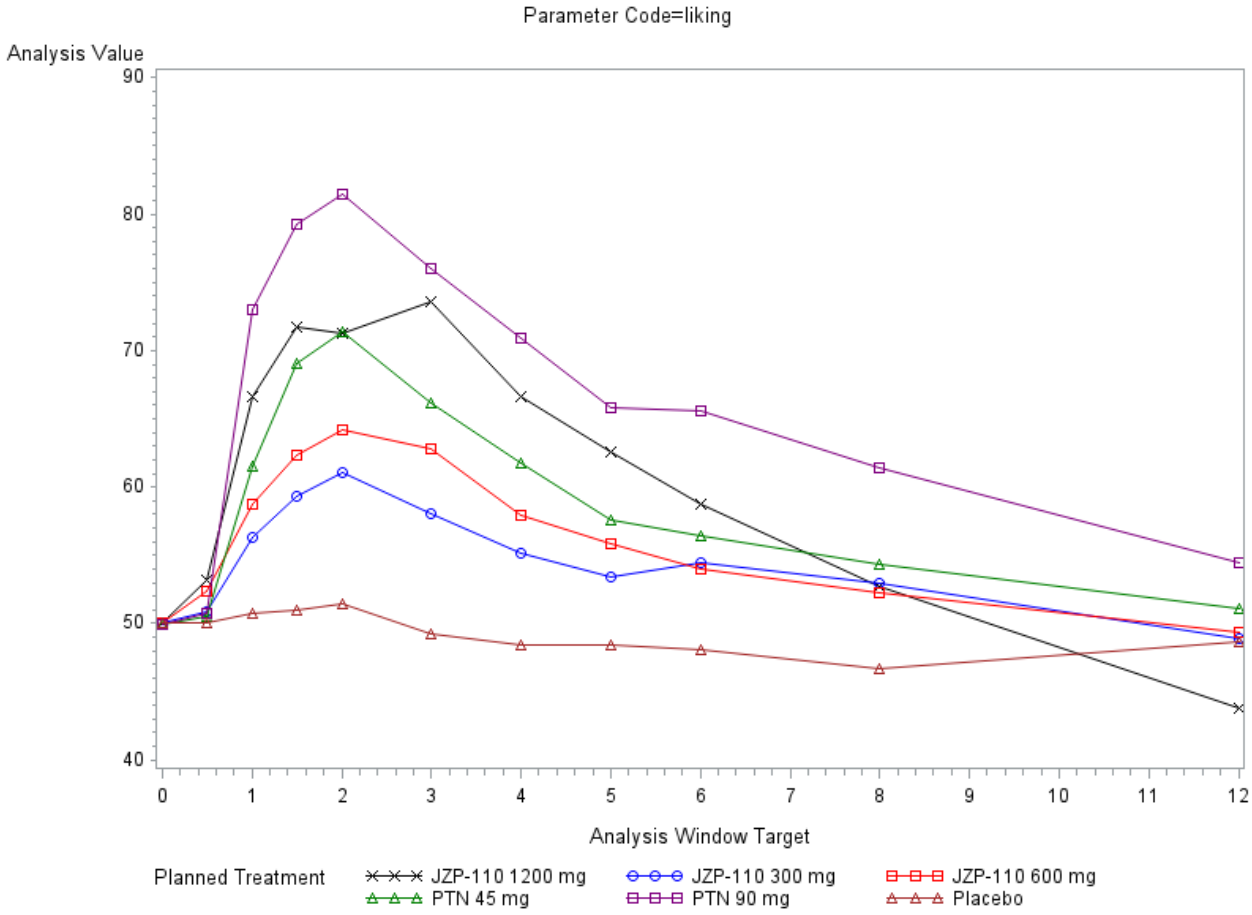


Figure 3: (Liu, Wei; DARRTS July 26, 2018). **Time Course of Mean High VAS Scores Over Post-Dosing Hour (Completers, N =37)**

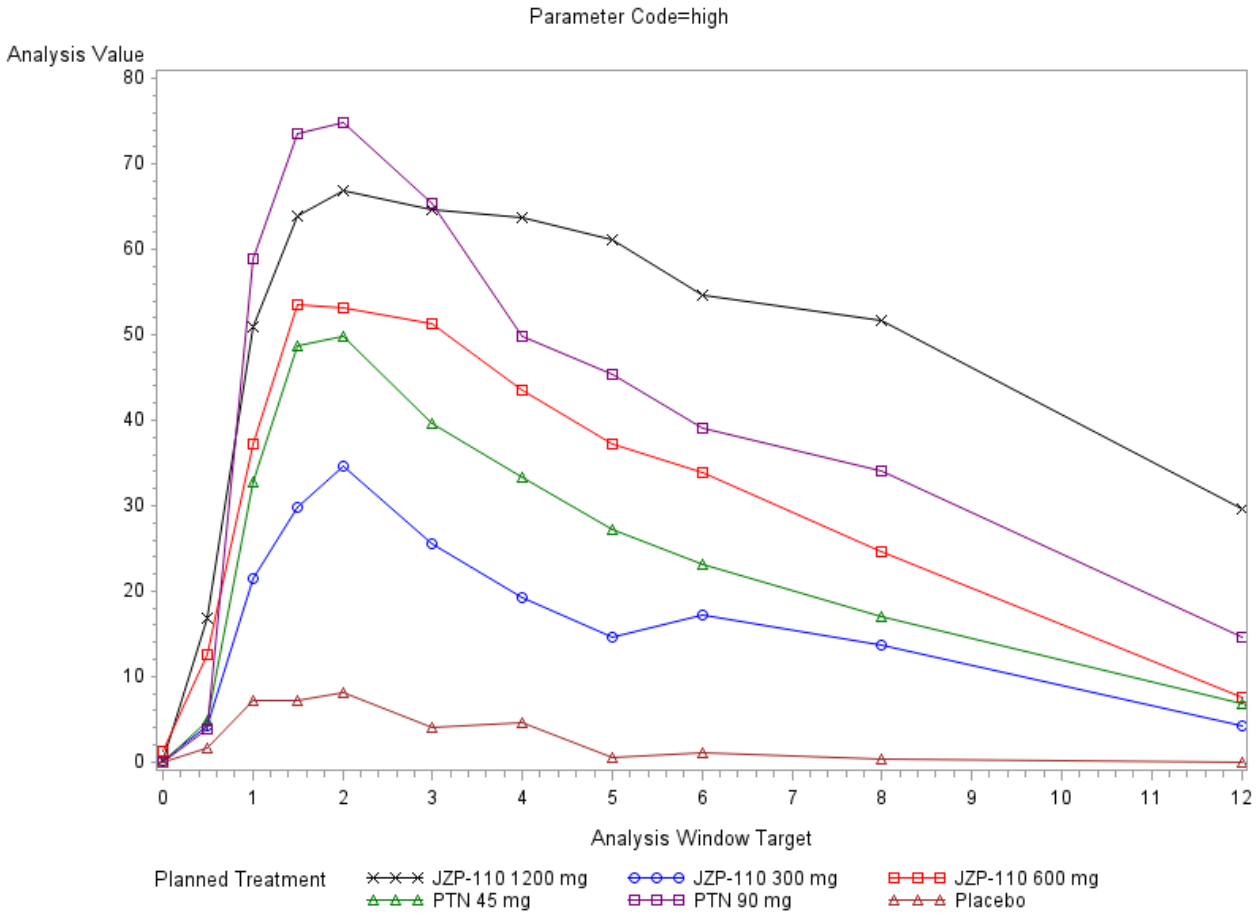


Table 13 summarizes the adjusted Mean Difference, 95% confidence interval, and p-value between Primary Endpoint for Controls (PTN 45mg and PTN 90 mg), Treatment (JZP-110 300 mg, JZP-110 600mg and JZP-110 1,200 mg) and Placebo (N=37)

Table 13: Statistical analysis for Drug Liking (N=37)

Measure	mean	SD	95% Confidence Interval		p-value
			Lower limit	Upper limit	
PTN 45 mg - Placebo	22.7	26.3	15.0	infinity	0.0499
PTN 90 mg - Placebo	36.6	19.0	31.0	infinity	<0.0001
PTN 45 mg - JZP-110 300 mg	11.0	37.1	0.6	infinity	0.0420
PTN 45 mg - JZP-110 600 mg	4.5	37.3	-6.0	infinity	0.2355
PTN 45 mg - JZP-110 1200 mg	-4.0	38.0	-14.7	infinity	0.7348
PTN 90 mg - JZP-110 300 mg	24.9	32.3	15.8	infinity	<0.0001
PTN 90 mg - JZP-110 600 mg	18.4	32.5	9.1	infinity	0.0014
PTN 90 mg - JZP-110 1200 mg	9.9	33.3	0.5	infinity	0.0419
JZP-110 300 mg - Placebo	11.7	26.4	infinity	19.4	0.5622
JZP-110 600 mg - Placebo	18.2	26.7	infinity	26.1	0.9352
JZP-110 1200 mg - Placebo	26.7	27.6	infinity	34.8	0.9978

Secondary endpoints:

Table 14 summarizes the adjusted square mean Emax for primary and secondary endpoints for controls (PTN 45mg and PTN 90 mg), treatment (JZP-110 300 mg, JZP-110 600mg and JZP-110 1,200 mg) and placebo (Mean ± SD) (N=37). As seen in **Table 14**:

High VAS: All doses of JZP-110 had mean values greater than placebo, less than PTN 90mg, and similar to PTN 45 mg indicating that subjects on JZP-110 experienced a high similar to PTN 45mg

Overall Drug Liking: All doses of JZP-110 had mean values similar to placebo and PTN 45mg, but lower than PTN 90 mg indicating that subjects on JZP-110 did not like the drug more than placebo at 24 hours.

Take Drug Again: All doses of JZP-110 had lower mean values than both doses of PTN and higher than placebo indicating that at 24 hours, subjects would take all doses of JZP-110 over placebo, but not over either dose of PTN

Table 14 Emax Values for the Primary and Secondary Endpoints for JZP-110 versus PTN and placebo

Measure	Placebo	Control Low Dose PTN 45 mg	Control High Dose PTN 90 mg	Treatment Low Dose JZP-110 300 mg	Treatment Mid Dose JZP-110 600mg	Treatment High/Dose JZP-110 1,200 mg
Drug Liking (bipolar)	50.7±2.0	73.4±26.2	87.3±18.9	62.4±26.3	68.9±26.7	77.4±27.6
High Vas (Unipolar)	6.1±29.3	51.2±45.3	84.0±23.8	34.5±48.2	67.9±36.0	64.3±53.4
Overall Drug Liking (bipolar)	46.4±19.8	54.1±31.7	65.9±41.8	49.1±40.2	46.9±31.8	40.8±46.8
Take Drug Again (unipolar)	11.2±32.3	34.5±57.3	52.6±68.8	20.0±38.6	20.0±46.1	25.6±61.0

In conclusion the positive effects (Drug Liking and High) of JZP-110 1,200 mg may be comparable to those of PTN 45 mg. The Drug Liking effects of JZP-110 300 mg and 600 mg were lower than those of both doses of PTN. As the overall experience and the willingness of subjects to take the drug again, the effects of the three JZP doses were lower than those of both doses of PTN.

The abuse related AEs for the HAP study are displayed in **Table 15**. Feeling of relaxation and elevated mood increased in a dose dependent manner with JZP-110, higher than placebo, and similar to PTN. Rates of abuse related AEs were similar in the JZP-110 and phentermine groups: Feeling of relaxation JZP-110: 5-19%, phentermine: 15-20%, elevated mood JZP-110: 8-24%, phentermine: 10-18%; euphoric mood JZP-110: 0%, phentermine: 0-3%.

Table 15: Abuse Related Treatment-Emergent Adverse Events by SOC and PT HAP study 14-001 - Test Phase (N %)

	Placebo (N=41)	**JZP-110 300 mg (N=38)**	**JZP-110 600 mg (N=41)**	**JZP-110 1200 mg (N=42)**	**PTN 45 mg (N=40)**	**PTN 90 mg (N=40)**
Feeling of relaxation	2 (4.9)	2 (5.3)	5 (12.2)	8 (19)	6 (15)	8 (20)
Feeling abnormal	1 (2.4)	3 (7.9)	2 (4.9)	4 (9.5)	1 (2.5)	3 (7.5)
Energy increased	0	1 (2.6)	4 (9.8)	3 (7.1)	0	3 (7.5)
Feeling jittery	0	1 (2.6)	1 (2.4)	3 (7.1)	0	1 (2.5)
Sedation	3 (7.3)	1 (2.6)	1 (2.4)	0	2 (5)	1 (2.5)
Disturbance in attention	1 (2.4)	0	0	1(2.4)	0	0
Hypervigilance	4 (9.8)	14 (37)	12 (29.2)	18 (43)	16 (40)	18 (45)
Elevated mood	1(2.4)	3 (7.9)	4 (9.8)	10 (23.8)	4 (10)	7 (17.5)

Insomnia	0	1 (2.6)	2 (4.9)	7 (16.7)	2 (5)	7 (17.5)
Irritability	1 (2.4)	0	2 (4.9)	0	4 (10)	3 (7.5)
Restlessness	0	0	0	6 (14.3)	1 (2.5)	1 (2.5)
Anxiety	0	1 (2.6)	2 (4.9)	0	1(2.5)	1(2.5)
Euphoric mood	1(2.4)	0	0	0	1(2.5)	0
Logorrhea	0	1(2.6)	0	1(2.4)	0	0
Hyperhidrosis	0	2 (5.3)	5 (12.2)	8 (19)	5 (12.5)	5 (12.5)

In summary, based on the HAP study results showing that the PD effects of Drug Liking and abuse-related AEs of JZP-110 are greater than placebo and similar to PTN (a Schedule IV controlled substance), we conclude that JZP-110 likely has an abuse potential similar if somewhat less than PTN.

4.2 Adverse Event Profile Through all Phases of Development

Phase 1 Studies: The Sponsor conducted 6 Phase 1 studies in healthy volunteer subjects (including 1 study to evaluate the effects of JZP-110 on QT/QTc interval, and 1 study in subjects with normal or impaired renal function). Table 16 displays the abuse related AEs in these studies.

Table 16: Abuse related AEs in Phase 1 Studies N (%) (Results pooled by CSS)

System Organ Class Preferred Term, n (%)	**Placebo N=120**	**Combined JZP-110 N=251**	**≤300 mg N=46**	**>300 - 800 mg N=123**	**>800 mg N=82**
Disturbance in attention	5 (4.2)	29 (11.6)	0	29 (23.6)	0
Somnolence	8 (6.7)	14 (5.6)	0	13 (10.6)	1 (1.2)
Affect lability	2 (1.7)	13 (5.2)	0	13 (10.6)	0
Hypervigilance	0	6 (2.4)	6 (13)	0	0
Euphoria	2 (1.7)	4 (1.6)		4 (3.3)	
Agitation	3 (2.5)	23 (9.2)		23(18.7)	

Disturbance in attention, affect lability, hypervigilance, and agitation occurred at a higher rate in JZP-110 treated subjects versus placebo.

Phase 2 and 3 Studies

A 6-Week, Randomized, Double-Blind, Parallel-Group, Active- and Placebo-Controlled Study to Assess the Efficacy of (b) (4) in Adult Subjects with Major Depressive Disorder (MDD) (b) (4) MDD-201 Phase 2a

The primary objective of this study was to determine the efficacy of 2 doses of (b) (4) in comparison with placebo during 6 weeks of treatment in adult subjects with moderate or severe major depression

without psychotic features. An active comparator (paroxetine) was included. This was a randomized, double-blind, parallel-group, active, and placebo-controlled, multicenter study. There were 2 phases: a pretreatment phase (screening/washout and a baseline visit) and a 6-week, double-blind treatment phase. Subjects were randomly assigned (1:1:1:1) to receive (b) (4) titrated to a target dose of 200 mg/day or 400 mg/day, matching placebo, or a fixed dose (20 mg/day) of paroxetine. A total of 490 subjects were enrolled. There also were no reports of diversion of drug from the study. The abuse-related AEs are displayed in Table 17.

Table 17: Abuse related AEs N (%) Study (b) (4) MDD-201 (Results pooled by CSS)

	Placebo N=121	**(b) (4) 200mg N=120**	**(b) (4) 400mg N=125**	**(b) (4) total N=245**	**Paroxetine N=122**
Insomnia	12 (9.9)	29 (24.1)	44 (35.2)	73 (29.8)	21 (17.2)
Agitation	2 (1.7)	5 (4.2)	10 (8)	15 (6.1)	2 (1.6)
Somnolence	9 (7.4)	7 (5.8)	5 (4)	12 (4.9)	15 (12.3)
Drug abuse	1 (0.8)	1 (0.8)	1 (0.8)	2 (0.8)	1 (0.8)
Euphoria	1 (0.8)	0	1 (0.8)	1 (0.4)	0

A Double-Blind, Placebo-Controlled, Randomized, Single Center, Parallel Design Study to Evaluate the Preliminary Efficacy and Safety of Three Dose Ranges of YKPlOA in Outpatients with Major Depressive Disorder SKUP-9801 Phase: 2a SKUP-9801

The primary objective of this study was to assess the efficacy and safety of YKPlOA in relieving major depressive illness in adult patients. This was a randomized, double-blind, placebo-controlled, dose-ranging, parallel-group, single center study of male and female patients aged 18 to 70 years who met the criteria for major depressive disorder (single or recurrent episode).

A total of 43 patients were screened for this study. Of these 43 patients, 35 were randomized to treatment: a low dose range (100-300 mg/day), a medium dose range (400-600 mg/day), a high dose range (700-900 mg/day), and matching placebo. Patients were randomized into one of the four treatment arms of the 8-week treatment phase. The abuse related AEs are displayed in Table 18.

Table 18: Abuse related AEs N (%) Study SKUP-9801 (Results pooled by CSS)

	Placebo N=8	**YKPIOA Low N=8**	**YKPlOA Medium N=9**	**YKPlOA High N=l0**
Agitation	3 (37.5)	2 (25)	4 (44.4)	4 (40)
Emotional lability	0	0	0	1(10)
Insomnia	2 (25)	2 (25)	2 (22.2)	7 (70)
Manic reaction	0	1 (12.5)	1 (11.1)	0
Somnolence	0	1 (12.5)	0	1 (10)

Thinking abnormal	0	1 (12.5)	0	2 (20)

Three-week, randomized study to assess the tolerability of 2 fixed doses (200 mg and 500 mg) of (b) (4) in adult subjects with major depressive disorder (MDD). (b) (4) USA-10; Phase 2a

The primary objective of this study was to determine the tolerability of (b) (4) in the treatment of adult subjects with MDD. This was a 3-week, randomized, double blind, placebo-controlled, 3-arm, parallel group, multicenter study in 75 outpatients with MDD. Subjects were randomly assigned in a 2:2:1 design to 1 of 3 blinded treatment groups: 200 mg/day (b) (4) 500 mg/day (b) (4) or placebo. Seventy-seven (77) subjects were randomized to treatment: placebo (n=16), 200 mg/day (b) (4) (n=32) and 500 mg/day (b) (4) (n=29). Sixty-five subjects (15 in the placebo group, 28 in the 200 mg, and 22 in the 500 mg (b) (4) dose group) completed the 3-week treatment phase. The abuse-related AEs are displayed in **Table 19**.

Table 19: Abuse related AEs N (%) Study (b) (4) USA-10 (Results pooled by CSS)

A four-week, double-blind, placebo-controlled, randomized, cross-over study of the safety and efficacy of ADX-N05 in the treatment of excessive daytime sleepiness ADX-N05 201 Phase 2

The objectives of this study were to evaluate the safety and efficacy of ADX-N05 administered as a once-daily (QD) regimen compared to placebo in the treatment of excessive daytime sleepiness in adult subjects with narcolepsy. This was a 4-week (28 days), double-blind, placebo-controlled, multi-center, randomized, cross-over study of the safety and efficacy of ADX-N05 in the treatment of excessive daytime sleepiness in adult subjects (18 to 65 years) with narcolepsy.

Subjects were randomly assigned to one of two treatment sequences: Sequence #1: Week 1: Placebo; Week 2: Placebo; Week 3: ADX-N05 150 mg/day; Week 4: ADX-N05 300 mg/day; or Sequence #2: Week 1: ADX-N05 150 mg/day; Week 2: ADX-N05 300 mg/day; Week 3: Placebo; Week 4: Placebo. Thirty-three (33) subjects were randomly assigned to study treatments. Insomnia occurred in 2 of 33(6.1%) ADX-N05 treated subjects and none in placebo subjects and anxiety occurred in 2 of 33 (6.1%) ADX-N05 treated subjects and none in placebo subjects.

	Placebo n=16	(b) (4) **200mg n=32**	(b) (4) **500mg n=29**	**All** (b) (4) **n=61**
Anxiety	1 (6.3)	4 (12.5)	10 (34.5)	14 (23)
Insomnia	0	5 (15.6)	7 (24.1)	12 (19.7)
Somnolence	4 (25)	6 (18.8)	3 (10.3)	9 (14.8)
Euphoria	0	2 (6.3)	2 (6.9)	4 (6.6)
Agitation	1 (6.3)	2 (6.3)	1 (3.4)	3 (4.9)
Concentration impaired	0	1 (3.1)	2 (6.9)	3 (4.9)

A twelve-week, double-blind, placebo-controlled, randomized, parallel group, multi-center study of the safety and efficacy of ADX-N05 in the treatment of excessive daytime sleepiness in subjects with narcolepsy ADX-N05 202 Phase 2

Objectives: Evaluate the efficacy and safety of ADX-N05 administered once-daily for up to 12 weeks in a dose range of 150 to 300 mg, compared to placebo, in the treatment of excessive daytime sleepiness in adult subjects with narcolepsy.

This was a 12-week, double-blind, flexible target-dose, placebo-controlled, multi-center, randomized, parallel-group study of the safety and efficacy of ADX-N05 in the treatment of excessive daytime sleepiness in adult subjects with narcolepsy. Subjects were randomly assigned to one of two treatment groups: Treatment Group #1: Weeks 1-4: ADX-N05 150 mg/day; Weeks 5-12: ADX-N05 300 mg/day; or Treatment Group #2: Weeks 1-12: Placebo. Ninety-three (93) subjects were randomly assigned to a treatment: 44 to ADX-N05 and 49 to placebo. The abuse-related AEs are displayed in Table 20.

Table 20: Abuse related AEs N% Study ADX-N05 202 (Results pooled by CSS)

	ADX-N05 N=44	**Placebo N=49**
insomnia	6 (13.6)	1 (2)
Anxiety	5 (11.4)	0
Agitation	3 (6.8)	0
Bruxism	3 (6.8)	0
Disinhibition	1 (2.3)	0
Dysphoria	1 (2.3)	0
Libido increased	1 (2.3)	0
Irritability	4 (9.1)	1(2)
Feeling abnormal	1 (2.3)	0

Six treatment emergent adverse events (TEAEs) (5 in the active group, 1 in the placebo group) occurred during the follow-up period (1 to 10 days after final dosing). ADX-N05 group: 1. severe conversion disorder. 2. frequent bowel movements. 3. and 4. mild post-surgical pain and mild postsurgical nausea, respectively (not related to study drug) and 5. mild dizziness. Placebo: mild upper respiratory tract infection

A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicenter Study of the Safety and Efficacy of JZP-110 in the Treatment of Excessive Sleepiness in Subjects with Narcolepsy. 14-002 Phase 3

Objectives:
Primary:

- To evaluate the efficacy of JZP-110 administered QD for up to 12 weeks in doses of 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with narcolepsy

This was a 12-week, randomized, double-blind, placebo-controlled, multicenter, 4-arm parallel group study of the safety and efficacy of JZP-110 in the treatment of excessive sleepiness in adult subjects with narcolepsy. Following the successful completion of Screening and Baseline visits, stratified randomization based on the presence or absence of cataplexy was used to assign subjects in a 1:1:1:1 ratio to receive JZP-110 75, 150, or 300 mg or placebo QD over the 12-week Treatment Phase. During this phase, subjects returned to the investigative site to complete efficacy and safety assessments at the end of Weeks 1, 4, 8, and 12. Subjects received their final dose of study drug at the Week 12 visit (final clinic visit).

A total of 239 subjects were enrolled in the study. Nine subjects randomized to JZP-110 (2 in the 75 mg JZP-110 group, 4 in the 150 mg JZP-110 group, and 3 in the 300 mg JZP-110 group) and no subjects randomized to placebo had AEs with an onset after the last dose of study drug. Symptoms related to withdrawal included dry mouth, myalgia, migraine, and anxiety. Compliance of more than 100% was noted in 9.6% of JZP patients and 3.4% of placebo patients. The abuse-related AEs are displayed in **Table 21**.

Table 21: Abuse related AEs N (%) Study 14-002 (Results pooled by CSS)

	Placebo N=59	**JPZ-110 75 mg N=59**	**JPZ-110 150 mg N=59**	**JPZ-110 300 mg N=59**	**Combined JZP-110 N=177**
Feeling jittery	0	1 (1.7)	0	2 (3.4)	3 (1.7)
Anxiety	1 (1.7)	1 (1.7)	3 (5.1)	5 (8.5)	9 (8.2)
Insomnia	0	2 (3.4)	0	3 (5.1)	5 (2.8)
Agitation	0	0	0	2 (3.4)	2 (1.1)
Panic attack	0	0	2 (3.4)	0	2 (1.1)
Affect lability	1 (1.7)	0	1 (1.7)	0	1 (0.6)
Mood altered	0	1 (1.7)	0	0	1 (0.6)
Mood swings	0	1 (1.7)	0	0	1 (0.6)
Pressure of speech	0	0	1 (1.7)	0	1 (0.6)

A Long-Term Safety and Maintenance of Efficacy Study of JZP-110 in the Treatment of Excessive Sleepiness in Subjects with Narcolepsy or Obstructive Sleep Apnea. Interim Clinical Study Report 14-005 Phase 3

Primary objective

- To evaluate the safety and tolerability of JZP-110 administered once daily (QD) for up to 52 weeks in doses of 75, 150, and 300 mg.

Subjects who had completed Study 14-002, 14-003, 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 and met the screening criteria were eligible to enroll. The study consisted of a 2-week Titration Phase for all subjects, followed by a Maintenance Phase. During the Maintenance Phase, a 2-week Randomized Withdrawal Period was conducted. At the beginning of the Randomized Withdrawal Period, subjects were assigned in a 1:1 ratio to continue to receive JZP-110 at the dose they were currently receiving or to receive placebo for 2 weeks. At the end of that period, subjects resumed JZP-110 treatment at the same dose they received at the beginning of the Randomized Withdrawal Period for the remainder of the study. After completion of the Maintenance Phase, all subjects entered a 2-week Safety Follow-Up period.

A total of 640 subjects were enrolled (227 with narcolepsy and 413 with OSA) in the study; 638 subjects (226 with narcolepsy and 412 with OSA) were treated and comprised the Safety Population for the Open-Label Phase. Overall treatment compliance ranged from 0-438% (96 [15.1%] with compliance over 100%; 7 [1.1%] compliance over 120%). A total of 56 TEAEs occurred in 32 (5%) subjects after final dose of study drug. Of these, AEs that may be indicative of withdrawal effects were muscular weakness, dizziness, insomnia, depersonalization, and headache. The abuse-related AEs are displayed in **Table 22** and AEs during the withdrawal period in **Table 23**.

Table 22: Abuse related AEs N% Study 14-005 **(Results pooled by CSS)**

Table 23. Treatment-Emergent Adverse Events (TEAEs) in the Randomized Withdrawal Period N (%) Study 14-005

	JZP-110 N= 638	Placebo N=142
Feeling jittery	29 (4.5)	0
Energy increased	1 (0.2)	0
Alcohol poisoning	2 (0.3)	0
Intentional overdose (not JZP110)	1 (0.2)	0
Disturbance in attention	7 (1.1)	0
Psychomotor hyperactivity	1 (0.2)	0
Insomnia	50 (7.8)	1 (0.7)
Anxiety	39 (6.1)	0
Irritability	17 (2.7)	0
Hypervigilance	4 (0.6)	0
Bipolar Disorder	1 (0.2)	0
Depersonalization	1 (0.2)	0
Derealization	1 (0.2)	0
Inappropriate affect	1 (0.2)	1 (0.7)
Mania	1 (0.2)	0
Tachyphrenia	1 (0.2)	0
Hyperhidrosis	10 (1.6)	0

A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicenter Study of the Safety and Efficacy of JZP-110 in the Treatment of Excessive Sleepiness in Subjects with Obstructive Sleep Apnea (OSA). 14-003 Phase 3

	Placebo N=142	JZP110 N=140
Headache	0	2 (1.4)
Insomnia	1(0.7)	2 (1.4)
Hypertension	0	2 (1.4)

Objectives: To evaluate the efficacy and safety of JZP-110 administered QD for up to 12 weeks in doses of 37.5, 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.

This was a 12-week, randomized, double-blind, placebo-controlled, multicenter, 5-arm parallel group study of safety and efficacy of JZP-110 in the treatment of excessive sleepiness in adult subjects with OSA. Following the successful completion of Screening and Baseline visits, stratified randomization on the basis of subject's compliant or noncompliant use of their primary OSA therapy was used to assign subjects in a 1:1:2:2:2 ratio to receive JZP-110 37.5, 75, 150, or 300 mg, or placebo QD over a 12-week

Treatment Phase. A total of 476 subjects were enrolled. Nine subjects (4 placebo and 5 JZP-110 treated [2 at 37.5 mg, 2 at 150 mg, and 1 at 300 mg]) experienced a total of 19 AEs after their last dose of study drug. None of these events were suggestive of withdrawal effects. Thirty-nine (39) subjects (10 [8.4%] placebo and 29 [8.2%] JZP-110) were >100% compliant with study drug treatment. Of the 39 subjects with >100% compliance, 35 had compliance ≤104%. Two subjects had treatment compliance >120%. The abuse related AEs are displayed in **Table 24**.

Table 24: Abuse related AEs N% Study 14-003 **(Results pooled by CSS)**

	Placebo N=119	**JZP-110 N=355**
Feeling jittery	0	14 (3.9)
Disturbance in attention	0	4 (1.1)
Psychomotor hyperactivity	0	1 (0.3)
Anxiety	0	25 (7.0)
Insomnia	2 (1.7)	15 (4.2)
Irritability	0	8 (2.3)
Bruxism	0	4 (1.1)
Agitation	1 (0.8)	3 (0.8)
Panic attack	0	2 (0.6)
Affect lability	0	1 (0.3)
Disinhibition	0	1 (0.3)
Emotional disorder	0	1 (0.3)
Euphoric mood	0	1 (0.3)
Hypervigilance	0	1 (0.3)
Tachyphrenia	0	1 (0.3)

A Six-Week, Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Safety and Efficacy of JZP-110 in the Treatment of Excessive Sleepiness in Subjects with Obstructive Sleep Apnea (OSA) 14-004 Phase 3

Primary Objective: To evaluate the efficacy of JZP-110 administered QD compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.

This was a 6-week, multicenter, double-blind, placebo-controlled, randomized-withdrawal study of the safety and efficacy of JZP-110 in the treatment of excessive sleepiness in adult subjects with OSA. Subjects with OSA were enrolled to receive a QD oral dose of 75, 150, or 300 mg JZP-110 or placebo. The study had four phases: A Screening phase, a Titration phase, a Stable-Dose phase, and a Double-Blind Withdrawal phase. Following screening, subjects entered the 2-week, open-label Titration Phase. Dosing started at 75 mg JZP-110 once-daily and was titrated up 1 dose level (to 150 mg/day or a maximum dose of 300 mg/day) once every 3 days. Subjects who were titrated to an efficacious and tolerable dose in the Titration Phase then entered the 2-week, open-label Stable-Dose Phase and remained on that same dose regimen. Subjects who completed the Week 4 Visit at the end of the Stable-Dose Phase, reported improvement on the Patient Global Impression of Change (PGIc) scale, and showed a numerical improvement in mean sleep latency on the Maintenance of Wakefulness Test

(MWT), and Epworth Sleepiness Scale (ESS) scores from the beginning of the Titration Phase (Day -1) to Week 4 were randomized into the Double-Blind Withdrawal Phase. Subjects who did not report improvement on the PGIc scale or did not improve on the MWT or ESS were discontinued from the study. Abuse-related AEs with onset pre-randomization are displayed in **Table 25**.

Subjects were assigned in a 1:1 ratio to continue JZP-110 at the dose received in the Stable-Dose Phase or to receive placebo for 2 weeks. One hundred and seventy-four (174) subjects were enrolled into the study and 124 were randomized.

Fourteen subjects (8.9%) had an overall compliance rate of >100%; 13 of these subjects were <105% compliant. One subject had a compliance rate of >120%.

After stopping active treatment at the end of Week 4, 6 subjects (9.7%) in the Placebo group experienced 8 TEAEs during the Double-Blind Withdrawal phase: atrioventricular block first degree, sinus arrhythmia, gastroenteritis viral, nail bed infection, neck pain, back pain, musculoskeletal pain, and Type 2 diabetes. Onset for all these events was Day 40 or later, approximately 10 to 11 days after last dose of JZP-110. Events with onset after the final dose of study medication across all phases were also reviewed. Eight TEAEs occurred in seven subjects after final dose of study drug. Of these, 4 events could be relevant in the context of treatment-withdrawal symptoms: excessive hunger, restless sleep, depression, and fatigue. These were reported for 3 subjects who were receiving active treatment when they completed the Double-Blind Withdrawal phase

Table 25: Abuse related AEs with Onset Pre-Randomization N (%) Study 14-004 (Results pooled by CSS)

	Titration Phase N=174	**Stable Dose Phase N=157**
Feeling jittery	4 (2.3)	0
Psychomotor hyperactivity	2 (1.1)	1 (0.6)
Disturbance in attention	1 (0.6)	0
Insomnia	10 (5.7)	1 (0.6)
Anxiety	7 (4.0)	1 (0.6)
Irritability	2 (1.1)	0
Agitation	1 (0.6)	0
Bruxism	1 (0.6)	0
Depersonalization	1 (0.6)	0
Derealization	1 (0.6)	0
Disinhibition	1 (0.6)	0
Mood swings	1 (0.6)	0
Hypervigilance	1 (0.6)	0

No abuse related AEs with Onset Post-Randomization occurred.

4.3 Safety Profile

Solriamfetol can cause blood pressure (BP) increases that can increase the risk of major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death

Abuse -related adverse events:
Healthy Volunteers: Disturbance in attention, affect lability, hypervigilance, and agitation occurred at a higher rate in JZP-110 treated subjects versus placebo.

MDD studies: In one of the studies euphoria was reported in 6.6% JZP-110 treated subjects and no placebo subjects. However, no euphoria was reported in two other studies. Thinking abnormal and manic reaction were reported in 3 and 2 patients, respectively in the JZP-110 group. Insomnia and anxiety were more prevalent in the JZP-110 group.

Narcolepsy: Insomnia, anxiety, and agitation occurred more commonly with JZP-110 than placebo. Bruxism and feeling jittery occurred in one study with JZP-110 but not in the other.

OSA: Feeing jittery (0-3.9%), psychomotor hyperactivity (0.3-1.1%), anxiety, insomnia, bruxism (0-1.1%), disinhibition (0-0.6%), hypervigilance (0-0.6%) occurred in JZP-110 treated subjects. Euphoric mood occurred in 0.3% (n=1) in one study, depersonalization 0.6% (n=1), derealization 0.6% (n=1), mood swings 0.6% (n=1), occurred in patients on JZP-110 in the second study

Long term study in narcolepsy and OSA: Feeling jittery (4.5%), energy increased (0.2%), disturbance in attention (1.1%), psychomotor hyperactivity (0.2%), hypervigilance (0.6%) depersonalization (0.2%), derealization (0.2%), mania (0.2%), tachyphrenia (0.2%), hyperhidrosis (1.6%), anxiety, insomnia and, irritability occurred in JZP-110 treated patients.

In summary, although abuse-related adverse events occurred in JZP-110 treated subjects, they occurred at a low rate, usually less than 5%. In only one MDD study euphoria was reported at 6.6%. Anxiety, insomnia, and agitation occurred with JZP-110 consistent with the stimulant activity of the drug.

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials

Compliance rates of more than 120% were low and ranged around 1%. There were no reports of JZP-110 overdose. The Sponsor conducted a review of missing kits which did not reveal a signal consistent with drug diversion, abuse, or misuse. Of the 1344 enrollments that resulted in dispensing of JZP-110 in the Phase 3 program, 298 subjects who were dispensed JZP-110 had at least 1 missing kit. The pattern suggested that for most subjects with missing kits, it was a one-time occurrence in an individual study. Most of the occurrences (n=270) were in Study 14-005, which had more subjects enrolled and a longer duration than the other studies and dispensed more kits at a time. Of these subjects, 241 (89.3%) had 4 or fewer missing kits, indicating that this could be due to a lack of returning study kits one time. Of the 298 subjects, only 1 subject had a calculated treatment compliance > 100%. A total of 11 subjects with missing kits were lost to follow-up.

4.5 Tolerance and Physical Dependence Studies in Humans

No dedicated physical dependence study was performed. Phase 3 clinical trials included an evaluation of effects that occurred after abrupt discontinuation of JZP-110. Validated withdrawal scales before and after

abrupt drug discontinuation were not performed. Withdrawal symptoms occurred in 0%- 6.8% of subjects treated with JZP-110 upon sudden withdrawal. These symptoms included severe conversion disorder, frequent bowel movements, dry mouth, myalgia, migraine, anxiety, depression, irritability, hyperhidrosis, muscular weakness, lethargy, dizziness, insomnia, speech disorder, tremor, agitation, depersonalization, headache, hypertension, atrioventricular block first degree, sinus arrhythmia, neck pain, back pain, musculoskeletal pain, excessive hunger, restless sleep, depression, fatigue, and palpitations. However, no consistent pattern of withdrawal symptoms occurred in any of the studies.

5. Regulatory Issues and Assessment

Solriamfetol is recommended for placement in Schedule IV of the CSA, based on the following considerations.

In the initial HAP study, which was not valid because the positive control (MPH) did not separate from placebo, euphoria occurred at similar rates (5-17%) in the active treatment groups (JZP-110 and MPH).

The data from the second HAP study, which was a valid study, show that for all primary and key secondary end points, JZP-110 has similar or lower abuse potential compared to the active control drug phentermine (a Schedule IV drug). Rates of abuse related AEs were similar in the JZP-110 and phentermine groups: Feeling of relaxation JZP-110: 5-19%, phentermine: 15-20%, elevated mood JZP-110: 8-24%, phentermine: 10-18%; euphoric mood JZP-110: 0%, phentermine: 0-3%

In clinical trials, although abuse-related AEs occurred in JZP-110 treated subjects, they occurred at a low rate, with usually less than 5% of subjects reporting these events. In only one MDD study euphoria was reported in 6.6% of subjects. Anxiety, insomnia, and agitation occurred with JZP-110 consistent with the stimulant activity of the drug.

Compliance rates of more than 120% were low and ranged around 1%. A review of missing kits did not reveal a signal consistent with drug diversion, abuse, or misuse.

No consistent pattern of withdrawal symptoms occurred upon abrupt discontinuation of JZP-110.

Based on the findings of the HAP study, low rate of abuse related AEs in clinical trials, absence of withdrawal symptoms, and lack of evidence of drug abuse and diversion during the clinical trials, we concur with the Sponsor that solriamfetol should be placed in Schedule IV of the CSA. Labeling recommendations are detailed in the Recommendations section.

6. Other Relevant Information

JZP-110 is a NME that has not been approved for marketing in the U.S. or any other country. Therefore, no post marketing data is available regarding its potential abuse potential and there is no information available regarding actual use or abuse in the community at large.

III. REFERENCES

Bowyer JF and Hanig JP (2014) Amphetamine- and methamphetamine-induced hyperthermia: Implications of the effects produced in brain vasculature and peripheral organs to forebrain neurotoxicity. *Temperature (Austin, Tex)* **1**:172-182.

Cole SO (1978) Brain mechanisms of amphetamine-induced anorexia, locomotion, and stereotypy: A review. *Neuroscience & Biobehavioral Reviews* **2**:89-100.

Malenka RC NE, Hyman SE, Holtzman DM (2015) *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience (3rd ed.)*. McGraw-Hill Medical., New York.

Roberts AJ, Casal L, Huitron-Resendiz S, Thompson T and Tarantino LM (2018) Intravenous cocaine self-administration in a panel of inbred mouse strains differing in acute locomotor sensitivity to cocaine. *Psychopharmacology* **235**:1179-1189.

Simon P, Hemet C, Ramassamy C and Costentin J (1995) Non-amphetaminic mechanism of stimulant locomotor effect of modafinil in mice. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* **5**:509-514.

Volkow ND, Wang GJ, Tomasi D and Baler RD (2013) Unbalanced neuronal circuits in addiction. *Current opinion in neurobiology* **23**:639-648.

Wiltshire T, Ervin RB, Duan H, Bogue MA, Zamboni WC, Cook S, Chung W, Zou F and Tarantino LM (2015) Initial locomotor sensitivity to cocaine varies widely among inbred mouse strains. *Genes, brain, and behavior* **14**:271-280.

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/s/

SHALINI M BANSIL
12/11/2018

EDWARD G HAWKINS
12/11/2018

MARTIN S RUSINOWITZ
12/11/2018

SILVIA N CALDERON
12/11/2018

DOMINIC CHIAPPERINO
12/11/2018

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	December 03, 2018
Reviewer:	Catherine Callahan, PhD, MA Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Division Deputy Director:	Sukhminder K. Sandhu, PhD, MS, MPH Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Sunosi (solriamfetol)
Application Type/Number: Applicant/sponsor:	NDA 211230 Jazz Pharmaceuticals Ireland Limited (Jazz)
OSE RCM #:	2018-2217

1. BACKGROUND INFORMATION

1.1. Medical Product

Sunosi (solriamfetol) is a phenylalanine derivative and selective dopamine and norepinephrine reuptake inhibitor (DNRI) with the proposed indication to improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA). (b) (4) increased risk of serious cardiovascular events such as acute myocardial infarction, coronary artery disease, angina pectoris, cerebrovascular accident, and atrial fibrillation; blood pressure increases requiring escalation in antihypertensive medication; and psychiatric symptoms including anxiety, insomnia, irritability, and agitation (Table 1). Solriamfetol is administered orally. The proposed dose is (b) (4)

Table 1. Increased Events of Interest in 12-Week Placebo-Controlled Parallel Group Studies in Narcolepsy and OSA (Safety Population) (Pool 1)

Event, n (%)	Placebo n =226	Solriamfetol n= 573
Cardiac disorders	3 (1.3)	23 (4.0)
Blood pressure increases	1 (0.4)	7 (1.2)
Escalation in anti-hypertensive medication	3 (1.3)	14 (2.4)
Psychiatric disorders	18 (8.0)	109 (19.0)

1.2. Describe the Safety Concern

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. 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.[1]

Administration of solriamfetol to rats and rabbits during the period of organogenesis at levels greater than the maximum recommended human dose (MRHD) resulted in the following adverse effects:[2,3]

- Solriamfetol administered orally to pregnant rats during the period of organogenesis at ≥ 2 times the MRHD caused maternal and fetal toxicity that included hyperactivity, significant decreases in body weight and food consumption, increased incidence of early embryo resorption and post-implantation loss as well as decreased fetal weight.
  - Solriamfetol was teratogenic at 9.5 times the MRHD.
  - In the cases with maternal toxicity, the mother had poor nutrition and weight loss. It is not clear if the drug had an effect on the developing pup or the mother's poor status did.

- When administered orally to pregnant rabbits during the period of organogenesis at 5 times the MRHD caused maternal toxicity including body weight loss and decreased food consumption.
  - Solriamfetol was teratogenic (the drug caused dose-dependent increases in the incidence of slight-to-moderate sternebrae mal-alignment) at ≥2.5 times the MRHD.
- Developmental toxicity in first generation rat pups after lactation day 20 included decreased body weight, weight gain, and delayed sexual maturation.
  - Mating and fertility of first generation pups were decreased at maternal doses 11 times the MRHD without affecting learning and memory.

In the solriamfetol clinical studies, women who were pregnant were excluded and birth control during participation was required for women of reproductive potential. However, a total of 2 pregnancies occurred after patients were exposed to solriamfetol. The mean elimination half-life for solriamfetol is approximately 7.1 hours. One patient discontinued solriamfetol because of migraine and depressive symptoms two weeks prior to confirmation of pregnancy (estimated gestational age 2 weeks) and delivered a healthy full-term baby who was reported to be meeting all developmental milestones at 6 months of age. Another patient who received solriamfetol for 199 days reported that she had delivered a full-term stillbirth (gestational age 41 weeks) on day 257 of the trial, but neither the pregnancy nor the stillbirth were confirmed. Overall, the data on pregnancy exposure during clinical trials are insufficient to inform the risk associated with solriamfetol.

In pregnant rats, after oral administration, solriamfetol was present in the fetus.[2] Thus, exposure to the fetus in women treated with solriamfetol during pregnancy is likely. Furthermore, solriamfetol is administered daily, which is an additional concern regarding exposure to the fetus in women who are pregnant, plan to become pregnant, or of childbearing potential while using solriamfetol.

In the current proposed labeling, as of September 4, 2018, the Risk Summary in Section 8.1 Pregnancy, states: "Available data from case reports are not sufficient to determine drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproductive studies, oral administration of solriamfetol during organogenesis caused maternal and fetal toxicities in rats and rabbits at doses ≥ (b) (4) and (b) (4) times and was teratogenic at doses (b) (4) and ≥ (b) (4) times, respectively, the maximum recommended human dose (MRHD) (b) (4) based on mg/m^2 body surface area. Oral administration of solriamfetol to pregnant rats during pregnancy and lactation at doses ≥ (b) (4) times the MRHD based on mg/m^2 body surface area resulted in maternal toxicity and adverse effects on fertility, growth, and development in offspring (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively."

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† *If checked, please complete Error! Reference source not found..*

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☒ Electronic database study with chart review
☐ Electronic database study without chart review
☐ Other, please specify: *Click here to enter text.*

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☐ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other

pregnancy outcomes.

Because broad-based signal detection is not currently available, other parameters were not assessed.

2.5. Please include the proposed PMR language in the approval letter.

The Division of Division of Psychiatry Products requests two PMRs related to pregnancy outcomes. As of December 3, 2018, the proposed PMR language, for these are:

> PMR 3475-1: A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to solriamfetol during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.
>
> PMR 3475-2: An additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to solriamfetol during pregnancy compared to an unexposed control population.

3. References

1. Dinatale M. Division of Pediatric and Maternal Health, FDA. The pregnancy and lactation labeling rule (PLLR). https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf. Accessed October 11, 2018.

2. New Drug Application (NDA) Pharm Tox Review. NDA 211230 Sunosi (solriamfetol). Accessed October 11, 2018

3. New Drug Application (NDA) Division of Pediatric and Maternal Health Memorandum. NDA 211230 Sunosi (solriamfetol). Accessed October 11, 2018

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/s/

CATHERINE L CALLAHAN
12/03/2018

KIRA N LEISHEAR
12/03/2018

SUKHMINDER K SANDHU
12/10/2018

JUDITH W ZANDER
12/11/2018

MICHAEL D NGUYEN
12/11/2018

ROBERT BALL
12/11/2018

MEMORANDUM

REVIEW OF REVISED LABELS

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 10, 2018
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 211230
Product Name and Strength:	Sunosi (solriamfetol) tablets 75 mg, 150 mg, and 300 mg
Applicant/Sponsor Name:	Jazz Pharmaceuticals Ireland Limited
FDA Received Date:	December 7, 2018
OSE RCM #:	2018-134-3
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Psychiatry Products (DPP) requested that we review the revised container labels for Sunosi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review memorandum.[a]

2 CONCLUSION

The revised container labels for Sunosi are acceptable from a medication error perspective. We have no further recommendations at this time.

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

[a]Holmes L. Labels and Labeling Review Memo for Sunosi (NDA 211230). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Nov 09. RCM No.: 2018-134-2.

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/s/

LORETTA HOLMES
12/10/2018

LOLITA G WHITE
12/10/2018

MEMORANDUM

REVIEW OF REVISED LABELS AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 9, 2018
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 211230
Product Name and Strength:	Sunosi (solriamfetol) tablets 75 mg, 150 mg (b) (4)
Applicant/Sponsor Name:	Jazz Pharmaceuticals Ireland Limited
FDA Received Date:	November 8, 2018
OSE RCM #:	2018-134-2
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Psychiatry Products (DPP) requested that we review the revised container labels and carton labeling for Sunosi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review memorandum.[a]

2 CONCLUSION

The revised container labels are unacceptable from a medication error perspective. The Applicant reoriented the linear barcode from a vertical position to a horizontal position which may impede the scannability of the barcode.

[a] Holmes L. Labels and Labeling Review Memo for Sunosi (NDA 211230). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Sep 21. RCM No.: 2018-134-1.

3 RECOMMENDATIONS FOR JAZZ PHARMACEUTICALS

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

A. Container Labels

We find that our previously requested revisions to the container labels and carton labeling were implemented. However, we note the orientation of the linear barcode was changed from a vertical position to a horizontal position. If the linear barcode is presented in a horizontal position, the barcode may wrap around the curvature of the container and not be scannable. Thus, we recommend that you reorient the linear barcode to a vertical position.

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/s/

LOLITA G WHITE on behalf of LORETTA HOLMES
11/09/2018

LOLITA G WHITE
11/09/2018

Clinical Inspection Summary

Date	11/07/2018
From	Jenn Sellers, M.D., Ph.D. Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Sarah Seung, RPM David Millis, Medical Officer Javier Muniz, Lead Medical Officer Division of Psychiatric Products (DPP)
NDA #	211230
Applicant	Jazz Pharmaceuticals, Inc.
Drug	Solriamfetol
NME	Yes
Therapeutic Classification	Selective Dopamine and Norepinephrine Reuptake Inhibitor (DNRI)
Proposed Indication	To Improve Wakefulness and Reduce Excessive Sleepiness in Adult Patients with Narcolepsy or Obstructive Sleep Apnea (OSA)
Consultation Request Date	02/27/2018
Inspection Summary Goal Date	11/21/2018
Action Goal Date	12/20/2018
PDUFA Date	12/20/2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Ahmed, Bogan, Rosenberg, Schmidt, and Thein were inspected in support of this NDA. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The compliance classification of the inspections of Drs. Ahmed, Bogan, Rosenberg, Schmidt was No Action Indicated (NAI). The compliance classification of the inspection of Dr. Thein was Voluntary Action Indicated (VAI).

II. BACKGROUND

The applicant submitted this original NDA for solriamfetol (JZP-110) to improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea.

The following protocols were inspected in support of this application:

Protocol 14-002, "A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicenter Study of the Safety and Efficacy of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Narcolepsy"

This study took place at 50 sites in North America and 9 in Europe, beginning May 19, 2015 and ending February 14, 2017. A total of 239 subjects were enrolled.

The study objective was to evaluate the efficacy of JZP-110 administered once daily for up to 12 weeks in doses of 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with narcolepsy.

The Co-Primary Efficacy Endpoints:

- Maintenance of Wakefulness Test (MWT): change from Baseline to Week 12 on the ability to stay awake as measured by mean sleep latency on the MWT

- Epworth Sleepiness Scale (ESS): change from Baseline to Week 12 in patient-reported excessive sleepiness measured by ESS score

The Key Secondary Efficacy Endpoint:

- Patient Global Impression of Change (PGIc): percentage of subjects reported as improved (minimally, much, or very much) on the PGIc at Week 12.

Protocol 14-003, "A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicenter Study of the Safety and Efficacy of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Obstructive Sleep Apnea (OSA)"

This study took place at 50 sites in North America and 9 in Europe beginning May 19, 2015 and ending December 23, 2016. A total of 476 subjects were enrolled.

The primary study objective was to evaluate the efficacy of JZP-110 administered once daily for up to 12 weeks in doses of 37.5, 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.

The Co-Primary Efficacy Endpoints:

- MWT: change in the mean sleep latency time (in minutes) as determined from the first four trials of a 40-minute MWT from Baseline to Week 12

- ESS: change in ESS score from Baseline to Week 12

The Key Secondary Efficacy Endpoint:

- Patient Global Impression of Change (PGIc): percentage of subjects reported as improved (minimally, much, or very much) on the PGIc at Week 12

Rationale for Site Selection

A site selection tool was used to identify clinical investigator (CI) sites for inspections.

- Dr. Ahmed's site had high enrollment for Study 14-002, high treatment effect, and participation in multiple studies for this NDA. This CI does not have history of inspections.

- Dr. Bogan's site had high enrollment, high reported adverse events (AEs), and high treatment effect. This CI was inspected in 2006 (NAI).

- Dr. Rosenberg's site was selected because the data from his site impacted the overall efficacy results of Trial 14-003. His site also had high enrollment and high protocol violations. This CI was inspected in 2009 (NAI).

- Dr. Schmidt's site had high enrollment for Study 14-002, high treatment efficacy and participation in multiple studies. This CI does not have history of inspections.

- Dr. Thein's site had high enrollment, high protocol violations, high treatment efficacy, high number of INDs, and participation in multiple studies for this NDA. Previously, he had a for-cause inspection in 2000, which was classified as VAI (failure to follow investigational plan; inadequate and inaccurate records).

III. RESULTS (by site):

Site #/ Name of CI/ Address	**Protocol #/ # of Subjects Enrolled**	**Inspection Dates**	**Classification**
Site # 100 **Manzoor Ahmed, M.D.** 18100 Jefferson Park Road, Suite 101 Middleburg Heights, OH 44130	14-002 Subjects: 8	22-25, 29-30 May & 1 June 2018	NAI
Site # 102 **Richard Bogan, M.D.** 1333 Taylor Street, Suite 6-B Columbia, SC 29201	14-003 Subjects: 15	12-25 May 2018	NAI
Site # 111 **Russell Rosenberg, Ph.D.** 1100 Johnson Ferry Road Suite 420 Atlanta, GA 30342	14-003 Subjects: 22	7-8, 11-14 June 2018	NAI
Site # 104 **Markus Schmidt, M.D.** 4975 Bradenton Avenue, Dublin, OH 43017	14-002 Subjects: 8	4-8 June 2018	NAI
Site # 164 **Stephen Thein, Ph.D.** 3003 Fourth Ave, San Diego, CA 92103	14-003 Subjects: 21	23 July - 3 Aug. 2018	VAI

Key to Compliance Classifications:
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations. Data unreliable

1. Manzoor Ahmed, M.D.

At this site for Protocol 14-002, 17 subjects were screened, 8 were enrolled, and 7 subjects completed the study. Subject # (b) (6) in JZP-110 150 mg group discontinued the study due to worsening of cataplexy. A complete review of the records of all 8 enrolled subjects was conducted which included, but were not limited to, informed consent forms, drug accountability records, financial disclosures, training records, delegation of authority, study eligibility, adverse event reporting, the primary and the secondary efficacy endpoint source documents, concomitant medications, and protocol deviations.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

2. Richard Bogan, M.D.

At this site for Protocol 14-003, 36 subjects were screened, 15 were enrolled, and 13 subjects completed the study. Two subjects discontinued the study. Subject # (b) (6) in JZP-110 150 mg group was lost to follow up. Subject # (b) (6) in JZP-110 300 mg group withdrew from the study due to continuing adverse events, which consisted of increased anxiety, decreased appetite, and increased episodes of dreaming. This inspection conducted a review of the study records of all 15 enrolled subjects, including all subject source document files, informed consent forms, drug accountability records, institutional review board approvals, case reports forms (CRFs) and site monitoring.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

3. Russell Rosenberg, Ph.D.

At this site for Protocol 14-003, 46 subjects were screened, 22 were enrolled, and 21 subjects completed the study. Subject # (b) (6) in JZP-110 150 mg group discontinued the study due to an adverse event of upset stomach. The inspection reviewed complete study records for 10 of the enrolled subjects, which included, but were not limited to, informed consent forms, financial disclosures, training records, delegation of authority, study eligibility, adverse event reporting, concomitant medications, and protocol deviations, the primary and the secondary efficacy endpoint data for all 22 enrolled subjects, as well as other relevant study records, such as the study protocol, IRB submissions and approvals, and drug accountability records.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

4. Markus Schmidt, M.D.

At this site for Protocol 14-002, 10 subjects were screened, 8 were enrolled, and 6 subjects completed the study. Two subjects in JZP-110 300 mg group discontinued the study. Subject # (b) (6) discontinued due to lack of efficacy demonstrated as increase in

sleepiness. Subject # (b) (6) discontinued due to positive urine drug screen for cannabinoids. A complete review of the records of all 8 enrolled subjects was conducted which included, but were not limited to, informed consent forms, financial disclosures, training records, delegation of authority, study eligibility, adverse event reporting, concomitant medications, and protocol deviations, all the primary and secondary efficacy endpoint data and drug accountability records.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

5. Stephen Thein, M.D.

At this site for Protocol 14-003, 48 subjects were screened, 21 were enrolled, and 18 subjects completed the study. Three subjects discontinued the study. Two of them from JZP-110 300 mg group discontinued due to adverse events. Subject # (b) (6) discontinued due to nausea and vomiting. Subject # (b) (6) discontinued due to panic attack. Subject # (b) (6) in JZP-110 37.5 mg group withdrew consent. A complete review of the records of the 21 enrolled subjects was conducted which included, but were not limited to, informed consent forms, financial disclosures, training records, delegation of authority, study eligibility, adverse event reporting, concomitant medications, and protocol deviations, all the primary and secondary efficacy endpoint data and drug accountability records.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection due failure to follow the protocol: Exclusion criterion # 12 required exclusion of subjects with presence of significant cardiovascular disease, including but not limited to: uncontrolled hypertension, systolic blood pressure ≥ 155 mm Hg or diastolic blood pressure ≥ 95 mm Hg (at screening, or consistently across Baseline measures according to protocol specifications). However, Subject # (b) (6) had screening blood pressures of 130/100 mm Hg and 132/101 mm Hg, and at Baseline, the subject had blood pressures of 135/98 mm Hg and 133/96 mm Hg. This subject met the exclusion criterion #12 and therefore was ineligible for the study but was still randomized. As mentioned above, this subject discontinued the study due to nausea and vomiting.

Dr. Thein adequately responded to the inspection finding in a letter dated August 17, 2018.

Reviewer's comment: The isolated violation does not appear to impact the study outcome. This protocol violation was not reported to FDA.

{See appended electronic signature page}

Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

cc:
Central Doc. Rm. NDA #211230
DPP /Project Manager/Sarah Seung
DPP/Division Director/Mitch Mathis
DPP/Deputy Division Director/Tiffany Farchione
DPP/Medical Officer/David Millis
DPP/Clinical Team Leader/Javier Muniz
OSI /Office Director/David Burrow
OSI/DCCE/Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analysts/Yolanda Patague

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/s/

JENN W SELLERS
11/07/2018

PHILLIP D KRONSTEIN
11/07/2018

KASSA AYALEW
11/07/2018

MEMORANDUM

REVIEW OF REVISED LABELS AND LABELING

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

Date of This Memorandum:	September 21, 2018
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 211230
Product Name and Strength:	Sunosi (solriamfetol) tablets 75 mg, 150 mg, (b) (4)
Applicant/Sponsor Name:	Jazz Pharmaceuticals Ireland Limited
FDA Received Date:	September 6, 2018
OSE RCM #:	2018-134-1
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Psychiatry Products (DPP) requested that we review the revised container labels and (b) (4) packaging ((b) (4) carton labeling) submitted for Sunosi (solriamfetol) tablets (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review.[a]

2 CONCLUSION

The revised container labels (b) (4) and carton labeling are unacceptable from a medication error perspective. We identified certain statements that need to be increased in prominence in order to promote the safe use of the product.

[a] Holmes L. Label and Labeling Review for Sunosi (NDA 211230). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Jul 30. RCM No.: 2018-134.

3 RECOMMENDATIONS FOR JAZZ PHARMACEUTICALS IRELAND LIMITED

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

A. All Container Labels, (b) (4) and Carton Labeling

The Medication Guide (MG) statement lacks prominence. Use a bold font for the MG statement.

(b) (4)

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

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/s/

LORETTA HOLMES
09/21/2018

LOLITA G WHITE
09/21/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: August 27, 2018 **Date consulted:** January 12, 2018

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Psychiatry Products (DPP)

Drug: Solriamfetol, Tablet

Drug Class: Selective dopamine and norepinephrine reuptake inhibitor (DNRI).

NDA: 211230

Applicant: Jazz Pharmaceuticals Ireland Limited

Subject: Pregnancy and Lactation Labeling as part of original NDA (New Molecular Entity)

Proposed Indication: To improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA).

Materials Reviewed:

DPMH consult request dated January 12, 2018 in DARRTS (Reference ID: 4207195)
Applicant's submission for original NDA 211230 a 505(b)(1) application, dated December 20, 2017 and the Prescribing Information (PI) for

solriamfetol
Applicant's submission for update of the safety information for Day 120 Safety Update of April 19, 2018
Labeling and registry review of Nuvigil by Leyla Sahin M.D. dated December 21, 2016 in DARRTS, (Reference ID: 4031507)
Pregnancy registry interim review (Status year 8, Reporting Period February 19, 2010 to February 28, 2018)

Consult Question:
DPP requests DPMH assistance with reviewing the applicant's Pregnancy and Lactation labeling subsections to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

INTRODUCTION

This is an original 505(b)(1) New Molecular Entity (NME) application for solriamfetol submitted on December 20, 2017, with a proposed indication to improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA). Solriamfetol is a selective dopamine and norepinephrine reuptake inhibitor (DNRI). Dopamine and norepinephrine may have effects on "wake-promoting" neurotransmitters, and dysfunction of the dopaminergic and norepinephrine pathways originating from the brainstem have been observed in animal models of sleep apnea and narcolepsy. Through the blockade of the dopamine and norepinephrine transporters, solriamfetol enhances dopamine and norepinephrine signaling in the brainstem arousal systems.
The Division of Psychiatry Products (DPP) consulted the Division of Pediatric and Maternal Health (DPMH) on January 12, 2018, to provide input for appropriate labeling of the *Pregnancy* and *Lactation* subsections of solriamfetol tablets to comply with the PLLR.

BACKGROUND

Regulatory History

On December 20, 2017, the applicant, Jazz Pharmaceuticals Ireland Limited (JAZZ), submitted this original 505(b)(1) application for solriamfetol tablets. Other drugs for the same indication have been previously approved, including Nuvigil (NDA 021875, approved on June 15, 2007) and Provigil (NDA 020717, approved on December 24, 1998), and both owned by Cephalon. The mechanism of action of these two drugs is unknown; however, they promote wakefulness "similar to sympathomimetic agents including amphetamine and methylphenidate, although the pharmacologic profile is not identical to that of the sympathomimetic amines".[1] They are indirect dopamine receptor agonist and bind in vitro to the dopamine transporter and inhibit dopamine reuptake.[2,3]

[1] Applicant's submission, January 12, 2018
[2] DRUGS@FDA
[3] Leyla Sahin M.D., Labeling review of Nuvigil, dated December 21, 2016 in DARRTS, (Reference ID: 4031507)

Drug Characteristics[4]

- The molecular weight for solriamfetol is 230.69 Daltons.
- The plasma protein binding of solriamfetol is low (13.3 to 19.4%)
- Solriamfetol is predominantly excreted unchanged in the urine and undergoes minimal metabolism in humans (≤1%)
- The mean elimination half-life for solriamfetol is approximately 7.1 hours.

REVIEW

PREGNANCY

Animal Data

As per the non-clinical reviewer, Jia Yao, the applicant has provided the following animal data with the submission:

- Solriamfetol administered orally to pregnant rats during the period of organogenesis at ≥ 2 times the MRHD caused maternal and fetal toxicity that included hyperactivity, significant decreases in body weight and food consumption, increased incidence of early resorption and post-implantation loss as well as decreased fetal weight.
  - Solriamfetol was teratogenic at 9.5 times the MRHD.
- When administered orally to pregnant rabbits during the period of organogenesis at 5 times the MRHD caused maternal toxicity including body weight loss and decreased food consumption.
  - Solriamfetol was teratogenic (the drug caused dose-dependent increases in the incidence of slight-to-moderate sternebrae mal-alignment) at ≥ 2.5 times the MRHD.
- Developmental toxicity in first generation rat pups after lactation day 20 included decreased body weight, weight gain, and delayed sexual maturation.
  - Mating and fertility of first generation pups were decreased at maternal doses 11 times the MRHD without affecting learning and memory.

For more information, the reader is referred to the non-clinical review by Jia Yao, Ph.D. in DARRTS.

Review of Literature

Applicant's Review

As per the applicant, no studies of solriamfetol have been conducted in pregnant women.

Review of Clinical Trials

Across the solriamfetol clinical program, 4 pregnancies (one in a placebo patient) and 3 pregnancies following maternal or paternal solriamfetol exposure have been reported:

1. One patient discontinued the drug prior to finding out she was pregnant (prior to 2 weeks of pregnancy). She delivered a normal infant,
2. A patient who had received solriamfetol reported a stillbirth, but this finding was not confirmed by the sponsor.

[4] Proposed labeling of solriamfetol,

3. A male subject's partner became pregnant and she reported no problems with the pregnancy as of the data cut-off date (no further information regarding the partner pregnancy status was available despite repeated attempts to contact the subject).

These limited clinical data are insufficient to draw meaningful safety conclusions about the effects of solriamfetol during pregnancy and lactation.

Pregnancy Registry
There is a drug-based Pregnancy Registry by Cephalon for both Nuvigil/Provigil because of potential safety signals for microcephaly, failure to thrive and small for gestational age in infants of mothers exposed to these drugs. The Center for Women's Mental Health at Massachusetts General Hospital is also conducting a Pregnancy Registry on women who have Attention Deficit Hyperactivity Disorders (ADHD) and use any psychiatric medications including Provigil for the indication of ADHD. No patients with ADHD and use of Provigil have been registered to date.

DPMH Review
In addition, DPMH searched PubMed, Embase, ReproTox and TERIS databases for information regarding solriamfetol and use during pregnancy. No published information was identified.

Summary
The data reviewed regarding the use of solriamfetol during pregnancy are very limited and are insufficient to inform a drug associated risk.

The Division should require PMR studies related to safety in pregnant women because of the potential safety signals identified in Provigil/Nuvigil and that the use of solriamfetol is anticipated in females of reproductive potential and during pregnancy. Therefore, DPMH recommends the following PMR:

> "*A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to solriamfetol up to six months prior to conception and/or during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.*
>
> *And*
>
> *An additional study that uses a different study design (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age in women exposed to solriamfetol during pregnancy*

compared to an unexposed control population."

LACTATION

Animal Data

As per the applicant, solriamfetol is present in rat milk. In a perinatal/postnatal developmental and reproductive study of solriamfetol, the mean solriamfetol concentrations in milk and in plasma increased with dose in an approximately proportional manner. Solriamfetol milk concentrations were higher than solriamfetol plasma concentrations. The mean solriamfetol milk/plasma ratio was similar between dose groups: 3.86 at 35 mg/kg/day, 4.25 at 110 mg/kg/day, and 3.30 at 350 mg/kg/day.

Reviewer comment:

When a drug is present in animal milk, it is likely that the drug will be present in human milk. However, the concentration of a drug in animal milk does not predict concentrations in human milk.

Review of Literature

The applicant did not provide any literature review. Therefore, no clinical information was provided by the applicant.

DPMH Review

DPMH conducted a literature search in PubMed, Embase, and the LactMed databases for solriamfetol or its metabolites and use in lactation, as well as in GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation and Hale TW Medications and Mother's Milk[5]. No additional information was identified regarding presence of solriamfetol or its metabolites in breast milk, the effects on the breastfed infant, or the effect of this drug on milk production.

Reviewer comment:

Solriamfetol is administered chronically, and mothers on treatment with solriamfetol should be aware that the breastfed child could be affected. Mothers should be advised to monitor the breastfed infant for adverse reactions, such as agitation, insomnia, anorexia and reduced weight gain. DPMH has previously recommended labeling language on the use of psychostimulants during lactation, varied from breastfeeding is not recommended during use of the stimulant drug (Adzenys, amphetamines) to the risk/benefit statement on breast feeding followed by Clinical Considerations (Concerta, Cotempla, Nuvigil). These recommendations were based on drugs that were determined to be transferred into breast milk leading to a Relative Infant Dose (RID) greater than 7. (b) (4)

Summary

Solriamfetol is present in rat milk. No information was identified regarding presence of solriamfetol or its metabolites in breast milk, the effects on the breastfed infant, or the effect

[5] Hale WT. Medications & Mothers' Milk. 2017, Seventh Edition. Springer Publishing Co., NY, NY

of this drug on milk production. DPMH recommends to include in the labeling the following statement: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for solriamfetol and any potential adverse effects on the breastfed infant with solriamfetol or from the underlying maternal condition." In addition, DPMH recommends adding the following Clinical Consideration: "Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia and reduced weight gain."

Because there is no information to guide safe use of solriamfetol during lactation and there is anticipated use of the drugs in females of reproductive potential, DPMH recommends a post marketing PMC for a lactation study (milk only).

MALES AND MALES OF REPRODUCTIVE POTENTIAL

Animal Data

As per the non-clinical reviewer, Jia Yao, the applicant has provided the following animal data with the submission:

Solriamfetol did not affect fertility or sperm parameters, when administered orally to male rats for 8 weeks at 3.5 times the MRHD, based on mg/m^2 body surface area.

At 11 times the MRHD based on mg/ m^2 body surface area, solriamfetol decreased sperm count and sperm concentration without affecting fertility.

Solriamfetol did not affect fertility when administered orally to female rats for 2 weeks premating, during mating, and through gestation day 7 at 9.5- times multiples of the MRHD, based on mg/m^2 body surface area.

Review of Literature

The applicant did not provide a literature search.

DPMH Review

DPMH conducted a literature search in PubMed, Embase, Reprotox and GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation. No additional information was identified regarding solriamfetol and use in Females and Males of Reproductive Potential.

Reviewer Comment

Solriamfetol is not mutagenic nor genotoxic; therefore, DPMH does not recommend inclusion of labeling for contraception or pregnancy testing.

Summary

Because solriamfetol is neither mutagenic nor genotoxic, evidence of teratogenicity in animal developmental toxicity studies where related to maternal toxicity, and no human data have established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes, DPMH does not recommend any labeling for contraception use or pregnancy testing prior to initiating treatment with solriamfetol.

CONCLUSIONS

As stated earlier, DPMH recommends a pregnancy registry [two studies to be included: A prospective, registry based observational exposure cohort study and an additional study that uses a different study design (for example a retrospective cohort study using claims or electronic medical record data or a case control study)] to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age in women exposed to solriamfetol during pregnancy compared to an unexposed control population. DPMH also recommends a lactation study (milk only) to characterize the drug in the breast milk and its effects on the breastfed child.

Solriamfetol labeling has been edited to comply with the PLLR. DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

- **Pregnancy, Subsection 8.1**
  - The "Pregnancy" subsection of solriamfetol labeling was formatted in the PLLR format to include: "Pregnancy Registry", "Risk Summary", and "Data" headings.

- **Lactation, Subsection 8.2**
  - The "Lactation" subsection of solriamfetol labeling was formatted in the PLLR format to include the "Risk Summary" and "Clinical Considerations" headings.

- **Females and Males of Reproductive Potential, Subsection 8.3**
  - The "Females and Males of Reproductive Potential" subsection of solriamfetol labeling was omitted because there is nothing to be reported.

Patient Counseling Information, Section 17

The "Patient Counseling Information" section of labeling was updated to correspond with sections 8.1 and 8.2 of labeling.

RECOMMENDATIONS

DPMH has the following recommendations for solriamfetol labeling.

FULL PRESCRIBING INFORMATION: CONTENTS

8 USE IN SPECIFIC POPULATIONS

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to solriamfetol during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling xxx or contacting the company at www.xxxxx.com

Risk Summary

Available data from case reports are not sufficient to determine drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproductive studies, oral administration of solriamfetol during organogenesis caused maternal and fetal toxicities in rats and rabbits at doses ≥ (b) (4) times and was teratogenic at doses (b) (4) times, respectively, the maximum recommended human dose (MRHD) of (b) (4) mg based on mg/m^2 body surface area. (b) (4) *(see Data).*

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

Data

Animal Data

Solriamfetol was administered orally to pregnant rats during the period of organogenesis at 15, 67, and 295 mg/kg/day, which are approximately (b) (4) times the MRHD

based on mg/m^2 body surface area. Solriamfetol at ≥ (b) (4) times the MRHD caused maternal toxicity that included hyperactivity, significant decreases in body weight, weight gain, and food consumption. Fetal toxicity at these maternally toxic doses included increased incidence of early resorption and post-implantation loss, and decreased fetal weight. Solriamfetol was teratogenic at (b) (4) times the MRHD, it increased the incidence of fetal malformations that included severe sternebrae mal-alignment, hindlimb rotation, bent limb bones, and situs inversus. This dose was also maternally toxic. The no-adverse-effect level for malformation is (b) (4) times and for maternal and embryofetal toxicity is approximately (b) (4) times the MRHD based on mg/m^2 body surface area.

Solriamfetol was administered orally to pregnant rabbits during the period of organogenesis at 17, 38, and 76 mg/kg/day, which are approximately (b) (4) times the MRHD based on mg/m^2 body surface area. Solriamfetol at (b) (4) times the MRHD caused maternal toxicity of body weight loss and decreased food consumption. Solriamfetol was teratogenic at ≥ (b) (4) times the MRHD, it caused fetal skeletal malformation (slight-to-moderate sternebrae mal-alignment) and decreased fetal weight. The no-adverse-effect level for malformation and fetal toxicity is approximately (b) (4) and for maternal toxicity is approximately (b) (4) times the MRHD based on mg/m^2 body surface area.

Solriamfetol was administered orally to pregnant rats during the period of organogenesis from gestation day 7 through lactation day 20 post-partum, at 35, 110, and 350 mg/kg/day, which are approximately (b) (4) times the MRHD based on mg/m^2 body surface area. At ≥ (b) (4) times the MRHD, solriamfetol caused maternal toxicity that included decreased body weight gain, food consumption, and hyperpnea. At these maternally toxic doses, fetal toxicity included increased incidence of stillbirth, postnatal pup mortality, and decreased pup weight. Developmental toxicity in offspring pups after lactation day 20 included decreased body weight, weight gain, and delayed sexual maturation. Mating and fertility of offspring pups were decreased at maternal doses (b) (4) times the MRHD without affecting learning and memory. The no-adverse-effect level for maternal and developmental toxicity is approximately (b) (4) the MRHD based on mg/m^2 body surface area.

8.2 Lactation

Risk Summary

There are no data available on the presence of solriamfetol or its metabolites in human milk, the effects on the breastfed infant, or the effect of this drug on milk production. Solriamfetol is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed child from TRADENAME or from the underlying maternal condition.

Clinical Considerations

(b) (4)

Monitor breastfed infants for adverse reactions, such as agitation, insomnia, anorexia and reduced weight gain.

17 PATIENT COUNSELING INFORMATION

Lactation

(b) (4) monitor infants for adverse reactions, such as agitation, insomnia, anorexia and reduced weight gain *[see Use in Specific Populations (8.2)]*

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/s/

CHRISTOS MASTROYANNIS
08/27/2018

LYNNE P YAO
08/27/2018

LABELS AND LABELING REVIEW

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

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

Date of This Review:	July 30, 2018
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 211230
Product Name and Strength:	Sunosi (solriamfetol) tablets 75 mg, 150 mg (b) (4)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Jazz Pharmaceuticals Ireland Limited
FDA Received Date:	December 20, 2017
OSE RCM #:	2018-134
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

The Division of Psychiatry Products (DPP) consulted the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the container labels, (b) (4) and prescribing information (PI) submitted for Sunosi (solriamfetol) tablets, NDA 211230, to determine if they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed container labels and prescribing information for Sunosi[a] (solriamfetol) to determine if there are any areas of concern or needed improvement from a medication safety perspective. We identified the following:

General Comment for All Container Labels (b) (4)

1. The place holder "Tradename" is used on the container labels (b) (4) instead of the conditionally approved proprietary name Sunosi. As such, we are unable to evaluate the presentation of the proposed name in the context of the surrounding information presented on the labels and labeling.
2. The controlled substance symbol placeholder ("CXX") is too large and distracts from important product identifying information.

[a] The proposed name Sunosi was found conditionally acceptable in OSE Review #2018-20504725 and 2018-20504851, dated April 23, 2018.

Container Labels

1. The net quantity statement is too prominent and is located too close in proximity to the statement of strength. The prominence and location of the net quantity statement draws attention away from the statement of strength and may contribute to wrong strength medication errors.
2. The "Rx Only" statement is too prominent which draws attention away from important product identifying information on the principal display panel.
3. The expiration date format is not indicated. The expiration date format should be indicated on the labels in order that we may assess the format from a medication error perspective.

(b) (4)

4 CONCLUSION & RECOMMENDATIONS

We identified areas of needed improvement in the size and/or positioning and presentation of certain statements on the container labels (b) (4). We provide recommendations in Section 4.1, below.

4.1 RECOMMENDATIONS FOR JAZZ PHARMACEUTICALS IRELAND LIMITED

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

A. General Comment

1. The place holder "Tradename" is on the container labels (b) (4). Delete the placeholder and replace with the conditionally approved proprietary name "Sunosi" (use your proposed trade dress).

2. The controlled substance symbol placeholder (“CXX”) is too large and distracts from important product identifying information. Decrease the size of the controlled substance symbol placeholder (and specify the designated schedule, if determined at the time of this request).

B. Container Labels

1. The net quantity statement is too prominent and is located too close in proximity to the statement of strength. The prominence and location of the net quantity statement draws attention away from the statement of strength and may contribute to wrong strength medication errors. Unbold the numerical portion (“30” or “100”) of the net quantity statement and move the statement away from the statement of strength. Consider moving the net quantity statement to the right bottom section of the principal display panel (PDP).

2. The “Rx Only” statement is too prominent which draws attention away from important product identifying information on the principal display panel. Unbold the “Rx Only” statement.

3. The expiration date format is not indicated. Please indicate the expiration date format that you intend to use on the labels. To minimize confusion and reduce the risk of use of expired drug product, we recommend using one of the following (or similar) formats:

DDMMMYYYY (e.g., 31JAN2013)
MMMYYYY (e.g., JAN2013)
YYYY-MMM-DD (e.g., 2013-JAN-31)
YYYY-MM-DD (e.g., 2013-01-31)

(b) (4)


(b) (4)


(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Sunosi received on December 20, 2018 from Jazz Pharmaceuticals Ireland Limited.

Table 2. Relevant Product Information for Sunosi	
Initial Approval Date	N/A
Active Ingredient	solriamfetol
Indication	Indicated to improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea
Route of Administration	Oral
Dosage Form	Tablet
Strengths	75 mg (scored), 150 mg (b) (4)
Dose and Frequency	The recommended dose range is (b) (4) mg once daily. (b) (4) Based on efficacy and tolerability, increase by doubling the dose at intervals of at least 3 days. Renal impairment: Dose range is (b) (4) mg in patients with moderate renal impairment and (b) (4) mg in patients with severe renal impairment. Not recommended for use in patients with end stage renal disease (ESRD).
How Supplied	30-count and 100-count bottles
Storage	Store at 20°to 25°C (68°to 77°F); excursions permitted between 15°to 30°C (59°to 86°F) (see USP controlled room temperature)
Container Closure	Child-resistant closure

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Sunosi labels and labeling submitted by Jazz Pharmaceuticals Ireland Limited.

- Container Labels received on December 20, 2017
- (b) (4)
- Prescribing Information (image not shown) received on December 20, 2017

G.2 Label and Labeling Images (not to scale)

Container Labels

(b) (4)

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

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

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/s/

LORETTA HOLMES
07/30/2018

LOLITA G WHITE
07/30/2018