Lisdexamfetamine

Pre-Review Report

Agenda item 5.1

Expert Committee on Drug Dependence

Thirty-sixth Meeting

Geneva, 16-20 June 2014

Acknowledgments

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Contents

Summary

As a central nervous system stimulant, lisdexamfetamine is used as an adjunct in the treatment of attention deficit hyperactivity disorder (ADHD). As a prodrug, lisdexamfetamine was specifically designed as an abuse-resistant product. After oral administration and absorption, enzyme hydrolysis following contact with red blood cells will break lisdexamfetamine into L-lysine, a naturally occurring essential amino acid and active d-amphetamine which is responsible for the drug's pharmacological activity. The safety and efficacy of lisdexamfetamine in the treatment of ADHD has been established in children 6–12 years of age, adolescents, and adults and the toxicology and adverse effect profile appears similar to other stimulant drugs for this indication. Although, lisdexamfetamine self-administration is limited in preclinical and clinical studies, lisdexamfetamine does produce similar subjective and discriminative effects as d-amphetamine in humans and animals, respectively. The observation that lisdexamfetamine produces substantial and sustained increases in catecholaminergic neurotransmission in the prefrontal cortex and striatum without inducing locomotor activation in preclinical studies is consistent with the clinical observations that lisdexamfetamine has a long duration of action and a reasonable separation between its beneficial effects in treating ADHD and the induction of psychostimulant adverse events. To date, there appears to be little evidence of non-medical use of lisdexamfetamine based on data from DAWN Live!, Internet and media monitoring, supply chain monitoring, post-marketing adverse event reports, and RADARS® especially in comparison to immediate release stimulant medications for ADHD. Nevertheless, the fact that lisdexamfetamine is a prodrug of d-amphetamine implies similar clinical oversight and cautions for the monitoring and scheduling of this CNS stimulant.

1. Substance identification

A. International Nonproprietary Name (INN)

Lisdexamfetamine

B. Chemical Abstract Service (CAS) Registry Number

0608137-32-2
0608137-33-3 (dimesylate)

C. Other Names

lisdexanfetamina (Spanish)
Lisdexamfetamine (English, French)
Lisdexamphetamine
L-lysine-D-amphetamine
NRP104

D. Trade Names(hydrobromide salt

Elvanse® (DK, GB, SE), Tyvense® (IE), Venvanse® (BR), Vyvanse® (US, CA)

E. Street Names

Currently there are not specific street names for lisdexamfetamine. However, common street names for amphetaminesmay be used when referring to lisdexamfetamine (i.e., Speed, Fet, Powder, White, Whizz, Fettle, Throttle and Base).

F. Physical properties

White to off-white powder that is highly soluble in water.

G. WHO Review History

Lisdexamfetamine has not been previously reviewed.

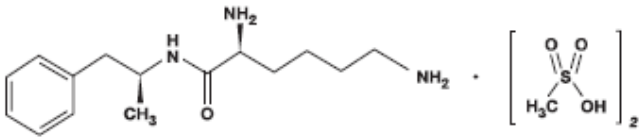
2. Chemistry

A. Chemical Name

IUPAC Name: (2S)-2,6-diamino-N-[(2S)-1-phenylpropan-2-yl]hexanamide, (2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamidedimethanesulfonate
CA Index Name: (2S)-2,6-diamino-N-[(1S)-1-phenylpropan-2-yl]hexanamide

B. Chemical Structure

Free base:



Molecular Formula:	$C15H25N3O$; $C15H25N3O•(CH4O3S)_2$
Molecular Weight:	263.378 g/mol
Melting point:	120-122°C
Boiling point:	488.015°C at 760 mmHg
Fusion point:	248.943°C

C. Stereoisomers

Lisdexamfetamine is a single-enantiomer - (dextro) amphetamine.

D. Synthesis

Lisdexamfetamine hydrochloride synthesis was first described in 2006 in US Patents to Mickle et al. and involved reacting d-amphetamine with (S)-2,5-dioxopyrrolidin-l-yl 2,6-bis (tert-butoxycarbonylamino)hexanoate to form a lysine-amphetamine intermediate bearing tert-butylcarbamate protecting groups. The intermediate is then treated with hydrochloric acid to remove the tert-butylcarbamate protecting groups and provide lisdexamfetamine as its hydrochloride salt. However, more recently, another patent application in 2012 to Bauer et al.provides a crystalline solid synthetic intermediate that is easier to purify by crystallization and provides greater than 99.9% (w/w) purity, even when using low-purity amphetamine. Other additional synthesis improvements have been proposed by Bhirud et al. in an Indian Patent Application (2013).

D. Chemical description

Lisdexamfetamine is an amide ester conjugate consisting of the amino acid L-lysine covalently bound to the amino group of d-amphetamine.

E. Chemical properties

Lisdexamfetamine dimesylate has low lipophilicity (logP-1.76) and high aqueous solubility within a biologically relevant pH range of 1-8. It should be stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F). Lisdexamfetamine should be dispensed in a tight, light-resistant container.

G. Chemical identification

The compound lisdexamfetamine contains d-amphetamine covalently linked to the essential amino acid L-lysine. As a prodrug, the compound lisdexamfetamine is pharmacologically inactive and its effects are due to its in vivo metabolic conversion to d-amphetamine. Controlled release of d-amphetamineoccurs following administration of lisdexamfetamine through

hydrolysis of the amide bond linking d-amphetamine and L-lysineprimarily by peptidase(s) associated with red blood cells.

3. Ease of convertibility into controlled substances

No free d-amphetamine exists in the lisdexamfetamine capsules therefore d-amphetamine does not become available through mechanical manipulation, such as crushing or simple extraction. A relatively sophisticated biochemical process is needed to obtain d-amphetamine from lisdexamfetamine. Lisdexamfetamine was incubated with 15 different commercially available enzymes that could be used to hydrolyze lisdexamfetamine into L-lysine and d-amphetamine; lisdexamfetamine was not hydrolyzed by any of these enzymes(1).

4. General pharmacology

Most published and unpublished preclinical studies have been conducted or financially supported by the sponsors and developers of lisdexamfetamine (Shire Pharmaceuticals, LLC) or their licensing affiliates in various countries.

4.1. Pharmacodynamics

Lisdexamfetamine is a prodrug and an inactive molecule until ingestion. After oral administration, enzyme hydrolysis following contact with red blood cells will break lisdexamfetamine into L-lysine, a naturally occurring essential amino acid and active d-amphetamine which is responsible for the drug's activity. Gastrointestinal pH does not alter this conversion and the attachment of the L-lysine slows down the relative amount of d-amphetamine available to the blood stream and therefore the CNS(2).

Novascreen Biosciences Corporation screened lisdexamfetamine in radioligand-binding studies and found no activity (<50% inhibition at 10μM) for over sixty G-protein or ion-channel receptors, enzymes, or transporters. The pharmacological effects for lisdexamfetamine are due to its conversion to d-amphetamine which then acts with moderate potency to inhibit the dopamine and norepinephrine transporters, the vesicular monoamine transporter 2, and weaker potency at the serotonin transporter. Therefore, d-amphetamine will increase catecholamines in the synaptic space via transporter inhibition and the reverse transport of catecholamines out of the nerve terminal(3).

Neuropharmacology and the effects on the central nervous system.
Lower oral dose of 0.5 and 1.5 mg/kg lisdexamfetamine failed to alter locomotor activity although a dose of 1.5 mg/kg produced a small increase in exploratory behaviour in rats for 15-60 min. A higher oral dose of 4.5 mg/kg increased locomotor activity for 45-300 min showing increases in such behaviours as sniffing, rearing, circling, and chewing for a least 210 min(4). Locomotor activity induced by lisdexamfetamine was gradual in onset, reaching a plateau 60–75 min after dosing and remaining elevated throughout the 5h observation period. In contrast, methylphenidate (30 mg/kg) also increased locomotor activity, but methylphenidate's effect was relatively fast in onset, peaking ~45 min after dosing and gradually declining thereafter.

In microdialysis experiments in rats, lisdexamfetamine dose-dependently increased extraneuronal concentrations of noradrenaline and dopamine in the prefrontal cortex

and dopamine efflux in the striatum(4-6). Using pharmacologically relevant doses, lisdexamfetamine increased the extracellular concentration of both catecholamines in the prefrontal cortex (PFC). The increases were gradual in onset reaching a peak after ~120 min and were maintained throughout the course of the experiment. Although 5-HT efflux in the PFC was increased by the highest dose of lisdexamfetamine, this effect was transient and probably not pharmacologically relevant. Lisdexamfetamine did not change the extracellular concentrations of metabolites DOPAC, HVA, or 5-HIAA.

Lisdexamfetamine's monoaminergic profile did not alter substantially when the dose shifted from the pharmacological to the non-therapeutic range. The rate of increase of extracellular dopamine induced by methylphenidate is much greater than lisdexamfetamine. In the striatum, PO lisdexamfetamine dose-dependently increased extracellular dopamine and 5-HT in a pattern similarly observed in the PFC(4)and these effects were similar to those observed after IP doses of lisdexamfetamine(5). This supports the PK and PD data demonstrating the route of administrations produce similar effects(6, 7).

In rats, the pharmacological profiles of lisdexamfetamine, methylphenidate and modafinil were essentially similar in that all three agents enhanced extracellular concentrations of dopamine and noradrenaline in the PFC, although some differences were also observed. When PO lisdexamfetamine was administered, smaller increases in striatal dopamine efflux were observed as compared to IP lisdexamfetamine and lisdexamfetamine was the only one of the stimulants tested that consistently increased the extracellular concentration of 5-HT in the PFC and striatum(3, 4). As 5-HT can have inhibitory effects on motor behavior(8, 9), this may be why less locomotor behavior was observed in ratscompared to methylphenidate. Therefore, the pharmacological effects of lisdexamfetamine are similar to those observed with d-amphetamine and methylphenidate, i.e., all agents produced large and sustained increases in striatal dopamine efflux, yet lisdexamfetamine produced less behavioural activation.

4.2. Routes of administration and dosage

Capsule, Oral: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg.

4.3. Pharmacokinetics

Lisdexamfetamine PO is rapidly absorbed via the gastrointestinal tract (duodenum, jejunum, and ileum) in animals and attains a maximum plasma concentration -0.25-3 h. Studies in vitro suggest lisdexamfetamine is a substrate for the peptide transport protein PEPT1 and maybe also PEPT2 (1). After lisdexamfetamine administration to rats, the plasma exposure to d-amphetamine as not differed when compared with immediate release d-amphetamine but the Cmax was 50% lower and the Tmax was doubled (5). Equivalent molar doses of lisdexamfetamine and d-amphetamine were administered orally to rats and brain concentrations were examined 1, 2, and 6 h later in studies performed by the sponsor. Only d-amphetamine was detectable in the brain after the administration of both compounds.

In humans after oral administration, peak plasma concentrations of lisdexamfetamine occur in approximately 1h with low, transient concentrations that are unquantifiable by 8h after administration. Gastrointestinal pH does not alter lisdexamfetamine and lisdexamfetamine is rapidly absorbed from the GI tract. Lisdexamfetamine is

metabolized by enzyme hydrolysis into l-lysine, a naturally occurring essential amino acid, and active d-amphetamine via first-pass intestinal and/or hepatic metabolism. No significant direct or time-dependent inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 was observed for lisdexamfetamine in human hepatic microsomes (10). In addition, Shire Development state that other experiments ruled out inhibition or induction of CYP2C8 or CYP3A4/5 enzymes or activity of lisdexamfetamine to be a P-gp inhibitor or substrate at concentrations of <300 or <100 μM, respectively. The absence of this enzyme activity indicates a lower potential for drug-drug interactions.

The attachment of the amino acid lysine slows down the relative amount of d-amphetamine available to the blood stream (2). The half-life of lisdexamfetamine is less than 1h and the half-life of the active drug, d-amphetamine, is then 9-13h. The onset of action occurs within 2h after oral administration and the peak plasma concentrations of d-amphetamine occur in approximately 3.5–3.7 h and last for approximately 10–12 h (2). The mean Tmax of d-amphetamine was longer and the mean Cmax was lower following lisdexamfetamine IV administration compared with d-amphetamine alone (10). A high-fat meal can delay time to this peak plasma concentration of d-amphetamine by about 1 h but does not affect magnitude of peak plasma concentration or AUC of d-amphetamine. Once converted to d-amphetamine, the d-amphetamine readily crosses the blood-brain barrier and is distributed to most body tissues including breast milk. Approximately 96% of a 70-mg radiolabeled oral dose of lisdexamfetamine was recovered in urine; parent drug accounted for about 2% of the recovered radioactivity. Changes in urinary pH may alter excretion of amphetamines (Shire US, prescribing information).

5. Toxicology

The predominant toxicology of lisdexamfetamine is related to that of d-amphetamine which is well-characterized. The toxicology reviewed below is focussed on toxicology for lisdexamfetamine per se. Based on LD50 studies, lisdexamfetamine is 5-fold less lethal by the oral route than d-amphetamine suggesting that lisdexamfetamine may saturate the processes involved in the absorption or metabolism of the inactive lisdexamfetamine to the active d-amphetamine. No effects on haematological endpoints or toxicological clinical endpoints were observed after repeated oral dose studies for 28 days in rats (11). However, an increase in mean platelet volume was observed in females rats after oral lisdexamfetamine for 3 months that resolved before 6 months. In dogs, no significant effects were observed besides pharmacological effects after a single IV infusion (Shire Development LLC).

No evidence of carcinogenicity was found in studies in which d-, l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 28 days or 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats(11)(Shire Development LLC). Genotoxicity was not observed in the bacterial reverse-mutation assay, mouse lymphoma assay, or the mouse erthyrocyte micronucleus test. Rats and rabbits were administered 40 and 120 mg/kg/day lisdexamfetamine, respectively, during periods of organogenesis and no evidence of teratogenicity was apparent (Shire Development LLC). Acute administration of high doses of amphetamine (d- or d,l-) has been shown to produce

long-lasting neurotoxic effects, including irreversible nerve fibre damage, in rodents. The significance of these findings to humans is unknown.

Studies in juvenile rats revealed reductions in body weight, food intake, and growth for males and females throughout an 8 week dosing period. Only reduced body weights continued for males after treatment for up to 91 days. No effects were observed on CNS development or reproductive function. In juvenile beagle dogs, oral lisdexamfetamine (5-12 mg/kg/day) between the ages of 10-26 weeks resulted in reduced activity and muscle tremors prior to the administration of the daily dose. Body weights were reduced up to 25% relative to control dogs and this weight reduction was partially reversed after treatment. No other significant clinical observations were noted (Shire Development LLC).

6. Adverse reactions in humans

When tested in subjects with a history of stimulant abuse, doses of 50-150 mg oral lisdexamfetamine dose-dependently increased systolic and diastolic blood pressure, and pulse compared to placebo and the 150 mg dose of lisdexamfetamine produced higher changes than 40 mg d-amphetamine (2). When administered IV, lisdexamfetamine produced attenuated systolic blood pressure changes compared to IV d-amphetamine and the time to peak effect was approximately 2-3 h post-administration compared to IV d-amphetamine (10).Mild to moderate adverse events were reported in 24%, 30%, and 41% of subjects receiving 50, 100, and 150 mg lisdexamfetamine in these experienced users with a history of stimulant abuse, reporting most commonly headache (2, 10).

The most common adverse effects for lisdexamfetamine are insomnia (13% to 27%), decreased appetite (children and adolescents 34% to 39%; adults 27%), xerostomia (adults 26%; children and adolescents 4% to 5%), and abdominal pain (children 12%). Other adverse effects include increased blood pressure (adults 3%), increased heart rate (adults 2%), irritability (children 10%), anxiety (adults 6%), dizziness (children 5%), akathisia (adults 4%), agitation (adults 3%), emotional lability (children 3%), restlessness (adults 3%), drowsiness (children 2%), tics (children 2%), hyperhidrosis (adults 3%), skin rash (children 3%), weight loss (children and adolescents 9%; adults 3%), vomiting (children 9%), diarrhoea (adults 7%), nausea (6% to 7%), anorexia (adults 5%), erectile dysfunction (adults 3%), decreased libido (adults <2%), tremor (adults 2%), dyspnea (adults 2%), and fever (children 2%) (LexicompDatabase, accessed March 2014).

Of concern for all stimulant products is the rare possibility of sudden unexplained death, stroke, and myocardial infarction that have been reported in adults with ADHD receiving usual dosages of stimulants. Also, sudden death has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of the drugs. A small number of cases of sudden unexplained death have been reported in children without structural cardiac abnormalities receiving amphetamine combinations although there were confounding factors present in some of these incidents. Possible sudden death and serious cardiovascular events can occur, particularly in individuals who abuse amphetamines (LexicompDatabase, accessed March 2014).

Any drug interaction that occurs with d-amphetamine will also occur with lisdexamfetamine. Agents that alter urinary pH can alter blood levels of amphetamine. Acidifying agents decrease amphetamine blood levels, while alkalinizing agents increase amphetamine blood levels.

7. Dependence potential

No studies were found on tolerance, sensitization, or dependence to lisdexamfetamine. However, abrupt discontinuation following high doses or for prolonged periods may result in symptoms of withdrawal (e.g., depression, extreme fatigue)(Lexicomp Database, accessed March 2014).

8. Abuse potential

In animal models of abuse liability, lisdexamfetamine shares many effects with d-amphetamine. In rats trained to discriminate 0.5mg/kg d-amphetamine IP from saline, d-amphetamine and methylphenidate IP and PO substituted fully. Lisdexamfetamine fully substituted after IP injections with a 1 min pretreatment time. In time course studies, lisdexamfetamine PO fully substituted when the pretreatment time was extended to 60 min but not at 15 minor 120min. Therefore, orally administered lisdexamfetamine produces discriminative effects that are delayed andlast less than 2h.Lisdexamfetamine had little effect on response rates. In rats trained to self-administer cocaine (0.32 mg/kg/injection), lisdexamfetamine did not main self-administration levels above saline responding at any dose in the whole group taken together although a few of rats did maintain a low rate slightly above saline responding(6). In monkeys trained to self-administer cocaine, intravenous lisdexamfetamine maintained self-administration at a rate that was statistically less than that for cocaine, but greater than that of placebo (Shire Development LLC).

The abuse potential of 50, 100, and 150 mg oral lisdexamfetamine was compared to 40 mg d-amphetamine, 200 mg diethylpropion, and placebo in subjects with a history of stimulant abuse. The dose of 150 mg lisdexamfetamine produced 'drug liking' significantly different than placebo at 4 h after dosing. Lower doses produced 'drug liking' approximately 3 h after dosing and although greater than placebo, were not statistically significant. Although the 100 mg dose of lisdexamfetamine is similar to 40 mg d-amphetamine in actual amphetamine content, subjects 'liked' 40 mg d-amphetamine better, had a lower 'feel drug effect', and higher 'disliking' scores for lisdexamfetamine. The free base d-amphetamine content of 150 mg lisdexamfetamine is 50% higher than the 40 mg d-amphetamine dose. The drug 'disliking' scores for the high dose of lisdexamfetamine were higher than amphetamine and all doses of lisdexamfetamine produced greater 'disliking' than placebo. Lisdexamfetamine had higher 'street value' than placebo but lower than d-amphetamine and diethylpropion. When asked for a preference for the different drugs and doses, 9/24 subjects preferred 150 mg lisdexamfetamine, 5/24 d-amphetamine, 4/24 diethylpropion, 3/24 100 mg lisdexamfetamine and 1/24 preferred 50 mg lisdexamfetamine or placebo (2).When IV lisdexamfetamine and an equivalent mole-weight doses d-amphetamine were compared in subjects with a history of stimulant abuse,50 mg lisdexamfetamine IV produced no significant 'drug liking' scores, 'disliking' scores, 'feel drug effect' scores, or significant changes on any of the ARCI subscales. IV d-amphetamine however produced significant 'liking' and 'euphoric' effects(10). When a post-hoc analysis of

these two studies was performed, the subjective effects or cardiovascular effects of 50 mg lisdexamfetamine were not significantly different whether delivered PO or IV (12).

A pharmacokinetic study in healthy men also provides some insight on potential abuse liability. In this study, intranasal administration of lisdexamfetamine resulted in d-amphetamine plasma concentrations and systemic exposure to d-amphetamine comparable to oral administration (13). Both PO and IN lisdexamfetamine dimesylate demonstrated a tolerability profile similar to that of other long-acting stimulants (12, 13). Taken together, these data suggest that attempts to increase reinforcing or subjective effects during recreational use by snorting or intravenous injection will not provide any advantage over simple oral administration.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

As a central nervous system stimulant, lisdexamfetamine is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD) (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction). The safety and efficacy of lisdexamfetamine in the treatment of ADHD has been established in controlled, randomized, double-blind clinical trials in children 6–12 years of age and adolescents (14-19) and adults (20-23). The summarized findings from these different clinical trials using various scales and dosing regimens indicated that the behavioural and symptomatic improvements observed with lisdexamfetamine were superior to those observed with placebo and not substantially different from those observed with mixed amphetamine salts. Recent comparisons in children previously maintained on methylphenidate without adequate control demonstrated improvement when switched to lisdexamfetamine (24, 25).

Current clinical trials are underway or recently completed to investigate the use of lisdexamfetamine for bipolar depression (26), major depressive disorder (27, 28), stimulant dependence, cognitive dysfunction in multiple sclerosis (29), chronic fatigue disorder (30), or other disorders with cognitive dysfunction as symptomology. However, in February 2014, Shire announced that two late-stage clinical trials had shown that lisdexamfetamine was not an effective treatment for depression.

10. Listing on the WHO Model List of Essential Medicines

Lisdexamfetamine is not listed in the 18th edition of WHO Model List of Essential Medicines (April 2013).

11. Marketing authorizations (as a medicine)

Lisdexamfetamine was originally developed by New River Pharmaceuticals, who were bought by Shire Pharmaceuticals shortly before lisdexamfetamine (Vyvanse®) began being marketed. On February 26, 2007, Shire Pharmaceuticals received US Food and Drug Administration (FDA) approval for the treatment of ADHD with lisexamfetamine.Health Canada approved the 30 mg and 50 mg capsules of Vyvanse® for the treatment of ADHD in pediatric patients aged 6 to 12 in February 2009, and for

adolescents and adults in November 2010. In July 2010, ANVISA, the Brazilian health authority, granted marketing authorization approval for lisdexamfetamine (Venvanse®) for the treatment of ADHD in children aged 6-12. The UK Medicines and Healthcare products Regulatory Agency acted as the Reference Member State on behalf of seven other European countries participating in the evaluation of lisdexamfetamine as Elvanse® (Denmark, Finland, Germany, Ireland (Tyvense®), Norway, Spain and Sweden). In February 2013, Elvanse® received marketing authorization in the UK and Europe. In July 2013, the Australian Therapeutic Goods Administration listed Vyvanse®; currently Vyvanse® is marketed by Shire Australia.

12. Industrial use

None.

13. Non-medical use, abuse and dependence

From market launch to February 2010, approximately 10.4 million prescriptions were filled for lisdexamfetamine. Data relevant to lisdexamfetamine non medical use were collected from postmarketing adverse event reports, DAWN Live!, internet and media monitoring, supply chain monitoring, and Drug Diversion and Poison Center Programs from the Research Abuse, Diversion and Addiction-related Surveillance (RADARS) System (Q3 2007-Q4 2009). Within this last report on RADARS®, there were 78 postmarketing adverse event reports of non-medical use and 99 DAWN Live! mentions. As of Q4 2009, the RADARS® System Poison Center call rates for lisdexamfetamine were 0.199/1,000 Unique Recipients of Dispensed Drug (URDD) compared to total extended-release amphetamines at 0.153/1,000 and total extended-release oral methylphenidate at 0.207/1,000. Likewise, the RADARS® System Drug Diversion rates were 0.026/1,000 URDD, versus 0.034/1,000 and 0.018/1,000, respectively. No exceptional orders were identified in supply chain monitoring, and no product complaints suggested diversion (31). More recent estimates from DAWN (2012) report 116 enrollments in addiction program (116 or 0.17% of total enrolled) and 2,014 emergency room visits (0.16% of total) for lisdexamfetamine.

A few internet postings about lisdexamfetamine discussed potential methods of tampering, liking or disliking, and poly drug use. In a manuscript of case studies on pharmaceutical risk management, survey analyses of the National Survey on Drug Use and Health, Monitoring the Future, Drug Abuse Warning Network (DAWN), and DAWN Live!, indicated no trend of increases in stimulant abuse since the introduction of Vyvanse®. Looking more closely at the brand-specific data through DAWN Live!, very few cases of Vyvanse® are listed(32).The website StreetRx.com allows submission of prices for diverted prescription drugs and searches for prices by geography and rate (cheap to overpriced). When evaluated using this format, lisdexamfetamine (Vyvanse®) had lower street prices than amphetamine formulations: 60% lower in StreetRx and 52% lower in the RADARS® System Drug Diversion Program's Street Price Questionnaire survey (33).

To date, there appears to be little evidence of non-medical use of lisdexamfetamine during its first 3 years post approval, based on data from DAWN Live!, Internet and media monitoring, supply chain monitoring, post-marketing adverse event reports, and

RADARS® especially in comparison to immediate release stimulant medications for ADHD.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

Amphetamines are abused through multiple routes of administration including intravenous, intranasally, and orally since amphetamines as a class demonstrate good aqueous solubility. However, lisdexamfetamine was specifically designed as an abuse-resistant product.As the metabolic route profoundly alters the pharmacokinetics of lisdexamfetamine's metabolite d-amphetamine, the pharmacodynamics and abuse potential are also altered. Lisdexamfetamine was developed with the goal of providing a long duration of effect that is consistent throughout the day, with reduced potential for abuse-related liking. Because no free d-amphetamine is present in lisdexamfetamine capsules, d-amphetamine does not become available through mechanical manipulation, such as crushing or simple extraction. A relatively sophisticated biochemical process is needed to obtain d-amphetamine from lisdexamfetamine.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit production, consumption and international trade

Lisdexamfetamine is manufactured by Shire Pharmaceuticals. There are currently at least 7 commercial sources for research and production for lisdexamfetamine from regions around the globe including Vijaya Pharmaceuticals, LLC (V-Pharma), APAC Pharmaceutical, LLC, and American Custom Chemicals Corp.

Since its release, the final aggregate production quotas for lisdexamfetamine in the USA from the Federal Register (74 FR 23881) were as follows: 2007 – 6,200kg; 2008 – 6,200 kg; 2009 – 8,200 kg; 2010 – 9,000 kg; 2011 - 10,400 kg; 2012 – 12,000 kg; 2013 – 21,000 kg. The established quotas for 2014 are 23,750kg suggesting an increased demand in the past years as further marketing has occurred.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit manufacture and traffic and related information

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

No current international controls under any of the international drug control conventions.

18. Current and past national controls

Lisdexamfetamine is controlled as Schedule II (US), S8 (AU), Schedule I (CA), and prescription only medicine (UK, EU).

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

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Annex 1:

Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of Lisdexamphetamine

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 64 Member States answered the questionnaire for lisdexamfetamine. Of these, only 22 respondents (AMR 6, EUR 13, WPR 3) had information on this substance.

LEGITIMATE USE

Thirteen respondents reported that lisdexamfetamine was currently authorized or in the process of being authorized/registered as a medical product in their country (AMR 3, EUR 9, WPR 1). Earliest authorization was in 2007 with 12 respondents stating the registered use as treatment of ADHD. It is available as capsules with 30mg, 50mg and 70mg strengths.
Different brand names mentioned are presented in the table below.

Name	Number of mentions
Elvanse	6
Vynase	3
Venvase, Samexid, Tyvense	1 each

Seven respondents stated that this substance was used in medical and scientific research and one stated that it was used in animal/veterinary care. Nine respondents stated they imported this medicine and 3 that it was manufactured in their own country. Estimated quantities reported varied from 3.3 kg to over 110 kg. Some countries did not have this information.

HARMFUL USE

Four respondents confirmed recreational/harmful use of lisdexamfetamine. However, five reported on the common routes of administration - 3 oral and 2 oral, inhaling/sniffing. Only 2 respondents answered the question regarding how lisdexamfetamine was obtained for such use, one stating this was via trafficking and the other via diversion plus trafficking. Common formulations available were reported as powder by one, tablet by three and powder/ tablet forms by two. One respondents stated that it was used only in clubs and another only in the general population. Two respondents reported withdrawal, tolerance and other adverse effects. These include anorexia, insomnia, dizziness, headaches, tachycardia and hypertension.

CONTROL

Of those with information on this substance, 13 reported that it was controlled under legislation that was intended to regulate its availability - 9 under “controlled substance act”, 2 under “medicines law” and 2 under “other” laws. On illicit activities, 1 reported trafficking and 2 reported diversion.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures*	945 (1)	1,377 (1)
Total quantity seized (kg)	1 (1)	1 (1)

* Three more reported numbers of seizure as zero for both 2011 and 2012

IMPACT OF SCHEDULING

Seventeen respondents reported that if lisdexamfetamine was placed under international control, they would have the laboratory capacity to identify the substance. One respondent indicated that the availability for medical use would be affected if placed under international control.

Annex 2:
Comments from Shire on Docket No. FDA-2013-N-1676

January 29, 2013

By E-filing via regulations.gov

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket no. FDA-2013-N-1676 International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Tapentadol; Tramadol; Ketamine; gamma-Butyrolactone; 22 Additional Substances; Request for Comments

Dear Sir/Madam,

Shire welcomes the opportunity to submit comments to the docket for: *International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Tapentadol; Tramadol; Ketamine; gamma-Butyrolactone; 22 Additional Substances;* and acknowledges the importance of FDA's role in promoting and protecting public health.

Introduction

These comments are submitted in response to the December 30, 2013 Federal Register Notice requesting comments concerning the abuse potential, actual abuse, medical usefulness, trafficking, and impact of scheduling changes on availability for medical use of 26 drug substances for use in preparing a response from the United States (US) to the World Health Organization (WHO) regarding the abuse liability and diversion of these drugs. In particular, these comments provide information specific to lisdexamfetamine (LDX). Lisdexamfetamine, a new chemical entity, is a prodrug with a pharmacokinetic profile that supports once-daily administration. The drug substance, lisdexamfetamine dimesylate, is pharmacologically inactive. Once absorbed, LDX is hydrolyzed, primarily by peptidase(s) associated with red blood cells, to lysine and active d-amfetamine (lisdexamfetamine t½ <1 hour). Even though LDX has an extended duration of action the product is not a formulated (or mechanical) extended release product.
Shire Pharmaceuticals (Shire) has manufactured LDX and marketed the product in the US under the brand name Vyvanse® since the Food and Drug Administration (FDA) approved the product in February 2007. The product is a Schedule II controlled substance. Since the marketing launch, Shire has been collecting and analyzing postmarketing surveillance data on trends in nonmedical use (abuse and misuse), diversion and tampering of LDX and other prescription stimulants. More than 4.4 million patients and 6 years of extensive postmarketing surveillance comprise the information.

WHO Questionnaire for the 36th Meeting of Expert Committee on Drug Dependence: Lisdexamfetamine

A. Legitimate Medical or Other Scientific Use of the Substance (Def 1)

1. Please state registered indications for this medicine:

   Lisdexamfetamine is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 and above.
2. Please indicate dosage form(s) and strength(s) available in your country.

   Table 1 provides dosage forms and strengths of lisdexamfetamine available in the US.

Table 1. Dosage Forms and Strengths of Lisdexamfetamine Available in the United States

	Dosage Form	Strength	Remarks
1.	Capsule	20mg	None
2.	Capsule	30mg	None
3.	Capsule	40mg	None
4.	Capsule	50mg	None
5.	Capsule	60mg	None
6.	Capsule	70mg	None

Lisdexamfetamine was first approved on 23 Feb 2007 in the US by the Food and Drug Administration (FDA) and has since been granted MA in the additional countries as listed below (see Table 2). Lisdexamfetamine is indicated for ADHD in all these countries.

Table 2. Cumulative Summary of Worldwide Marketing Authorization Status of Lisdexamfetamine

Cumulative Summary of Worldwide Marketing Authorization Status (updated 31 July 2013)			
Country	**Trade Name**	**Status**	**Approval Date**
Australia	VYVANSE	Marketed	22 July 2013
Brazil	VENVANSE	Marketed	05 Jul 2010
Canada	VYVANSE	Marketed	19 Feb 2009
Denmark	ELVANSE	Marketed	14 Feb 2013
Finland	ELVANSE	Authorized	4 June 2013
Germany	ELVANSE	Marketed	18 March 2013
Ireland	TYVENSE	Marketed	8 Feb 2013
Norway	ELVANSE	Authorized	21 Feb 2013
Spain	ELVANSE	Authorized	19 Jun 2013
Sweden	ELVANSE	Authorized	22 July 2013
United Kingdom	ELVANSE	Marketed	1 Feb 2013
United States	VYVANSE	Marketed	23 Feb 2007
Total	**Approved in 12 countries**		

3. Please list alphabetically the brand names available in your country:

   Vyvanse
4. Are there any other uses for lisdexamfetamine in health care (such as for diagnostic tests) in your country?

   There are no other approved uses for LDX in the US.
5. Is lisdexamfetamine used for medical or scientific research in your country?

Shire is currently investigating the utility of LDX in the treatment of binge eating disorder in adult patients (Phase 3 in US) and as adjunctive therapy in major depressive disorder in adult patients (Phase 3 in US).

6. Is lisdexamfetamine used for animal care (veterinary use)?

   No, LDX is not approved for animal care.

7. Is there any other legitimate (Def. 1) use of lisdexamfetamine (e.g. industry uses)?

   No, beyond treatment of ADHD in patients 6 and above, there are no additional approved uses of LDX currently approved in the US.

8. If there is any legitimate (Def. 1) use of lisdexamfetamine, how is lisdexamfetamine sourced?

   Shire purchases lisdexamfetamine from approved, registered US-based contract manufacturers

9. What is the estimated approximate amount needed for legitimate use of lisdexamfetamine in your country per year?

   In the US, Shire estimates that approximately 18,000 – 23,000 kg of lisdexamfetamine dimesylate is currently required to support the legitimate medical and scientific use of lisdexamfetamine per year. Lisdexamfetamine that is manufactured in the US is used to supply product to global markets that have approved the medical use of Shire's LDX product.

10. Is lisdexamfetamine used for cultural or ceremonial purposes?

    No, LDX has no cultural or ceremonial purpose in the US.

B. Harmful Use of the Substance (Def 2)

1. Is there recreational/harmful use of lisdexamfetamine in your country?

   Yes, there is evidence of limited recreational/harmful use of LDX in the US. Information about harmful use of LDX is available from federal and independent, well-recognized proprietary data sources. The data presented below represent LDX and the comparator methylphenidate or, where available, extended-release (ER) methylphenidate. In the US, all amphetamine and methylphenidate medicines are Scheduled II controlled substances. These products also have comparable indications for the treatment of ADHD.
   Multiple data sources show that harmful use of LDX and methylphenidate/ER methylphenidate products are generally low and similar to one another, as compared to illicit stimulants such as methamphetamine and cocaine which are associated with substantially higher rates of harm and addiction.
   Federal surveys in the US do not specifically query for Vyvanse. Brand-specific information is presented below from proprietary databases and other data sources (described below in item 5)

   i. Common route(s) of administration (Oral, Injection, Inhaling or sniffing)

      In cases of recreational use of LDX, oral use is the most common route of administration among adults and adolescents being admitted for substance abuse treatment (NAVIPPRO ASI-MV and NAVIPPRO CHAT).

      Monitoring of Internet-based drug discussion forums has revealed that most Internet abusers report using LDX orally. There have been discussions regarding use of LDX via alternative routes such as snorting or injection. However, in contrast to street cocaine and methamphetamine which are well known to provide greatly heightened effects by smoking,

insufflating and injecting and are often used by these routes, the drug abusing community seems to have reached consensus that these alternative routes do not significantly affect the subjective effects of LDX in the abuser and there is little evidence of abuse by these routes. Additionally, abusers have discussed methods to convert LDX to dextroamphetamine in order to inject or insufflate the drug. These strategies have also been determined to be largely ineffective and requiring enormous effort, skill, resources and time. As a result, alternative routes of administration of LDX are largely discouraged within the drug abusing community.

ii. How is lisdexamfetamine obtained?

LDX used for recreational purposes is obtained through diversion from prescribed patients and not from pharmacy robberies, breeches in the distribution pipeline, or "pill mill" medical clinics.

Among adults and adolescents being admitted for substance abuse treatment in 2012, the most common source of diverted LDX was a friend or family member (reported by 48% of adults and 50% of adolescents), followed by dealer (23% and 20%, respectively), and use of one's own prescription (22% and 13%, respectively) (NAVIPPRO ASI-MV and NAVIPPRO CHAT).

Internet monitoring posts discussing how LDX is obtained for recreational purposes also indicate that friends and family are the primary source of diverted LDX.

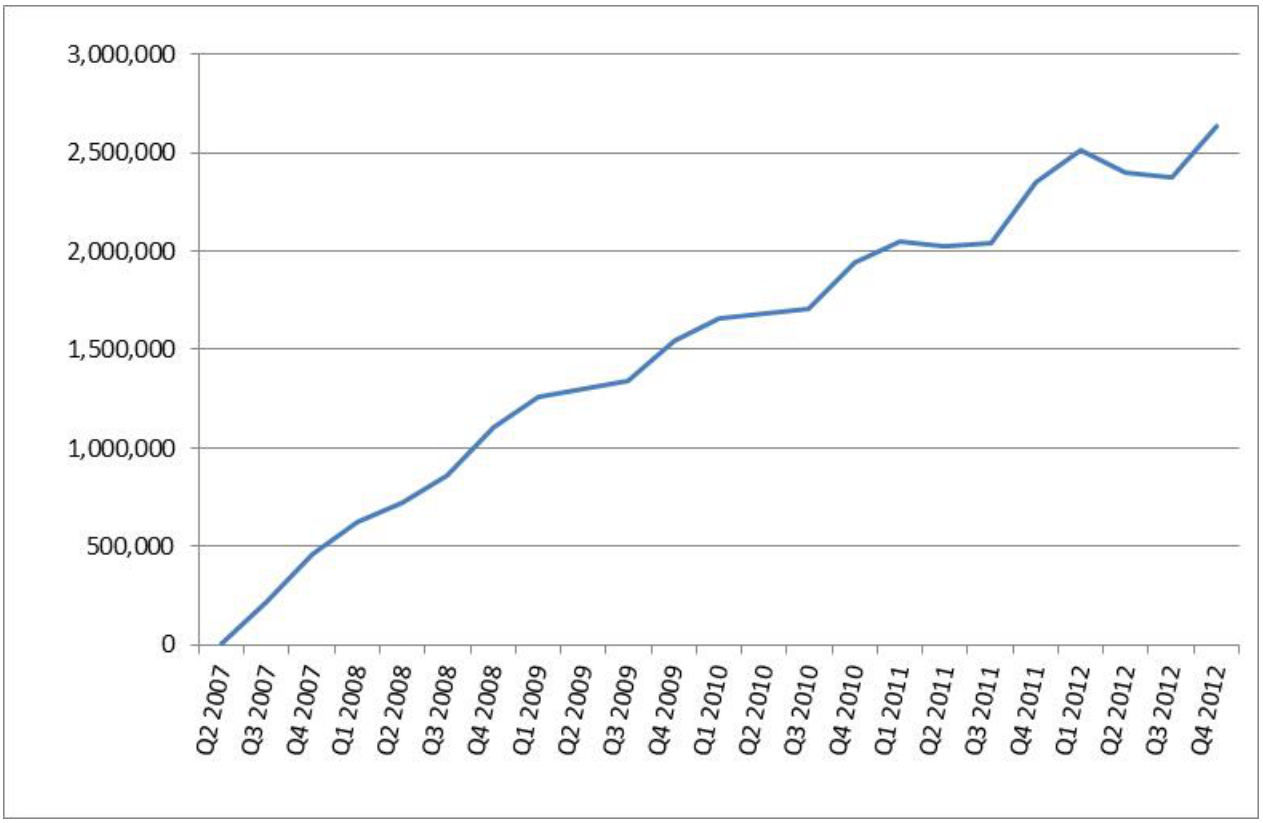
iii. Common formulation(s) available:

Lisdexamfetamine is supplied by the manufacturer in a capsule form.

2. Any other information on recreational/harmful use of lisdexamfetamine:

As context for information on recreational/harmful use of lisdexamfetamine, data are provided on US prescriptions. Since approval in February 2007 sales of the drug have increased substantially (see Figure 1).

Figure 1: Vyvanse Prescriptions, by Quarter (Q2 2007 – Q4 2012), IMS



Data on recreational/harmful use are presented below from two proprietary data sources providing information on children and adolescents.

The National Monitoring of Adolescent Prescription Stimulants Study (NMAPSS) surveyed 10 to 18-year-olds (N=11,048) recruited from ten US regions. The survey was conducted in the autumn of 2008, spring of 2009, autumn of 2010, and spring of 2011 for a total of four waves of data collection over 4 years. (NMAPSS methods have been described in Cottler et al., 2013)

Reported rates of past-month nonmedical use were found to be low and similar for both Vyvanse and Concerta (Table 3).

Table 3. Past 30 Day Nonmedical Use of Vyvanse and Concerta, NMAPSS

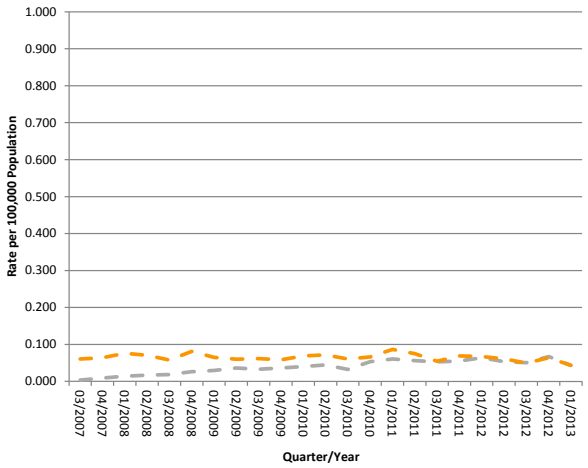
	Past 30-Day Nonmedical Use (N=10,924†) % of Total
Vyvanse (lisdexamfetamine)	0.40
Concerta® (extended release methylphenidate)	0.64

* Among those who completed Part II of the NMAPSS booklet
† Completed Part II booklet and not in Dexedrine®, Focalin, and Metadate (DFM) only group

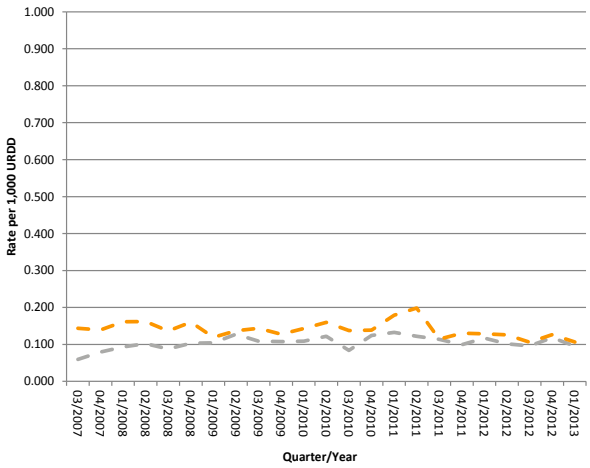
The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System collects brand-specific data about nonmedical use and diversion of prescription medications throughout the US, contributing to the understanding of trends and specific geographic regions where nonmedical use and diversion of prescription medications have occurred (Cicero et al., 2007).
The RADARS System provides data in the form of two rates: per 100,000 population and per 1,000 unique recipients of dispensed drug (URDD). Each individual filling a prescription for a drug in a given quarter is counted as a single URDD, regardless of the number of prescriptions received during that time.
Data collection for prescription stimulants began in the third quarter of 2007. The data are provided for the RADARS System Poison Center Program. This study collects data on spontaneous phone calls from consumers and health care professionals to poison centers in the US regarding intentional and unintentional exposures to potential poisons. A case coded as an intentional exposure (abuse, intentional misuse, suicide, or intentional unknown) is used as a surrogate for misuse and abuse. In Q4 2012, 50 of the 57 US poison centers participated in the RADARS System. Of those 50 participating poison centers, 50 submitted data in Q4 2012.
Calls for Vyvanse to US poison centers have increased marginally since product approval. As shown in Figure 2 (panel a), among those under 18 years of age, calls to US poison centers (population rates) regarding intentional exposures are low and similar for Vyvanse and Concerta and its generic equivalents. This is anticipated with any new launch of a controlled prescription product, and as the market has matured, the data have been tracking closely with Concerta and its generic equivalents for more than 2 years. Using the 1,000 unique recipients of dispensed drug (URDD) rate (taking product availability into account), intentional exposure rates for Vyvanse and Concerta and its generic equivalents have been low and stable over time and tracking closely since Q1 2009 (Figure 2, panel b).

Figure 2: Youth (under 18 Years of Age) Intentional Exposure Rates for Vyvanse and Concerta + Generic Equivalents (a) per 100,000 Population and (b) per 1,000 URDD for All Sites, (RADARS System Poison Center Program; Q3 2007 – Q4 2012)

a) Rate per 100,000 population



b) Rate per 1,000 unique recipients of dispensed drug



Vyvanse Concerta

3. Quantity of substance used by an average misuse per sitting (average dose used):

   We are not aware of data on the average dose used per sitting.
4. Please provide any information on the extent/magnitude of public health or social harm from the use of lisdexamfetamine (Def. 2) in your country.
   Table 4 presents overdose deaths, addiction program enrollment, emergency room visits and dependence to lisdexamfetamine in the US in 2012.

Table 4. Overdose deaths, addiction program enrollment, emergency room visits and dependence to lisdexamfetamine in the United States, 2012.

	Overdose deaths reported*	Addiction Program enrollment** N (% of total)	Emergency room visits † N (% of total)	Dependence
Numbers in 2012				
Total		68,382	1,244,872	N/A
Rx Stimulants		975 (1.43%)	40,648‡ (3.27%)	N/A
Lisdexamfetamine	2+2§	116 (0.17%)	2,014 (0.16%)	N/A
Methylphenidate		N/A	4,918£ (0.40%)	N/A

ER methylphenidate		201 (0.29%)	N/A	N/A

N/A = not available

* Overdose deaths were identified from the Shire Global Safety System (SGSS) which captures cases reported to the Shire Global Pharmacovigilance and Risk Management department (GPVRM).

** Addiction program enrollment data were obtained from the NAVIPPRO Addiction Severity Index Multi-media Version (ASI-MV®) Connect. These data represent past 30-day nonmedical use among adults entering substance abuse treatment.

† Emergency room visits due to nonmedical use were obtained from the Drug Abuse Warning Network (DAWN), a public health surveillance system that monitors drug-related visits to hospital emergency departments (EDs). This is the 2011 estimate of emergency department visits for nonmedical use. DAWN has not yet released ED visit estimates for 2012. DAWN does not provide data at the formulation level (e.g., ER methylphenidate).

‡ DAWN reports on "All CNS Stimulants", which includes prescription products (e.g., amphetamine-dextroamphetamine, methylphenidate, modafinil), and products available without a prescription (i.e., caffeine-containing products).

§ In the SGSS, four deaths have been recorded involving lisdexamfetamine. Lisdexamfetamine was the primary suspect drug in 2 deaths. In the other 2 deaths, other drugs were identified as the more likely primary cause of death.

£ Includes all methylphenidate, not just ER. DAWN does not differentiate between IR and ER methylphenidate products.

5. Are there reports of withdrawal, tolerance, other adverse effects or medical illnesses caused by lisdexamfetamine in your country?

   The Vyvanse prescribing information (Revised December 2013) includes language consistent with all prescription stimulants approved for marketing in the US, all of which are Schedule II. Specifically, the Vyvanse prescribing information states that tolerance "may occur during the chronic therapy of CNS stimulants including Vyvanse". Similarly, physical dependence "may occur in patients treated with CNS stimulants including Vyvanse. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include extreme fatigue and depression."
   In clinical trials, the most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in children, adolescents, and/or adults were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.
6. Please indicate the sources of information on harm.

   Data are presented from the following data sources:

Data Source	**Description**
Drug Abuse Warning Network (DAWN) Emergency Department	A public health surveillance system that monitors drug-related hospital emergency departments (EDs).
Internet monitoring	Monitoring of select Internet sites in which substance abusers discuss nonmedical use and diversion of drug products
National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) Comprehensive Health Assessment for Teens (CHAT®)	Proprietary data stream that collects self-reported product-specific data from adolescents who are being admitted for substance abuse treatment In 2012, 105 facilities, across 16 states, contributed CHAT data. Of those 105 facilities, 33 were located in Missouri.
NAVIPPRO Addiction Severity Index Multi-media Version (ASI-MV®) Connect	Proprietary data stream that collects self-reported product-specific data from adults who are being admitted for substance abuse treatment

	In 2012, 588 facilities, across 36 states, contributed ASI-MV data
National Forensic Laboratory Information System (NFLIS)	Collects drug chemistry analysis results and related information from cases analyzed by state, local and federal forensic laboratories that analyze substances secured in law enforcement operations
National Monitoring of Adolescent Prescription Stimulants Study (NMAPSS)	Four-wave, 4 year survey of 10 to 18-year-olds recruited from ten US regions
Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Drug Diversion Program	Collects brand-specific data on cases of diversion from more than 300 law enforcement prescription drug investigators from jurisdictions in all 50 US states and Washington, DC
Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program	Collects brand-specific data on spontaneous phone calls from consumers and health care professionals to US poison centers regarding intentional and unintentional exposures to potential poisons
Shire Global Safety System (SGSS)	Cases of nonmedical use and diversion reported to the Shire Global Pharmacovigilance and Risk Management department (GPVRM).

C. Control of the Substance

1. Are there illicit activities involving lisdexamfetamine?

    a. Clandestine manufacture.

    There is no evidence of clandestine manufacture of LDX.

    b. The manufacture (synthesis) of the chemical itself

    There is no evidence of illicit synthesis of LDX.

    c. The processing into the consumer product, i.e. adding it to herbal material, packaging

    There is no evidence of processing of LDX into a consumer product.

    d. Trafficking

    There is no evidence of trafficking.

    e. Diversion

    There is evidence of minimal small-scale diversion. As discussed above in section B, among adults and adolescents being admitted for substance abuse treatment in 2012, the most common source of diverted LDX was a friend or family member (reported by 48% of adults and 50% of adolescents), followed by dealer (23% and 16%, respectively), and use of one's own prescription (22% and 13%, respectively) (NAVIPPRO ASI-MV and NAVIPPRO CHAT).

    f. Internet market

There is no evidence of Internet marketing.

2. Data on seizures

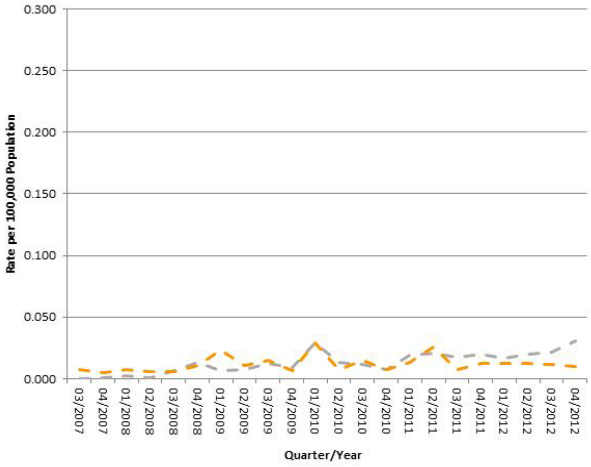
We note that information on seizures is most readily available from the US Drug Enforcement Administration.
According to data released by the National Forensic Laboratory Information System (NFLIS), in 2012, NFLIS laboratories identified 191,974 stimulants (unweighted), representing about 14% of all drugs identified. LDX has never appeared in the top 25 most frequently listed drugs. As shown in Table 5, in 2012, LDX was the 6th most frequently reported stimulant (unweighted).
Table 5: Number and percentage of stimulant reports in the US, NFLIS, 2012

Stimulant Reports	Number	Percent
Methamphetamine	162,655	84.73%
Amphetamine	8,821	4.59%
1-Benzylpiperazine (BZP)	4,182	2.18%
alpha-PVP	2,642	1.38%
Methylphenidate	2,280	1.19%
Lisdexamfetamine	1,298	0.68%
4-MEC	995	0.52%
Trazodone	891	0.46%
Pentedrone	882	0.46%
Phentermine	619	0.32%
Cathinone	533	0.28%
Citalopram	287	0.15%
Sertraline	264	0.14%
Amitriptyline	261	0.14%
Benocyclidine	238	0.12%
Butylone	238	0.12%
Other stimulants	4,888	2.55%
Total Stimulant Reports	191,974	100.00%
Total Drug Reports	1,420,811	

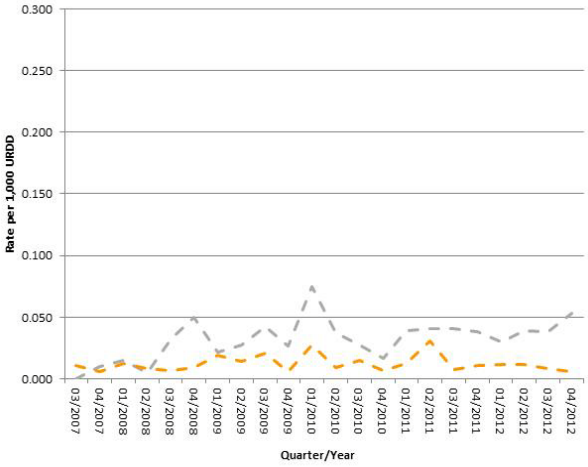
The RADARS Drug Diversion Program surveys more than 300 law enforcement prescription drug investigators from jurisdictions in all 50 US states and Washington, DC. Figure 3 (panels a and b) shows that rates of diversion of Vyvanse and Concerta and its generic equivalents are very low. Population rates of Vyvanse diversion are similar to Concerta and its generic equivalents for the most recent 7 quarters (generally below 0.025). At the URDD level, Vyvanse diversion rates remain low and similar to Concerta and its generic equivalents although tracking slightly higher, keeping in mind that the overall rate is very low (generally below 0.05). As context, ER oxycodone, which is exclusively OxyContin, is shown separately (Figure 3, panel c) to illustrate the much higher rates (note the difference in scale from Vyvanse and Concerta). The recent downward trend in ER oxycodone reflects the 2010 introduction of reformulated OxyContin, which is designed to be abuse deterrent.

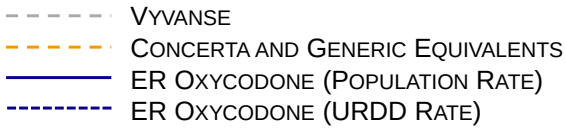
Figure 3. RADARS System Drug Diversion Program: Vyvanse, Total Concerta (Concerta + Generic), and ER Oxycodone Rates, All Sites, Q3 2007 – Q4 2012

a) Rate per 100,000 population

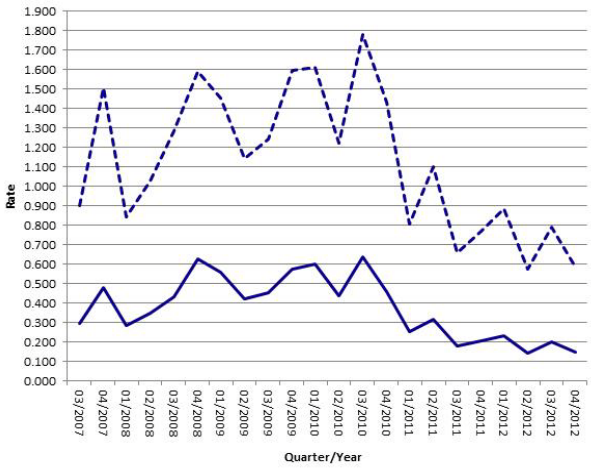


b) Rate per 1,000 unique recipients of dispensed drug





c) ER oxycodone rates



D. Impact of Scheduling

1. If lisdexamfetamine is placed under international control, do you think its availability for medical use will be affected?

   If placed under international control as a Schedule II product then availability for medical use is unlikely to be affected.

If you have any questions, please do not hesitate to contact us.

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