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# Lisdexamfetamine Mesilate

Rec INNM; USAN

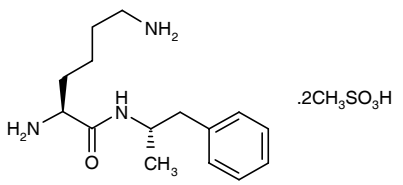
*Treatment of Attention Deficit Hyperactivity Disorder*

L-Lysine-*d*-amphetamine dimesylate
NRP-104
SPD-489
Vyvanse™

$N^1$-[1(*S*)-Methyl-2-phenylethyl]-L-lysinamide bis(methanesulfonate)

2(*S*),6-Diamino-*N*-[1(*S*)-methyl-2-phenylethyl]hexanamide bis(methanesulfonate)

InChI=1/C15H25N3O.2CH4O3S/c1-12(11-13-7-3-2-4-8-13)18-15(19)14(17)9-5-6-10-16;2*1-5(2,3)4/h2-4,7-8,12,14H,5-6,9-11,16-17H2,1H3,(H,18,19);2*1H3,(H,2,3,4)/t12-,14-;;/m0../s1




$C_{17}H_{33}N_3O_7S_2$
Mol wt: 455.5919

CAS: 608137-33-3

CAS: 608137-32-2 (free base)

CAS: 819871-04-0 (hydrochloride)

EN: 377425

**Abstract**

Attention deficit hyperactivity disorder (ADHD) is a common, complex neuropsychiatric and behavioral disorder characterized by inattention, distractibility, hyperactivity and impulsivity. There are currently two classes of approved agents for ADHD: psychostimulants (*e.g.*, methylphenidate and amphetamine) and the nonstimulant atomexetine. Psychostimulants appear to be the most effective agents, with improvement observed in the majority of patients. However, these agents are associated with a high liability for addiction and abuse. In an attempt to reduce this high risk, a series of *d*-amphetamine prodrugs were synthesized, from which lisdexamfetamine mesilate (NRP-104, SPD-489, Vyvanse™) emerged. Lisdexamfetamine is inactive until hydrolyzed in the digestive tract, after which it exhibits a prolonged duration of action. Moreover, the agent appears to have less abuse potential than *d*-amphetamine. Lisdexamfetamine was approved by the FDA in February 2007 for the treatment of ADHD in children, and it is being evaluated clinically for use in adults.

## Synthesis

Lisdexamfetamine can be synthesized as follows:

The condensation of $N^2$,$N^6$-bis-(*tert*-butoxycarbonyl)-L-lysine succinimidyl ester (I) with *d*-amphetamine (II) by means of DIEA in dioxane gives the protected carboxamide (III), which is deprotected by means of HCl in dioxane to afford the target lisdexamfetamine (1, 2). Scheme 1.

## Background

Attention deficit hyperactivity disorder (ADHD) is a complex neuropsychiatric and behavioral disorder that is characterized by inattention, distractibility, hyperactivity and impulsivity. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV classification system, there are four major subtypes of ADHD: the inattentive type, the hyperactive/impulsive type, the combined type and the not otherwise specified type, in which an individual exhibits some characteristics of ADHD but does not meet sufficient criteria to reach full diagnosis. ADHD is believed to affect 7-12% of the U.S. pediatric population, making it the most common behavioral and psychological disorder encountered in pediatric medicine. Symptoms of ADHD persist into adulthood in from 4% to 80% of individuals diagnosed with the disorder as children (3-7).

It is believed that in ADHD both environmental and genetic factors alter the developing brain. There are several nongenetic risk factors that are associated with ADHD and these include prenatal exposure to nicotine and alcohol, maternal metabolic disorders, prenatal and perinatal hypoxia, iron deficiency, lead exposure, trauma, cerebral infarct, hyperbilirubinemia, meningitis, encephalitis and adverse psychosocial conditions.

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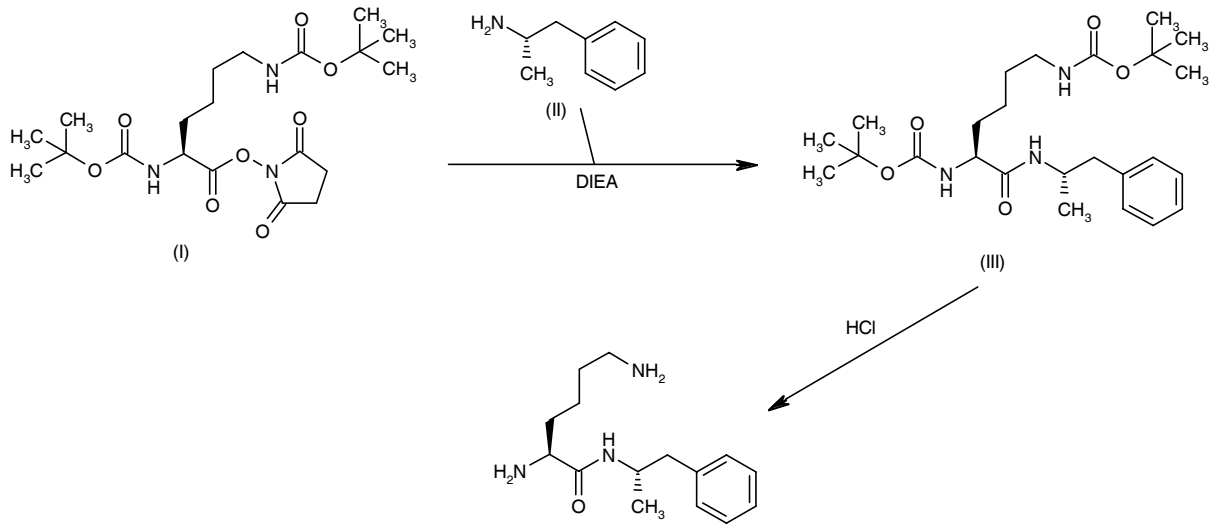
**Scheme 1: Synthesis of Lisdexamfetamine**




However, the leading cause of ADHD appears to be genetic, with studies in twins reporting the heritability for ADHD as 60-94%. ADHD has been linked to polymorphism in genes for the dopamine transporter (DAT1) and dopamine receptors (D4 and D5). In addition, genes for the 5-$HT_{1B}$ and 5-$HT_{2A}$ receptors, dopa-β-hydroxylase, synaptosomal-associated protein (SNAP)-25 and catechol-*O*-methyltransferase (COMT) are also suspected of contributing to ADHD pathology. Although the exact neurochemical dysfunction in ADHD remains to be elucidated, researchers speculate that dysregulation of dopamine and norepinephrine systems is predominantly responsible. This dysfunction could be due to lack of or delay in maturation of frontostriatal circuitry (3, 4, 8-16).

ADHD can be treated with both pharmacological and nonpharmacological interventions. However, significantly better outcomes on core symptoms of ADHD are obtained with optimized pharmacological management alone. To date, there are two classes of approved agents for ADHD: psychostimulants (*e.g.*, methylphenidate and amphetamine) and the nonstimulant antidepressant atomoxetine (Table I). Psychostimulants act predominantly on the dopaminergic system and studies have indicated that 9 of 10 patients respond, although trial and error may be required to find an effective agent. Improvements can be seen on symptoms such as overactivity, attention span deficits, impulsivity, self-control and aggressiveness, although not all behavioral symptoms may be alleviated. Although psychostimulants appear to be the most effective therapy to date, they are associated with major health concerns since misuse can cause addiction. Administration in the U.S. therefore must be closely controlled so that the midday dose is given by a school nurse, which can result in social stigma. Thus, in an attempt to reduce the potential liability for addiction and abuse, researchers continue to search for new psychostimulants that may eliminate the need for a midday dose. Several agents are currently under active development for the treatment of ADHD, as shown in Table II. The most advanced is the psychostimulant lisdexamfetamine mesilate (NRP-104, SPD-489, Vyvanse™), an amphetamine prodrug consisting of *d*-amphetamine conjugated to L-lysine, which was identified from a series of synthesized single-amino-acid, dipeptide and tripeptide *d*-amphetamine prodrugs. The agent is inactive until hydrolyzed in the digestive tract, after which it exhibits a prolonged duration of action, with efficacy lasting for a full treatment day. Moreover, the agent appears to be associated with less abuse potential than *d*-amphetamine alone. Lisdexamfetamine was therefore chosen for further development for the treatment of ADHD (3, 17).

## Pharmacokinetics and Metabolism

The pharmacokinetics and bioavailability of single intranasal (i.n.) doses (3 mg/kg) of lisdexamfetamine and *d*-amphetamine were compared in rats. The parameters obtained for the two agents were considerably different and indicated that the prodrug decreased and delayed the bioavailability of *d*-amphetamine. The *d*-amphetamine $AUC_{last}$ value with lisdexamfetamine as compared to *d*-amphetamine itself was 95% less (56 ng.ml/h *vs.* 1032 ng.ml/h), the $C_{max}$ was approximately 96% less (78.6 ng/ml *vs.* 1962.9 ng/ml) and the $t_{max}$ was about 12 times longer (1 h *vs.* 0.083 h). High concentrations of intact lisdexamfetamine were also observed ($AUC_{inf}$ = 9139 ng.ml/h; $C_{max}$ = 3345.1 ng/ml). It was concluded that only a minimal amount of *d*-amphetamine is delivered i.n. and

*Table I: Drugs marketed for the treatment of ADHD (from Prous Science Integrity®).*

| Drug | Source |
|---|---|
| **Psychostimulants** | |
| *Methylphenidate formulations* | |
| Dexmethylphenidate hydrochloride (Ritadex/Focalin) | Celgene/Novartis |
| Methylphenidate hydrochloride (Ritalin, Metadate, Daytrana, Concerta) | Novartis/UCB/Shire/McNeil |
| Pemoline (Cylert*) | Abbott |
| *Amphetamine formulations* | |
| Mixed amphetamine salts (Adderall XR) | Shire |
| Dextroamphetamine sulfate (Dexedrine, DextroStat) | GlaxoSmithKline/Shire |
| Methamphetamine hydrochloride (Desoxyn) | Abbott |
| Lisdexamfetamine mesilate (Vyvanse) | New River Pharmaceuticals/Shire |
| **Nonstimulant antidepressant** | |
| Atomoxetine hydrochloride (Strattera) | Lilly |

*Discontinued in 2005 due to the availability of generics.

*Table II: Drugs under active development for the treatment of ADHD (from Prous Science Integrity®).*

| Drug | Source | Phase |
|---|---|---|
| Altropane | Boston Life Sciences | III |
| ABT-894 | Abbott | II |
| CX-717 | Cortex | II |
| CX-701 | Cortex | Preclinical |
| CX-1501 | Cortex | Preclinical |

thus the abuse potential using this route of administration is low (18).

An open-label study conducted in 12 healthy adults examined the pharmacokinetics of multiple doses of lisdexamfetamine (70 mg p.o. once daily for 7 consecutive days). Steady-state *d*-amphetamine levels were observed by day 5 and elimination of intact lisdexamfetamine was complete at about 6 h postdosing. $AUC_{0\text{-}24h}$, $AUC_{0\text{-}\infty}$, $C_{max}$ and $t_{max}$ values for *d*-amphetamine and the intact prodrug were 1113 and 60.66 ng.h/ml, 1453 and 61.06 ng.h/ml, 90.1 and 47.9 ng/ml, and 3.68 and 1.14 h, respectively (19).

Another study conducted in 12 healthy adult stimulant abusers examined the pharmacokinetics of oral lisdexamfetamine (30-150 mg as single escalating doses at 48-h intervals). Subjects also received randomly dispersed doses of amphetamine sulfate (40 mg) and placebo. The $AUC_{last}$ value over the first 4 h for amphetamine with 100 mg lisdexamfetamine was lower than that observed with amphetamine sulfate (165.3-231.1 ng/ml *vs.* 245.5-316.8 ng/ml); $t_{max}$ values for amphetamine were longer with lisdexamfetamine as compared to amphetamine sulfate (3.78-4.25 h *vs.* 1.88-2.74 h). Exposure was reduced at higher doses (> 130 mg). The prodrug was found to be rapidly cleared ($t_{1/2}$ = 0.44-0.76 h) and adverse events reported were mild in severity. Results suggest that lisdexamfetamine undergoes rate-limited hydrolysis and may possess a better safety profile and lower abuse potential than amphetamine (20).

## Safety

In the open-label study in 12 healthy volunteers, multiple doses of the agent were well tolerated, with no ECG abnormalities observed. The majority of adverse events related to treatment were mild to moderate in severity and included anorexia, insomnia, tachycardia, hyperkinesia, abdominal pain, euphoric mood, headache and upper respiratory infection. One severe case of tachycardia requiring discontinuation was observed in a female patient after the first dose (19).

A double-blind, crossover study in 9 adult stimulant abusers showed that i.v. lisdexamfetamine (50 mg over 2 min at 48-h intervals) had significantly less abuse potential than i.v. *d*-amphetamine (20 mg). Mean peak plasma levels for *d*-amphetamine (77.7 ng/ml) were achieved rapidly at 5 min postdosing and then quickly decreased. In contrast, the mean peak levels of *d*-amphetamine with the prodrug were 33.8 ng/ml, which occurred at 3 h postdosing and were maintained throughout the 4-h observation period. A significantly greater mean maximum response to *d*-amphetamine was obtained on the primary variable of Subject Liking Visual Analog Scale (VAS) as compared to placebo and lisdexamfetamine. Lisdexamfetamine did not produce euphoria or amphetamine-like effects, although a significant increase in blood pressure was observed with lisdexamfetamine (21).

## Clinical Studies

A multicenter, randomized, double-blind, placebo-controlled, crossover phase II study conducted in an analogue classroom environment in 52 children (6-12 years) with ADHD compared the efficacy and safety of oral lisdexamfetamine (30, 50 or 70 mg/day) with placebo and extended-release mixed amphetamine salts (Adderall XR®; optimal subject dose: 10, 20 or 30 mg). The study included a 1-week screening phase, a 3-week

Adderall XR® dose-optimization phase and the 3-week randomized, double-blind, crossover phase. Fifty subjects completed the study. Both agents were well tolerated, with no serious adverse events, deaths or clinically significant changes in Q-T interval reported. Diastolic blood pressure was higher at 2.5-5 h after morning dosing in patients treated with Adderall XR® and lisdexamfetamine compared to placebo. Both agents were significantly better than placebo in controlling ADHD symptoms and behaviors according to the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) Deportment Rating Scale (0.8 for combined doses of both agents *vs.* 1.7 for placebo). In addition, both lisdexamfetamine and Adderall XR® significantly improved secondary efficacy outcome measures as compared to placebo according to scores for SKAMP attention (1.2 for combined doses of both agents *vs.* 1.8 for placebo), as well as Permanent Product Measure of Performance (PERMP)-attempted (133.3 and 133.6, respectively, *vs.* 88.2 for placebo) and PERMP-corrected scores (129.6 and 129.4, respectively, *vs.* 84.1 for placebo). There was no significant difference between lisdexamfetamine and Adderall XR® (22).

A 4-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study in 290 children (6-12 years of age) demonstrated the safety and efficacy of lisdexamfetamine (30, 50 and 70 mg/day). The study included a 1-week screening period, a 1-week washout period followed by a 4-week double-blind phase. A total of 230 patients completed the study. All doses of the agent were well tolerated. No serious adverse events or deaths were reported and over 95% of the adverse events were mild or moderate in severity. Treatment-related adverse events were consistent with those associated with amphetamine and the incidence of adverse events decreased over time. Significant reductions in ADHD-Rating Scale (AHDH-RS) total scores from baseline were observed with all lisdexamfetamine doses compared to placebo (50%, 54% and 59% reductions, respectively, *vs.* 15% on placebo). *Post hoc* responder analysis indicated responder rates of 66%, 72% and 80% for the respective lisdexamfetamine doses compared to 17% for placebo (23).

Two phase III studies are under way examining the efficacy and safety of a daily morning dose of lisdexamfetamine in adults diagnosed with moderate to severe ADHD (24, 25). The U.S. FDA approved lisdexamfetamine mesilate (Vyvanse™) in February 2007 for the treatment of ADHD in pediatric patients (26).

## Drug Interactions

A study using pooled human liver microsomes preincubated with or without NADPH showed that lisdexamfetamine (0.01-100 μM) was unable to inhibit human cytochrome P-450 isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. These results indicate that the agent has a low potential for drug interactions (27).

## Sources

New River Pharmaceuticals, Inc. (US); developed in collaboration with Shire plc (UK, US) (according to a recent agreement, Shire will acquire New River Pharmaceuticals).

## References

1. Mickle, T., Krishnan, S., Moncrief, J.S., Lauderback, C. (New River Pharmaceuticals, Inc.). *Pharmaceutical compositions for prevention of overdose or abuse*. EP 1675555, WO 2005032474.

2. Mickle, T., Krishnan, S., Bishop, B., Lauderback, C., Moncrief, J.S., Oberlender, R. (New River Pharmaceuticals, Inc.). *Abuse resistant amphetamine compounds*. EP 1644019, JP 2007500242, US 2005054561, US 7105486, WO 2005000334.

3. Prous Science Disease Briefings: Attention Deficit/Hyperactivity Disorder (online publication). Updated 2007.

4. Biederman, J., Faraone, S.V. *Attention-deficit hyperactivity disorder*. Lancet 2005, 366: 237-48.

5. Woodruff, T.J., Axelrad, D.A., Kyle, A.D., Nweke, O., Miller, G.G., Hurley, B.J. *Trends in environmentally related childhood illnesses*. Pediatrics 2004, 113(4): 1133-40.

6. Centers for Disease Control and Prevention (CDC). *Mental health in the United States. Prevalence of diagnosis and medication treatment for attention-deficit/hyperactivity disorder-United States, 2003*. MMWR Morb Mortal Wkly Rep 2005, 54(34): 842-7.

7. Faraone, S.V., Biederman, J., Spencer, T., Wilens, T., Seidman, L.J., Mick, E., Doyle, A.E. *Attention-deficit/hyperactivity disorder in adults: An overview*. Biol Psychiatry 2000, 48(1): 9-20.

8. Voeller, K.K. *Attention-deficit hyperactivity disorder (ADHD)*. J Child Neurol 2004, 19(19): 798-814.

9. Willcutt, E.G., Doyle, A.E., Nigg, J.T., Faraone, S.V., Pennington, B.E. *Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review*. Biol Psychiatry 2005, 57(11): 1336-46.

10. Farone, S.V., Perlis, R.H., Doyle, A.E., Smoller, J.W., Goralnick, J.J., Holmgren, M.A., Sklar, P. *Molecular genetics of attention-deficit/hyperactivity disorder*. Biol Psychiatry 2005, 57(11): 1313-23.

11. McGough, J.J. *Attention-deficit/hyperactivity disorder pharmacogenomics*. Biol Psychiatry 2005, 57(11): 1367-73.

12. Willcutt, E.G., Pennington, B.F., DeFries, J.C. *Twin study of the etiology of comorbidity between reading disability and attention-deficit/hyperactivity disorder*. Am J Med Genet 2000, 96(3): 293-301.

13. Hudziak, J.J., Heath, A.C., Madden, P.F. et al. *Latent class and factor analysis of DSM-IV ADHD: A twin study of female adolescents*. J Am Acad Child Adolesc Psychiatry 1998, 37(8): 848-57.

14. Thapar, A., O'Donovan, M., Owen, M.J. *The genetics of attention deficit hyperactivity disorder*. Hum Mol Genet 2005, 14(Suppl. 2): R275-82.

15. Durston, S., Tottenham, N.T., Thomas, K.M. et al. *Differential patterns of striatal activation in young children with and without ADHD*. Biol Psychiatry 2003, 53(10): 871-8.

16. Durston, S., Hulshoff, P.H.E., Schnack, H.G. et al. *Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings*. J Am Acad Child Adolesc Psychiatry 2004, 43(3): 332-40.

17. Mickle, T.C., Bera, S., Guenther, S. et al. *Prodrugs of d-amphetamine with improved safety properties*. 230th ACS Natl Meet (Aug 28-Sept 1, Washington, D.C.) 2005, Abst MEDI-246.

18. Boyle, L., Moncrief, S., Krishnan, S. *Pharmacokinetics of NRP104/SPD489 (lisdexamfetamine dimesylate) following administration of single intranasal dose in rats*. 46th Annu New Clin Drug Eval Unit (NCDEU) Meet (June 12-15, Boca Raton) 2006, Abst II-3.

19. Ermer, J.C., Krishnan, S. *A multiple-dose pharmacokinetic study of NRP104/SPD489 (lisdexamfetamine dimesylate) following 7-day administration*. 46th Annu New Clin Drug Eval Unit (NCDEU) Meet (June 12-15, Boca Raton) 2006, Abst II-2.

20. Krishnan, S., Jasinski, D. *Pharmacokinetics of oral NRP104/SPD489 (lisdexamfetamine dimesylate) versus D-amphetamine in healthy adults with a history of stimulant abust*. 68th Annu Sci Meet Coll Problem Drug Depend (June 17-22, Scottsdale) 2006, Abst 423.

21. Jasinski, D.R., Krishnan, S. *Abuse liability of intravenous L-lysine-D-amphetamine (NRP104)*. 68th Annu Sci Meet Coll Problem Drug Depend (June 17-22, Scottsdale) 2006, Abst 365.

22. Biederman, J., Boellner, S.W., Childress, A., Lopez, F.A., Krishnan, S., Hodgkins, P. *Improvements in symptoms of attention-deficit/hyperactivity disorder in school-aged children with lisdexamfetamine (NRP104) and mixed amphetamine salts, extended-release versus placebo*. 159th Annu Meet Am Psychiatr Assoc (May 20-25, Toronto) 2006, Abst.

23. Biederman, J., Krishnan, S., Hodgkin, P., Findling, R.L. *Efficacy and safety of lisdexamfetamine (NRP104) in children aged 6 to 12 years with attention-deficit/hyperactivity disorder (ADHD)*. 159th Annu Meet Am Psychiatr Assoc (May 20-25, Toronto) 2006, Abst.

24. *An open-label study of NRP104 in adults with attention deficit hyperactivity disorder (ADHD) (NCT00337285)*. ClinicalTrials.gov Web site, March 13, 2007.

25. *Study to assess the safety and efficacy of NRP104 in adults with attention-deficit hyperactivity disorder (ADHD) (NCT00334880)*. ClinicalTrials.gov Web site, March 13, 2007.

26. *Vyvanse approved for ADHD*. DailyDrugNews.com, February 26, 2007.

27. Krishnan, S., Moncrief, S. *An evaluation of the cytochrome P450 inhibition potential of lisdexamfetamine in human liver microsomes*. Drug Metab Dis 2007, 35(1): 180-4.