IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

LCS Group, LLC, Plaintiff, v. **Shire LLC**, **Shire Development LLC**, and **Shire PLC**, Defendants.	Civil Case No. _____ **COMPLAINT** **JURY TRIAL DEMANDED**

For its Complaint, Plaintiff LCS Group, LLC ("LCS") states as follows.

Jurisdiction and Venue

1. This Court has subject matter jurisdiction over the claims herein, including under 28 U.S.C. § 1332(a)(1).

2. This Court has personal jurisdiction over Defendants because each resides and/or regularly conducts business in New York and has incurred the liability complained of herein in New York, and at least for the first Defendant because it has consented to this Court's jurisdiction concerning this dispute.

3. Venue is proper under 28 U.S.C. §§ 1391(b).

Parties

4. LCS is a Connecticut company with a principal place of business in Connecticut. LCS is owned and managed by Dr. Louis C. Sanfilippo ("Dr. Sanfilippo").

5. On information and belief, Defendant Shire LLC is a Kentucky company with a principal place of business in Kentucky, Defendant Shire Development LLC is a Delaware

company with a principal place of business in Massachusetts and/or Pennsylvania, and each is a subsidiary of Defendant Shire Plc of Ireland (collectively, "Shire").

Factual Background

6. Dr. Sanfilippo is the inventor of U.S. Patent 8,318,813 ("the '813 patent"), granted and issued in November 2012 and attached herewith as Exhibit 1. The '813 patent relates to methods for the treatment of Binge Eating Disorder ("BED"), as defined in the DSM-IV-TR, with the drug lisdexamfetamine dimesylate (*e.g.*, Vyvanse®).

7. Dr. Sanfilippo assigned the '813 patent to LCS, which subsequently assigned it in 2015 to Lucerne Biosciences, LLC, with LCS remaining the exclusive licensee. Dr. Sanfilippo has been the sole Manager and Member of LCS since the company was formed in Connecticut in March 2008. LCS again owns the '813 patent.

Pre-Contractual Communications between Shire and Dr. Sanfilippo

8. For several years before November 2012 and as early as 2008, Dr. Sanfilippo and Shire were in communication regarding the inventions of the '813 patent, giving Shire several years to conduct due diligence confirming the integrity and validity of the '813 patent before it ultimately issued in 2012.

9. For example, in 2010 Dr. Sanfilippo's counsel specifically informed Shire's Tatjana May and James Harrington of the published international patent application disclosing the inventions of the '813 patent.

10. In November 2012, Dr. Sanfilippo's communications included telephone calls with Shire's Peter Cicala, which included a disclosure to Shire that Dr. Sanfilippo's wife was then ill with cancer.

11. Also in November 2012, Ed Haug of the Haug Firm, patent counsel to Shire, informed Dr. Sanfilippo by email that his law firm was "meeting with Shire in the next few weeks after we are able to analyze your IP [but] it will take some time for us and Shire to complete its review."

12. Dr. Sanfilippo's family situation was discussed with Shire again in future communications, as was Shire's continuing due diligence related to evaluating the '813 patent. For example, in May 2013, Dr. Sanfilippo and his attorney Joe Lucci had an in-person meeting in New York with Shire's Peter Cicala and Susannah Henderson, and Shire's counsel Ed Haug and Sandra Kuzmich of the Haug Firm. Following the meeting, on May 21, 2013, Shire's Peter Cicala wrote to attorney Joe Lucci stating, "I just wanted to let you know we haven't forgotten about Dr. Sanfilippo. We are still working on our patent evaluation. I will be in touch as soon as I have some news for you."

The October 24, 2013 Confidential Disclosure Agreement Between LCS and Shire

13. Attached herewith as Exhibit 2 is a "Confidential Disclosure Agreement" effective October 24, 2013 between LCS and Shire ("CDA"). The CDA was prepared by Shire and signed on October 29, 2013 by Shire's Manager and Chief IP Counsel, James J. Harrington.

14. Shire's Peter Cicala pressed LCS for the CDA, which was entered just before Shire publicly announced positive Phase III trial results for Vyvanse in BED as defined by DSM-IV-TR criteria, as specifically covered by the '813 patent.

15. By its express terms, the purpose of the CDA was to "facilitate the Parties' discussions regarding a potential business opportunity involving U.S. Patent No. 8,318,813."

16. Paragraph 7 of the CDA provides, in part, that "[i]n addition to the confidentiality obligations set forth in this Agreement, each Party hereby agrees . . . not to discuss publically

[sic] or with any third party that . . . U.S. Patent No. 8,318,813 includes claims that could relate to the use of lisdexamfetamine dimesylate or Vyvanse®."

17. The purpose and benefit of the foregoing provision was (a) for Shire, that LCS would negotiate exclusively with Shire and not simultaneously with one or more of its competitors, and (b) for LCS, that Shire would not challenge the validity of the '813 patent, in particular, via a Petition for Inter-Partes Review ("IPR") before the United States Patent Office ("PTO"), which inherently is a public proceeding and also typically involves obtaining third-party expert witness testimony related to the patent's claims.

18. Shire never terminated the CDA or the confidentiality and non-publicity obligations under Paragraph 7, nor gave any indication that the parties were no longer bound by the terms of the CDA in general or its confidentiality and non-publicity obligations under Paragraph 7, in particular.

19. In fact, in about March 2014, Shire agreed to a request by LCS for an addendum to the CDA providing, in part, that "Shire hereby agrees that LCS may disclose Highly Proprietary and Confidential Information that LCS receives from Shire to Tina Passalaris, who has been advised of the confidential nature of such Highly Proprietary and Confidential Information, and who has read and agrees to comply with the CDA."

20. Tina Passalaris was Dr. Sanfilippo's wife, and the foregoing request evidences the seriousness with which LCS, for one, honored and followed the confidentiality and non-publicity obligations under the CDA.

Shire's Bad Faith IPR Petition

21. Despite knowing full well that the '813 patent was valid based on its years of communications with LCS and Dr. Sanfilippo, and its ongoing due diligence under the CDA,

Shire filed an IPR Petition (prepared and signed by the Haug Firm and authorized by Shire's counsel David Banchik) seeking to invalidate the '813 patent on May 9, 2014, just a few months after binding LCS and itself to the terms of the CDA.

22. Shire relied exclusively on a false and fraudulent declaration prepared by Shire and the Haug Firm, and signed by Dr. Timothy Brewerton. The petition (including the declaration) is attached herewith as Exhibit 3.

23. Brewerton's declaration was knowingly false and fraudulent because, in summary, it was and is clearly at odds with the relevant medical literature on eating disorders, obesity and stimulant drugs, including being at odds with Brewerton's own published work related to the diagnosis and treatment of eating disorders. The relevant literature as well as Shire's own public statements to investors and the general public regarding Vyvanse® to treat Binge Eating Disorder, as compared to the declaration, evidences Shire's extensive use of misleading statements and egregious misrepresentations of the relevant state of the prior art, and its omission of other material, dispositive information, all in service of the aim of depriving LCS of its valuable patent rights.

24. In addition to knowing that the IPR Petition was frivolous, on information and belief, Shire and its involved executives and counsel knew, at least as early as the signing of the CDA, that LCS did not have the financial resources to litigate the IPR on its merits, particularly to completion. Litigating an IPR generally requires a budget of at least $500,000.00, particularly in the pharmaceutical arts and particularly as against a corporate behemoth like Shire.

25. Although LCS appeared in the IPR and attempted to mount an opposition on the merits, LCS could not marshal enough financial resources to maintain its opposition, resulting in the PTO entering an adverse judgment—only on procedural grounds—in June 2015. As a result,

Shire and its co-conspirators, including the Haug Firm, were successful in their fraudulent scheme to invalidate the '813 patent via procedural fiat and in violation of the CDA, and deprive LCS of its extremely valuable patent rights.

26. On information and belief, Shire and its involved executives and counsel also knew, at least as early as the signing of the CDA, that LCS was hamstrung by Dr. Sanfilippo's serious family matters, including the fact that his wife was at that time undergoing treatment for cancer, which took her life in January 2015.

27. As evidenced by Shire's bad faith IPR Petition, Shire made the promises under Paragraph 7 of the CDA fraudulently and with malice, intending not to keep its promises but instead, with the intention of muzzling LCS while at the same time (a) delaying the parties' discussions under the CDA, (b) communicating with a third-party expert witness regarding the patent's claims with the intent of utilizing and publicizing such third-party testimony, and (c) preparing to file—publicly—an IPR in an attempt to have the '813 patent declared invalid as a result of LCS not having the resources to defend the IPR proceeding on its merits, as opposed to the merits themselves, which Shire knew did not support a good faith argument that the '813 patent was invalid.

28. The valuable patent rights LCS lost as a result of the wrongful conduct of Shire and its involved executives and counsel include, but are not limited to, the exclusive right to use, sell and/or license products covered by the '813 patent for the remainder of the term of the patent, through 2030, which rights have a value into the billions based on Shire's own sales.

29. Indeed, on January 30, 2015, the U.S. Food & Drug Administration approved Vyvanse® in the treatment of Binge Eating Disorder in adults with moderate to severe symptoms. Shire immediately began marketing the drug for this indication in the United States.

30. Since its introduction several years ago, Shire's Vyvanse® has generated significant sales revenue for Shire (about $2 billion per year in recent years), mainly in the United States and for the treatment of Attention Deficit Hyperactivity Disorder.

31. In addition, Shire's wrongful conduct usurped LCS's ability to teach and produce literature about treating Binge Eating Disorder based on the very language of the '813 patent, which language is now included in Shire's prescribing and marketing literature related to Vyvanse®, including in the drug's package insert.

32. Needless to say, Defendants' duplicity, fraud and bad faith breach of the CDA caused LCS extreme financial distress and harm, and caused its lone Manager and Member, Dr. Sanfilippo, extensive personal, financial and emotional distress, particularly at a very difficult time while dealing with his wife's cancer diagnosis and treatment, deterioration, and ultimate passing, much too young.

33. Paragraph 10(a) of the CDA provides, in part, that "[t]he Parties irrevocably agree that the United States District Court for the Southern District of New York shall have exclusive jurisdiction to deal with any disputes arising out of or in connection with this Agreement and that, accordingly, any proceedings arising out of or in connection with this Agreement shall be brought in the United States District Court for the Southern District of New York," and further, that each party "expressly consents and submits to the personal jurisdiction of the federal and state courts in the state and county of New York."

First Claim—Breach of Contract

34. LCS hereby repeats and re-alleges the foregoing allegations as if fully set forth herein.

35. In Paragraph 7 of the CDA, Shire "agree[d] . . . not to discuss publically [sic] or with any third party that . . . U.S. Patent No. 8,318,813 includes claims that could relate to the use of lisdexamfetamine dimesylate or Vyvanse®."

36. LCS honored Paragraph 7 of the CDA by discussing the '813 patent exclusively with Shire, and not with any third parties. LCS even went so far as to pursue an addendum to the CDA before having any discussions with Dr. Sanfilippo's wife, but by the time it was agreed to (after much delay) by Shire, her health had deteriorated and the addendum was never executed.

37. Shire never communicated any termination of the CDA or any termination of the confidentiality and non-publicity obligations under Paragraph 7 of the CDA.

38. In breach of the CDA, in May 2014 Shire filed—publicly—an IPR with the PTO in an attempt to have the '813 patent declared invalid. In the IPR petition itself, Shire publicly disclosed that the '813 patent "includes claims that could relate to the use of lisdexamfetamine dimesylate or Vyvanse®." *See, e.g.*, Exhibit 3 at 13 and *passim*.

39. Shire also breached the CDA in retaining Dr. Brewerton as an expert witness for its IPR petition, clearly with the intent of making public his testimony regarding the patent's claims which specifically relate to the use of lisdexamfetamine dimesylate or Vyvanse®.

40. Shire's breach of the CDA caused LCS to suffer actual damages including lost profits, in an amount to be determined at trial, plus consequential damages including attorney fees and expenses, and it also resulted and continues to result in unjust enrichment to Shire. LCS' damages are at least into the hundreds of millions over the period from issuance until expiry of the '813 patent beyond 2030.

41. LCS also has suffered and continues to suffer irreparable injury which cannot be remedied adequately unless Shire is enjoined immediately from further breaches.

42. As a result of Shire's wrongful conduct, LCS is entitled to damages in an amount to be determined at trial.

Second Claim—Breach of Contract Based on Implied Duty of Good Faith and Fair Dealing

43. LCS hereby repeats and re-alleges the foregoing allegations as if fully set forth herein.

44. In Paragraph 7 of the CDA, Shire "agree[d] . . . not to discuss publically [sic] or with any third party that . . . U.S. Patent No. 8,318,813 includes claims that could relate to the use of lisdexamfetamine dimesylate or Vyvanse®."

45. Under the CDA, Shire had an implied obligation to refrain from acting in bad faith, arbitrarily, or irrationally.

46. LCS reasonably believed at all times (as would any reasonable business in its position) that one purpose of the CDA was to prohibit Shire from making public, whether through an IPR Petition or in any manner that would jeopardize LCS's patent rights, any information about the '813 patent, particularly that it "includes claims that could relate to the use of lisdexamfetamine dimesylate or Vyvanse®."

47. LCS also reasonably believed at all times (as would any reasonable business in its position) that Shire would not use any information provided to it during its due diligence and/or pursuant to the CDA to harm LCS, including seeking to invalidate its patent.

48. Shire at all times had knowledge that one purpose of the CDA was to prohibit Shire from making public, whether through an IPR Petition or in any manner that would jeopardize LCS's patent rights, any information about the '813 patent.

49. Shire's public disclosures about the '813 patent, based on knowingly fraudulent assertions no less, could not have been made in good faith.

50. Shire's public disclosures about the '813 patent and efforts to destroy LCS's valuable patent rights were done in bad faith, and had the effect of depriving LCS of the fruits of its bargain under the CDA while Shire ignored its obligation of confidentiality and sought to destroy LCS's valuable patent rights.

51. Indeed, the CDA bound LCS to confidentiality, and by abiding by the CDA's terms in good faith, LCS was unable to pursue other lucrative opportunities for its patent rights.

52. By contrast, Shire acted pursuant to a wrongful scheme to destroy LCS's patent rights and in doing so has defeated the purpose and benefits of the CDA for LCS.

53. Shire's conduct was wholly inconsistent with the justified expectations of LCS, and was willful, intentional, and in deliberate disregard of the interests of LCS.

54. As a result of Shire's wrongful conduct, LCS is entitled to damages in an amount to be determined at trial.

Third Claim—Interference With Prospective Economic Advantage

55. LCS hereby repeats and re-alleges the foregoing allegations as if fully set forth herein.

56. Each Defendant was aware of the prospective economic advantage to LCS, including but not limited to the market for LCS' many prospective assignees and/or licensees for the '813 patent, many of which are Shire's competitors.

57. Upon information and belief, through their acts including (a) intentionally drawing out and "stalling" the discussions with Dr. Sanfilippo and LCS, (b) using the CDA to muzzle LCS, (c) delaying the parties' discussions under the CDA, (d) secretly preparing to challenge the validity of the '813 patent and retaining an expert witness regarding the patent's claims relating to the use of use of lisdexamfetamine dimesylate or Vyvanse® for such purpose,

and (e) filing an IPR against the '813 patent, each Defendant interfered with LCS' prospective business with other potential assignees and/or licensees of the '813 patent, many of which are Shire's competitors.

58. Each Defendant intended to wrongfully interfere with LCS' prospective economic advantage, and the intentional interference has caused LCS to suffer actual damages including lost profits, in an amount to be determined at trial, plus consequential damages. Each Defendant's intentional interference with prospective economic advantage also has resulted and continues to result in its own unjust enrichment. LCS' damages are at least into the hundreds of millions over the period from issuance until expiry of the '813 patent beyond 2030.

59. Each Defendant committed its acts of intentional interference with prospective economic advantage willfully and maliciously to injure LCS' business and improve its own, thereby entitling LCS to an award of exemplary damages and attorney fees in an amount to be determined at trial.

Fourth Claim—Fraud

60. LCS hereby repeats and re-alleges the foregoing allegations as if fully set forth herein.

61. Each Defendant made false representations with the intent to deceive LCS and Dr. Sanfilippo, including but not limited to the following: (a) that Shire intended to comply, and not breach, the CDA which by its express terms intended to (i) protect confidentiality, (ii) "facilitate the Parties' discussions regarding a potential business opportunity," and (iii) not publicize that the '813 patent "includes claims that could relate to the use of lisdexamfetamine dimesylate or Vyvanse®;" and (b) that the relevant "prior art" medical literature on eating disorders, obesity

and stimulant drugs supported the contention that the claimed inventions of the '813 patent were obvious to a person of ordinary skill in the art before September 2006.

62. On information and belief, each Defendant made the foregoing promises and misrepresentations fraudulently and with malice, intending to deceive LCS and induce justifiable reliance, including with the intention of muzzling LCS and Dr. Sanfilippo while at the same time delaying the parties' discussions under the CDA so that Shire could prepare and file—publicly—an IPR in an attempt to have the '813 patent declared invalid as a result of LCS not having the resources to defend the IPR on its merits.

63. In addition, Defendants filed the IPR Petition on May 9, 2014, relying exclusively on a false and fraudulent declaration prepared by Defendants and signed by Brewerton.

64. Each Defendant knew and was aware of the falsity of its misrepresentations.

65. LCS had a belief in the truth of Defendants' representations, in part, because each Defendant represented itself as having integrity and honesty.

66. Each Defendant intended that its fraudulent misrepresentations would cause and induce LCS to honor its own non-publicity and confidentiality obligations and pursue a business opportunity with Shire exclusively and in good faith, so as to provide Defendants with the time necessary to prepare and file the IPR and enjoy further ill-gotten gains.

67. LCS justifiably and detrimentally relied on Defendants' misrepresentations because it honored its own confidentiality obligations and pursued a business opportunity with Shire exclusively and in good faith, over a long period of time when it could have been pursuing other business opportunities with third parties, including one or more of Shire's competitors.

68. Defendants' fraudulent misrepresentations have caused LCS to suffer actual damages including lost profits, in an amount to be determined at trial, plus consequential

damages. Defendants' fraud also has resulted and continues to result in their own unjust enrichment. LCS' damages are at least into the hundreds of millions over the period from issuance until expiry of the '813 patent beyond 2030.

69. Each Defendant committed its acts of fraud willfully and maliciously to injure LCS' business and improve its own, thereby entitling LCS to an award of exemplary damages and attorney fees in an amount to be determined at trial.

Prayer For Relief

Plaintiff LCS prays for judgment as follows:

A. Declaring that Shire breached the CDA;

B. Declaring that Shire breached the CDA by violating the covenant of good faith and fair dealing;

C. Declaring that each Defendant intentionally interfered with LCS' prospective economic advantage;

D. Declaring that each Defendant committed fraud against LCS;

E. An accounting for damages, including Plaintiffs' lost profits, lost royalty damages, consequential damages, enhanced damages, treble damages, pre-judgment and post-judgment interest, litigation expenses, costs and attorney fees;

F. Requiring an accounting for damages adequate to compensate for the breach of contract, intentional interference with prospective economic advantage, and fraud, including LCS' lost profits and amounts attributable to each Defendant's unjust enrichment, consequential damages, treble damages, exemplary damages, attorney fees, pre-judgment and post-judgment interest, and costs; and

G. Such other and further relief as this Court deems just and proper.

DEMAND FOR JURY TRIAL

Pursuant to Fed. R. Civ. P. 38(b), Plaintiff demands hereby a jury trial on any issues triable of right by a jury.

Dated: March 26, 2018

Respectfully submitted,

/s/ Stephen M. Lobbin

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US008318813B2

(12) **United States Patent**
Sanfilippo

(10) **Patent No.: US 8,318,813 B2**
(45) **Date of Patent: Nov. 27, 2012**

(54) **METHOD OF TREATING BINGE EATING DISORDER**

(75) Inventor: **Louis Sanfilippo**, New Haven, CT (US)

(73) Assignee: **LCS Group, LLC**, New Haven, CT (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **12/666,460**

(22) PCT Filed: **Jan. 24, 2008**

(86) PCT No.: **PCT/US2008/001002**

§ 371 (c)(1),
(2), (4) Date: **Oct. 6, 2010**

(87) PCT Pub. No.: **WO2009/035473**

PCT Pub. Date: **Mar. 19, 2009**

(65) **Prior Publication Data**

US 2011/0021564 A1 Jan. 27, 2011

Related U.S. Application Data

(60) Provisional application No. 60/972,046, filed on Sep. 13, 2007.

(51) **Int. Cl.**

A61K 31/137	(2006.01)
A61K 45/06	(2006.01)
A61P 25/26	(2006.01)
A61P 25/30	(2006.01)
A61K 31/4458	(2006.01)
A61K 31/16	(2006.01)
A61K 31/35	(2006.01)
A61K 31/423	(2006.01)
A61P 3/04	(2006.01)

(52) **U.S. Cl.** **514/654**; 514/626; 514/630

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

The invention provides methods of treating binge eating disorders, obesity resulting from binge eating behavior, and depression. The invention includes methods of treating certain co-morbidities in ADHD and ADD patients; for example the invention includes methods of treating generalized anxiety disorder, obsessional and ruminative thought disorders, and obsessive/compulsive behavior in ADHD and ADD patients. The invention also includes combination methods of treatment in which an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog is administered with one or more other active agents. Packaged pharmaceutical compositions containing an amphetamine or methylphenidate prodrug, instructions for using the prodrug to treat certain disorders, and optionally one or more other active agents are provided by the invention.

13 Claims, No Drawings

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METHOD OF TREATING BINGE EATING DISORDER

This application claims the benefit of U.S. Provisional Patent Application Ser. No. 60/972,046 filed Sep. 13, 2007, and to PCT/US08/001002, filed Jan. 24, 2008, which are incorporated by reference herein in their entirety.

FIELD OF INVENTION

The inventor has discovered that amphetamine prodrugs and methylphenidate prodrugs are useful for treating a number of central nervous system disorders. Methods of treating binge eating disorders, obesity resulting from binge eating behavior, and depression are included herein. The invention includes methods of treating certain co-morbidities in ADHD (Attention-Deficit Hyperactivity Disorder) and ADD patients; for example the invention includes methods of treating generalized anxiety disorder, obsessional and ruminative thought disorders, and obsessive/compulsive behavior in ADHD and ADD patients. Methods of treatment include methods in which the amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog is the only active agent. The invention also includes combination methods of treatment in which an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog is administered with one or more other active agents. Methods of use described herein include informing a user that an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog may be used to treat any of the disorders listed above. The invention includes pharmaceutical compositions comprising an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog together with one or more other active agents in a single dosage form. Packaged pharmaceutical compositions containing an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog with instructions for using the composition to treat one of the disorders listed above are also provided.

BACKGROUND

Binge Eating Disorder and Obesity Resulting from Binge Eating Disorder

Binge Eating Disorder is a form of Eating Disorder Not Otherwise Specified according the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). As defined by the DSM-IV-TR, it is characterized by recurrent binge eating episodes.

Commonly described symptoms of binge eating disorder include frequent dieting and weight loss, hoarding of food, hiding empty food containers, eating late at night, attribution of one's successes and failures to weight, avoiding social situations where food may be present, and feeling depressed or anxious. Binge eating also may cause rapid and unhealthy weight gain (or loss), weight fluctuations, and chronic erratic eating behavior. Binge eating disorder and symptoms associated with binge eating disorder may result in obesity though obesity is not necessarily a result of binge eating disorder. Further, patients with binge eating disorder are often not obese and may even have a below normal weight.

The biological basis of binge eating disorder is poorly understood. Binge eating disorder is difficult to treat and carries significant medical and psychiatric risks. Pharmacologic interventions have been of limited success and sometimes cause a worsening of binge eating symptoms. A number of psychotropic medications, including but not limited to antidepressants, antipsychotics, antimanic agents, and mood modulating medications are known to cause binge eating, dysregulation of appetite, and weight gain. Binge eating behaviors and weight gain may be a direct effect of such medication(s). Psychotropic medications may also exacerbate an underlying binge eating disorder in some patients.

Medical complications associated with binge eating disorder include high blood pressure, high cholesterol and triglycerides, kidney disease (and failure), gallbladder disease, arthritis, bone deterioration, stroke, upper respiratory infections, skin disorders, menstrual irregularities, ovarian abnormalities, and pregnancy complications. Psychiatric problems associated with, or exacerbated by, binge eating disorder include depressive disorders, mood disorders, anxiety disorders, ADHD and ADD, personality disorders, other eating disorders, suicidal thoughts, and substance abuse disorders.

Individuals with binge eating disorder may respond to treatment with antidepressants, though such medications may contribute to a worsening of binge eating symptoms, along with weight gain, either at the outset of treatment or over time.

Depression

Depression is often difficult to treat, as some patients fail to respond to an initial pharmacologic intervention and a decision must be made to switch agents, augment with another medication(s), or combine multiple pharmacologic agents. Combining medications, while often helpful, can sometimes be problematic with added side effect burdens. Side effects of certain psychotropic medication sometimes used to offer adjunct treatment to patients already taking antidepressants may include weight gain and obesity.

Individuals treated for major depressive disorders may show a positive response or full remission of symptoms to medication treatment, though recent clinical evidence suggests remission rates following an adequate course of monotherapy treatment may as low as 30-40%. Further, clinical studies suggest an unusually large percentage of depressed individuals treated with antidepressant medication, greater than 30-40% in various clinical studies, show only a partial response (for example, full remission is not achieved but there is some measure of improvement in depressive symptoms). Some patients may be 'refractory' or 'resistant' to treatment and fail to respond to one, or in some cases, multiple monotherapy and combination antidepressant medication treatments.

Major depressive disorders similarly may lead to deteriorating physical health and may increase the risk of morbidity and mortality in patients with concurrent medical conditions.

Similarly, depressive disorders are often associated with, or may exacerbate, other mood disorders, anxiety disorders, attention deficit hyperactivity disorder (ADHD or ADD), psychotic disorders, personality disorders, eating disorders, cognition and cognitive disorders, substance abuse disorders, and suicidal ideation.

There exists an unmet and important clinical need for treatments for binge eating disorders, obesity resulting from binge eating behavior, and depression that is only partially responsive to medication and intractable (e.g. 'treatment-resistant') depression. The present invention fulfills this need and provides additional advantages described herein.

SUMMARY OF THE INVENTION

The inventor has discovered that amphetamine prodrugs, including lisdexamfetamine dimesylate, methylphenidate prodrugs, and certain methylphenidate analogs, are useful for treating binge eating disorders, obesity resulting from binge eating behavior, and depression. Furthermore amphetamine prodrugs, methylphenidate prodrugs, and certain meth-

ylphenidate analogs have been found useful for treating certain co-morbidities in ADHD and ADD patients. The invention includes methods of treating generalized anxiety disorder, obsessional and ruminative thought disorders, and obsessive/compulsive behavior in patients, particularly in ADHD/ADD patients. Methods of using amphetamine prodrugs, methylphenidate prodrugs, or methylphenidate analogs, as a monotherapy for treating these conditions and disorders or in combination with one or more other active agents are provided herein.

The invention includes a method of treating binge eating disorder or obesity resulting from binge eating behavior, comprising diagnosing a patient as having a binge eating disorder or obesity resulting from binge eating behavior and providing an effective amount of amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog to the patient.

The invention also includes a method of treating depression comprising diagnosing a patient as having depression and providing an effective amount of amphetamine prodrug, methylphenidate prodrug, methylphenidate analog to the patient.

The invention further provides a method of treating generalized anxiety disorder, obsessional and ruminative thought disorders, or obsessive/compulsive behavior in a patient having ADHD or ADD or other patient. In an ADHD or ADD patient this method comprises diagnosing a patient having ADHD or ADD and as also having at least one of generalized anxiety disorder, obsessional and ruminative thought disorders, or obsessive/compulsive behavior, and providing an effective amount of amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog to the patient.

In each of these methods the amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog may be provided as the only active agent, i.e. as a monotherapy, or may be provided together with one or more other active agents, i.e. as a combination, adjunct, or augmentation therapy.

In a separate embodiment, the invention includes a method of using an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog comprising informing a user that the amphetamine prodrug, methylphenidate prodrug, methylphenidate analog may be used to treat binge eating disorder or obesity resulting from binge eating behavior. The invention also includes a method of using an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog comprising informing a user that the amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog may be used to treat depression. The invention further includes a method of using an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog comprising informing a user that the amphetamine prodrug, methylphenidate prodrug, methylphenidate analog may be used to treat certain co-morbidities in ADHD and ADD patients, or may be used to treat certain CNS disorders in patients not diagnosed with ADHD or ADD, including generalized anxiety disorder, obsessional and ruminative thought disorders, and obsessive/compulsive behavior. The invention includes (i) lisdexamfetamine dimesylate and (ii) one or more other active agent(s) combined in a single dosage form.

The invention includes articles of manufacture comprising an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog in a container and printed labeling. The printed labeling states that the amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog is useful for treating a binge eating disorder, obesity resulting from binge eating behavior, or depression. In other embodiments the printed labeling states that the amphetamine prodrug, methylphenidate prodrug, methylphenidate analog is useful for treating generalized anxiety disorder, obsessional and ruminative thought disorders, and obsessive/compulsive behavior in a patient, particularly in a patient having ADHD or ADD.

DETAILED DESCRIPTION

Terminology

Prior to setting forth the invention in detail, it may be helpful to provide definitions of certain terms to be used herein. Compounds of the present invention are described using standard nomenclature. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item.

An "active agent" means any compound, element, or mixture that when administered to a patient alone or in combination with another agent confers, directly or indirectly, a physiological effect on the patient. When the active agent is a compound, salts, solvates (including hydrates) of the free compound or salt, crystalline and non-crystalline forms, as well as various polymorphs of the compound are included. Compounds may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g. asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these compounds can additionally be mixtures of diastereomers. For compounds having asymmetric centers, it should be understood that all of the optical isomers in pure form and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms, with all isomeric forms of the compounds being included in the present invention. In these situations, the single enantiomers, i.e., optically active forms can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column. A "dosage form" means any unit of administration of an active agent.

"Binge eating disorder" is a form of Eating Disorder Not Otherwise Specified. As defined by the DSM-IV-TR, it is characterized by recurrent binge eating episodes. Such episodes include eating larger amounts of food than normal during a short period of time (for instance, within a two hour period) and a lack of control over eating during the binge episode (for instance, one cannot stop eating). According to the DSM-IV-TR, binge eating disorders are associated with three or more of the following symptoms: eating until uncomfortably full; eating large amounts of food when not physically hungry; eating much more rapidly than normal; eating alone on account of embarrassment over how much one is eating; and feeling disgusted, depressed or guilty after overeating. Additionally, individuals with binge eating disorder feel distress about their binging behavior. The DSM-IV-TR also characterizes binge eating to occur, on average, at least 2 days a week for six months, while not being associated with the regular use of inappropriate compensatory behaviors such as purging or excessive exercise and not occurring exclusively during the course of bulimia nervosa or anorexia nervosa. As used herein "depression" includes major depressive disorder, dysthymic disorder, depressive disorder not other-

wise specified (for instance, premenstrual dysphoric disorder), and depressive episodes that may be present in another disorder (e.g. as in other mood disorders such as bipolar disorder or a mood disorder due to a general medical condition).

Depressive disorders represent one of four classes of mood disorders listed in the DSM-IV-TR; the other major forms of mood disorders include bipolar disorders, mood disorders due to a general medical condition, and substance-induced mood disorders, all of which may demonstrate symptoms of depression or low mood. Major depressive episodes may be present in a depressive disorder, which according to the DSM-IV-TR include major depressive disorder, dysthymic disorder, and depressive disorder not otherwise specified (for instance, premenstrual dysphoric disorder).

Depressive symptoms or features such as low mood, diminished interest in activities, psychomotor slowing or agitation, changes in appetite, poor concentration or indecisiveness, excessive guilt or feelings of worthlessness, and suicidal ideations may occur in the context of depressive disorders, bipolar disorders, mood disorders due to a general medical condition, substance-induced mood disorders, other unspecified mood disorders, and also may be present in association with a range of other psychiatric disorders, including but not limited to psychotic disorders, cognitive disorders, eating disorders, anxiety disorders and personality disorders. The longitudinal course of the disorder, the history and type of symptoms, and etiologic factors help distinguish the various forms of mood disorders from each other.

A "major depressive episode, according to the DSM-IV-TR, involves five or more of the following symptoms in the same 2 week period, signifying a change from previous functioning, of which one symptom is either 1) depressed mood or 2) a loss of interest or pleasure. The other symptoms include weight loss or weight gain, insomnia or hypersomnia, psychomotor retardation or agitation, fatigue or lethargy, feelings of worthlessness or excessive guilt, poor concentration, or recurrent thoughts of death or suicide. Such symptoms cause significant distress or impairment and are not due to a general medical or substance abuse condition.

"Depression symptoms rating scale" refers to any one of a number of standardized questionnaires, clinical instruments, or symptom inventories utilized to measure symptoms and symptom severity in depression. Such rating scales are often used in clinical studies to define treatment outcomes, based on changes from the study's entry point(s) to endpoint(s). Such depression symptoms rating scales include, but are not limited to, The Quick Inventory of Depressive-Symptomatology Self-Report ($QIDS\text{-}SR_{16}$), the 17-Item Hamilton Rating Scale of Depression ($HRSD_{17}$), the 30-Item Inventory of Depressive Symptomatology ($IDS\text{-}C_{30}$), or The Montgomery-Asperg Depression Rating Scale (MADRS). Such ratings scales may involve patient self-report or be clinician rated. A 50% or greater reduction in a depression ratings scale score over the course of a clinical trial (starting point to endpoint) is typically considered a favorable response for most depression symptoms rating scales. "Remission" in clinical studies of depression often refers to achieving at, or below, a particular numerical rating score on a depression symptoms rating scale (for instance, less than or equal to 7 on the $HRSD_{17}$; or less than or equal to 5 on the $QIDS\text{-}SR_{16}$; or less than or equal to 10 on the MADRS).

Binge eating behavior may be assessed by different methods though is commonly determined by the frequency of binge eating episodes occurring over a specific period of time (i.e., the number of binges per week; or the mean number of binges over two week periods). Another form of assessment may quantify the number of "binge-days", that is, the number of days in which the patient has binged in any form (i.e., whether once or multiple times) and determining the frequency of binge-days over a specific time frame.

"Generalized Anxiety Disorder" as defined by the DSM_IV-TR, and as the term is used herein, is a disorder meeting the following criteria: A. At least 6 months of "excessive anxiety and worry" about a variety of events and situations. Generally, "excessive" can be interpreted as more than would be expected for a particular situation or event. Most people become anxious over certain things, but the intensity of the anxiety typically manifests in the following manner:

A. There is significant difficulty in controlling the anxiety and worry.

B. The presence for most days over the previous six months of 3 or more (only 1 for children) of the following symptoms: 1. Feeling wound-up, tense, or restless, 2. Easily becoming fatigued or worn-out, 3. Concentration problems, 4. Irritability, 5. Significant tension in muscles, and 6. Difficulty with sleep.

C. The symptoms are not part of another mental disorder.

D. The symptoms cause "clinically significant distress" or problems functioning in daily life. "Clinically significant" is the part that relies on the perspective of the treatment provider. Some people can have many of the aforementioned symptoms and cope with them well enough to maintain a high level of functioning.

E. The condition is not due to a substance or medical issue. The severity of Generalized Anxiety Disorder may be assessed using a commonly accepted test for assessing the anxiety severity, such as the Hamilton Anxiety Rating Scale (HAM-A) or the Generalized Anxiety Disorder Severity Scale (GADSS).

"Obsessive behavior" may arise in many different clinical forms, including recurrent thoughts, impulses or images; perseverative thinking patterns; or highly ruminative mental behavior. Such symptoms often, but not necessarily, occur in the context of obsessive-compulsive disorder. "Compulsive behavior," sometimes referred to as 'compulsions', may similarly take a myriad of clinical forms, from more conventional obsessive-compulsive disorder symptoms (i.e., "checking", "ordering" or "hoarding" behaviors) to such symptoms as compulsive gambling and substance abuse, sexual and internet compulsions, and compulsive exercising or lying. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) is often used to assess symptom severity for patients that have both obsessions and compulsions, with scores reflecting symptoms severity (for instance, 0-7 as 'sub-clinical' through 32-40 as 'severe').

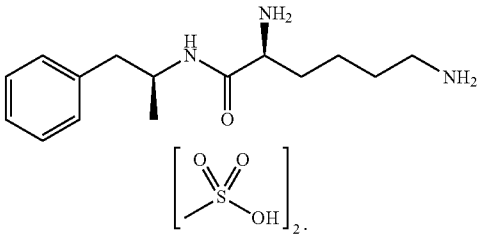
"Obesity" is defined as a BMI (Body Mass Index)>30 (kg/m^2).

"Efficacy" means the ability of an active agent administered to a patient to produce a therapeutic benefit in the patient.

The terms "amphetamine prodrug" and "methylphenidate prodrug" refer to any product that contains either an amphetamine (CAS Reg. No. 300-62-9) or methylphenidate (CAS Reg. No. 113-45-1) compound conjugated to a chemical moiety such that the conjugated amphetamine or methylphenidate must undergo a conversion in a patient's body to become the active amphetamine or methylphenidate form. "Amphetamine" includes dextro and levo amphetamine forms and all pharmaceutically acceptable amphetamine salts. Conversion typically involves metabolism. "Methylphenidate" also includes all methylphenidate optical isomers and all pharmaceutically acceptably methylphenidate salts. For example "methylphenidate" includes pure dexmethylphenidate

(α-phenyl-2-piperidineacetatehydrochloride, (R,R')-(+)-) and racemic mixtures of d- and l-methylphenidate forms.

Lisdexamfetamine dimesylate, CAS Reg. No. 608137-32-3, (2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide dimethanesulfonate, is an amphetamine prodrug in which L-lysine is covalently bound to d-amphetamine. Lisdexamfetamine dimesylate is sold under the trade name VYVANSE (Shire). It has the chemical formula:



"Lisdexamfetamine" is typically administered as a dimesylate salt but includes all pharmaceutically acceptable salts of lisdexamfetamine free base. The term "lisdexamfetamine" also encompasses all polymorphs and hydrates of this drug.

"Informing" in any of the above embodiments of the invention may occur by reference to, or providing, information material. Informing can also occur by presentation at a seminar, conference, or other educational presentation; or by providing an active agent with informational material to a user; or in a conversation between a pharmaceutical sales representative and a medical care worker or between a medical care worker and a patient.

"Informational material" means any media providing information. Media includes printed, audio, visual, or electronic media. Examples of information material are flyer, an advertisement, a package insert for a pharmaceutical product, printed labeling, an internet web site, an internet web page, an internet pop-up window, or information recorded on a compact disk, DVD, an audio recording, or any other recording or electronic medium.

A "medical care worker" means any worker in the health care field who may need information regarding an active agent, including information on safety, efficacy, dosing, administration, or pharmacokinetics. Examples of medical workers include physicians, pharmacists, physician's assistants, nurses, caretakers, emergency medical workers, and veterinarians.

A "patient" means any human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In some embodiments the patient is a human patient.

As used herein "a pharmaceutical supplier" means any person (other than a medical care worker), business, charitable organization, governmental organization, or other entity involved in the transfer of active agent between entities, for profit or not. Examples of pharmaceutical suppliers include pharmaceutical distributors, pharmacies (online or physical), foreign businesses or individuals importing active agent into the United States, the hospitals, HMOs and the Veterans Administration.

"Pharmaceutically acceptable salts" includes derivatives of the disclosed compounds, wherein the parent compound is modified by making non-toxic acid or base addition salts thereof, and further refers to pharmaceutically acceptable solvates, including hydrates, of such compounds and such salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid addition salts of basic residues such as amines; alkali or organic addition salts of acidic residues such as carboxylic acids; and the like, and combinations comprising one or more of the foregoing salts. The pharmaceutically acceptable salts include non-toxic salts and the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; other acceptable inorganic salts include metal salts such as sodium salt, potassium salt, cesium salt, and the like; and alkaline earth metal salts, such as calcium salt, magnesium salt, and the like, and combinations comprising one or more of the foregoing salts.

Pharmaceutically acceptable organic salts include salts prepared from organic acids such as acetic, trifluoroacetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC—$(CH_2)_n$—COOH where n is 0-4, and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, and the like; and amino acid salts such as arginate, asparginate, glutamate, and the like, and combinations comprising one or more of the foregoing salts.

"Providing" includes giving, selling, distributing, transferring (for profit or not), manufacturing, compounding or dispensing.

A "product" or "pharmaceutical product" is a dosage form of an active agent plus published material and optionally packing.

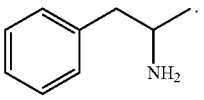
"Safety" means the incidence of adverse events associated with administration of an active agent, including adverse effects associated with patient-related factors (e.g., age, gender, ethnicity, race, target illness, abnormalities of renal or hepatic function, co-morbid illnesses, genetic characteristics such as metabolic status, or environment) and active agent-related factors (e.g., dose, plasma level, duration of exposure, or concomitant medication).

The term "therapeutically effective amount" or "effective amount" means an amount effective, when administered to a human or non-human patient, to provide any therapeutic benefit. A therapeutic benefit may be an amelioration of symptoms, e.g., an amount effective to decrease the symptoms of binge-eating disorder or a major depressive disorder. In certain circumstances a patient may not present symptoms of a condition for which the patient is being treated. Thus a therapeutically effective amount of a compound is also an amount sufficient to provide a significant positive effect on any indicia of a disease, disorder or condition e.g. an amount sufficient to significantly reduce the frequency and severity of binge eating behavior or depressive symptoms. A significant effect on an indicia of a disorder or condition includes a statistically significant in a standard parametric test of statistical significance such as Student's T-test, where $p<0.05$; though the effect need not be significant in some embodiments.

A "user" is a patient, a medical care worker, or a pharmaceutical supplier.

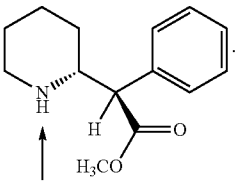
Amphetamine and Methylphenidate Prodrugs

Amphetamine has the chemical formula



Amphetamine prodrugs, and methods of preparing amphetamine prodrugs have been described previously. U.S. Pat. No. 7,105,486, which describes the preparation of lisdexamfetamine, is hereby incorporated by reference at cols. 20 to 22 for its teachings regarding the synthesis of amino acid amphetamine prodrugs. In addition to amino acid prodrugs it is possible to prepare a number of other amphetamine prodrugs by reacting the amphetamine amino group with a chemically labile moiety. It is within the ability of those of ordinary skill in the art of chemical synthesis to prepare carboxamide amphetamine prodrugs by reacting amphetamine with an aliphatic aldehyde and to prepare carbamate amphetamine prodrugs by reacting amphetamine with an aliphatic organic acid.

Methylphenidate has the chemical formula

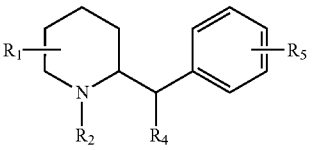


The arrow indicates a chemically accessible site at which labile groups may be added to create methylphenidate prodrugs. Amino acid methylphenidate prodrugs may be prepared via the general methods described in U.S. Pat. No. 7,105,486 for the preparation of amphetamine amino acid prodrugs. Amino acid methylphenidate prodrugs may comprise methylphenidate covalently bound to a single amino acid at the piperidine nitrogen or bound to a di- or tri-peptide at this position. It is also a matter of routine organic synthesis to prepare carboxamide and carbamate methylphenidate prodrugs by reacting methylphenidate with an aliphatic aldehyde or aliphatic organic acid.

Methylphenidate contains a secondary amine group and amphetamine contains an amino group both of which may be reacted to form prodrugs having a chemical moiety covalently attached to the amine or amino group of the parent drug compound. Prodrugs of amine-containing compounds have been disclosed in U.S. Patent Application No. 2007/0123468, which is hereby incorporated by reference at paragraphs [0078]-[0137] for its teaching regarding general classes of amine prodrugs, at paragraph [0140] for its teaching regarding amphetamine and methylphenidate prodrugs, at paragraphs [0176]-[0181] for its teachings of methylphenidate prodrug structures, and at paragraphs [0184]-[0189] for its teaching regarding prodrugs synthesis.

Methylphenidate Analogs

Methylphenidate analogs are compounds have a structure highly similar to methylphenidate, and like methylphenidate bind to the brain dopamine transporter and affect the reuptake of dopamine in the brain, but which have an extended duration of action relative to methylphenidate. Methylphenidate analogs include compounds having the general formula



where at least one of R_2 and R_4 is a non-hydrogen substituent differing from the group that occurs at the corresponding position in methylphenidate and R_1 and R_5 are independently chosen from hydrogen, halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy, and the like. Methylphenidate analogs have been disclosed in U.S. Non-provisional Patent Application No. 2006/0100243, which is hereby incorporated by reference at paragraphs [0007]-[0021] for its teachings regarding the methylphenidate analog structures, at paragraphs [0055]-[0063] for its teachings regarding the methylphenidate analog structure and synthesis, and at paragraphs [0083]-[0085] for its exemplary synthesis of methylphenidate analogs.

Methods of Treatment

The invention provides methods of treating binge eating disorders, obesity resulting from binge eating behavior, and depression. The invention includes methods of treating certain co-morbidities in ADHD and ADD patients; the invention includes methods of treating generalized anxiety disorder, obsessional and ruminative thought disorders, and obsessive/compulsive behavior in patients, particularly in ADHD and ADD patients. The amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog may be the only active agent administered (monotherapy) or may be combined with one or more other active agents (combination, adjunct, or augmentation therapy).

The invention also provides methods of treating depression, weight gain and/or obesity associated with depression, and weight gain and/or obesity due to taking anti-depressant medications.

The invention provides a method of treating chronic fatigue syndrome, fatigue, amotivation, or cognitive deficits associated with fatigue comprising diagnosing a patient as having chronic fatigue syndrome, fatigue, amotivation or cognitive deficits associated with fatigue and providing an effective amount of amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog to the patient.

In a first embodiment the invention includes a method of treating binge eating disorder or obesity resulting from binge eating behavior, comprising diagnosing a patient as having a binge eating disorder or obesity resulting from binge eating behavior and providing an effective amount of amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog to the patient, wherein the amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog is provided as the only active agent or is provided together with one or more additional active agents.

In another embodiment the invention provides a method of treating depression comprising (i) diagnosing a patient as having depression and (ii) providing an effective amount of amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog to the patient, wherein the amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog is provided as the only active agent or is provided together with one or more additional active agents.

Psychosocial intervention may play an important role in treatment of both depression and binge eating disorder. Psychosocial intervention includes cognitive-behavior therapy,

dialectical-behavior therapy, interpersonal therapy, psychodynamic therapy and group therapy.

While amphetamine and methylphenidate based stimulant medications have been associated with the side effect of appetite suppression and enhanced mood, their release mechanisms are of short or intermediate duration. As plasma levels of these drugs drop, patients typically experience symptoms associated with low drug levels. Even extended release amphetamine or methylphenidate formulations leave individuals with a 'wear off' effect for a sufficient part of the day, in which the medication loses its effects including appetite suppressant properties. 'Wear off' effects lead to problematic symptoms or side effects, sometimes of a 'rebound' nature, including the urge to have more medication, feeling dysphoric or low, feeling hungry or eating more, binge eating, fatigue, amotivation, and poor concentration.

Lisdexamfetamine dimesylate, given its slower and gradual release, confers certain significant advantages not seen previously with other amphetamine or methylphenidate stimulants. There is minimal 'wear-off' effect, a smoother distribution of drug over time, and no apparent need for dosing beyond once per day as significant effects have been demonstrated for up to 12 hours after administration. The unique clinical profile of lisdexamfetamine dimesylate offers all the benefits of a stimulant treatment for a full day, a much-needed advance required for sustained clinical benefit in depressive and binge eating disorders. Such a profile is particularly significant for depressive disorders, where a low mood is characteristically present through the entire day and often worse later in the day. Problems with concentration or fatigue, associated with depression or which may be associated with other conditions, may receive notably significant benefit as well. Additionally, treatment of binge eating behavior with lisdexamfetamine dimesylate, where symptoms may intensify toward the end of the day or in the evening or may have some relation to feelings of dysphoria as other stimulant medications 'wear off', would achieve surprisingly positive benefit. Lisdexamfetamine dimesylate is thought to confer less 'euphorgenic' properties, which may also mitigate feeling down as the medication "wears off."

Lisdexamfetamine dimesylate, sold under the trade name VYVANSE (Shire), is FDA approved for the treatment of Attention-Deficit Hyperactivity Disorder. Other psychostimulant treatments for Attention-Deficit Hyperactivity Disorder include both amphetamine (e.g. ADDERALL and ADDERALL XR) and methylphenidate (e.g. RITALIN and CONCERTA) preparations. Stimulant drugs, including lisdexamfetamine dimesylate, are believed to act via potentiation of dopamine and norepinephrine neurotransmission in the central nervous system.

Amphetamine prodrugs, including lisdexamfetamine, methylphenidate prodrugs, and certain methylphenidate analogs are unexpectedly effective for treating a number of disorders exacerbated by non-chemically modified immediate release and extended release amphetamine and methylphenidate including binge eating disorder and depression. In certain embodiments a patient is diagnosed as having a binge eating disorder or obesity related to binge eating behavior and an amount of amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog is provided to the patient; wherein the amount is effective to reduce the number of binge eating episodes in a one month time period, to produce a weight loss of 5% or greater of the patient's body mass within a six month treatment period, or significantly reduce the patient's triglyceride levels by 20% or more over a six month treatment period.

Methods of treatment include administering an effective amount of an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog wherein the effective amount is an amount effective to decrease the number of binge eating episodes per month or decrease the number of days in a month in which the patient experiences a binge eating episode.

In other embodiments the effective amount of amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog is an amount effective to decrease depressive symptoms. Preferably the decrease in depressive symptoms is a 50% or greater reduction of symptoms identified on depression symptom rating scale or is constituted by a depression symptom rate scale score below a particular value that may signify remission of a depressive episode (for instance, less than or equal to 7 on the $HRSD_{17}$).

The invention provides methods of treating weight gain associated with depression or caused by treatment with antidepressant medications.

Treatment approaches for major depressive disorder or other disorders in which depressive symptoms are present typically do not include the management of obesity. Similarly, treatment approaches for obesity typically do not address depressive symptoms. Pharmacologic treatments for mood disorders may actually contribute to weight gain, obesity, or increased abdominal girth, with potentially untoward psychological effects or medical sequelae such as hypertriglyceridemia, metabolic syndrome, or type II diabetes. While the mood disorder or depressive symptoms may be effectively treated with such pharmacologic agents, associated weight gain can carry a number of serious risks. Treatments that address both depression and obesity, as either monotherapy or as adjunct treatment, are much needed clinically and would serve a population with unmet clinical needs. Further, as demonstrated by the putative link of binge eating to such conditions as depression and obesity, pharmacologic interventions that ameliorate binge eating may have particular added value.

The relationship between mood disorders and obesity has been examined in a number of clinical and demographic studies, though the relationship is complicated and poorly understood. Current paradigms that link the two conditions suggest the possibility that shared genetic vulnerabilities, neurobiology (in particular the hypothalamic-pituitary-adrenocortical [HPAC] axis), or social factors may play important roles. Demographic studies suggest obesity, including associated conditions of 'overweight' and 'abdominal obesity,' are common to patients treated for mood disorders and represent a risk factor for depression, in particular for females, children, and individuals with child-onset major depression. It is well established that major depressive disorder commonly will present with 'atypical' features, as recognized in the DSM-IV-TR, with symptoms of weight gain, low energy, and inactivity. Binge eating symptoms may also accompany such forms of depression. Interestingly, obese individuals with binge eating disorder or behavior have been shown to have higher rates of mood disorders. There is research to suggest that women having major depressive disorder may be particularly disposed to weight gain and obesity and, as such, may represent either a distinct subset of depression or of obesity, which may even be linked to polycystic ovarian syndrome. More recent data suggests an even more conclusive link between obesity and atypical features of depression in women with bipolar disorder. In fact, the DSM-IV-TR recognizes that 'atypical' features of depression are 2-3 times more common in women than in men.

The invention further includes methods of using lisdexamfetamine dimesylate, comprising informing a user that the lisdexamfetamine dimesylate may be used to treat binge eating disorders, obesity resulting from binge eating behavior, or depression. The invention includes methods of using lisdexamfetamine dimesylate comprising informing a user that the lisdexamfetamine dimesylate may be used to treat certain co-morbidities in ADHD and ADD patients, including methods of treating generalized anxiety disorder, obsessional and ruminative thought disorders, and obsessive/compulsive behavior in ADHD and ADD patients. The user may be informed of the usefulness of lisdexamfetamine dimesylate, or other amphetamine prodrug, a methylphenidate prodrug, or a methylphenidate analog for the treatment of the above-mentioned disorders and conditions by reference to a package insert associated with the container. The informing may also be by reference to information material; by reference to a package active agent insert, a flyer or an advertisement; by presentation of information at a seminar, conference, or other educational presentation; or by a conversation between a pharmaceutical sales representative and a medical care worker.

Frequency of dosage may vary depending on the compound used and the particular condition or disorder to be treated or prevented. For most disorders a dosage regimen of once per day is preferred. Dosage regimens in which the amphetamine prodrug or methylphenidate prodrug is administered 2 times daily may occasionally be more helpful. In certain embodiments, 2.5 mg to 250 mg lisdexamfetamine dimesylate is administered per day or 15 to 100 mg lisdexamfetamine dimesylate per day, or about 50 mg per day lisdexamfetamine dimesylate is administered. Lisdexamfetamine dimesylate is typically administered once daily in the morning, with preferred dosing in the range of 15-70 mg per day, though in some embodiments daily doses of less than 15 mg, for example from about 2.5 mg to about 15 mg, or from about 2.5 to about 12.5 mg are useful for treating binge eating behaviors or depression.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease in the patient undergoing therapy. Patients may generally be monitored for therapeutic effectiveness using assays suitable for the condition being treated or prevented, which will be familiar to those of ordinary skill in the art.

Combination Methods

The invention provides a method of treating of central nervous system disorders in which an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog is provided to a patient together with one or more additional active agents. Such methods are referred to as "combination methods" of treatment. Combination methods of treating binge eating disorders, obesity resulting from binge eating behavior, and depression are included herein. The invention includes combination methods of treating certain co-morbidities in ADHD and ADD patients; for example the invention includes combination methods of treating generalized anxiety disorder, obsessional and ruminative thought disorders, and obsessive/compulsive behavior in ADHD and ADD patients.

The additional active agent may be administered separately from the amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog or may be combined with the additional active agent.

The invention also includes combination methods of treatment in which an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog is administered together with one or more forms of therapy, psychosocial support, or medical management. Such forms of psychosocial intervention include cognitive-behavior therapy, dialectical-behavior therapy, interpersonal therapy, psychodynamic therapy and group therapy.

The invention also includes combination methods of treatment in which the one or more other active agent(s) is an appetite suppressant, a weight loss drug, an anti-obesity agent, an anti-diabetes agent, an antidepressant, an anxiolytic, a selective serotonin reuptake inhibitor, a serotonin 5HT receptor partial agonist or antagonist, a norepinephrine dopamine reuptake inhibitor, a serotonin norepinephrine dopamine reuptake inhibitor, a serotonin 5-HT1a partial agonist, a serotonin 5-HT1b agonist, a serotonin 5-HT2 antagonist, a serotonin 5-HT6 antagonist, a serotonin-2 antagonist reuptake inhibitor, a serotonin-1 agonist reuptake inhibitor, a mixed serotonin antagonist reuptake inhibitor/partial agonist/dopamine agonist, an alpha-2 antagonist/serotonin 5HT2-3 receptor antagonist, a serotonin modulator or stimulator, a mixed serotonin antagonist/melatonin agonist, a mixed serotonin dopamine antagonist, a tricyclic antidepressant, a tetracyclic antidepressant, a bis-aryl-sulphanyl modulator, a beta-3 adrenoreceptor stimulator or agonist, a beta-3 adrenoreceptor antagonist, a nicotinic acetylcholine receptor agonist or antagonist, an enkephalinergic modulator, an aprepitant, a neurokinin (NK) antagonist, a NK1, 2, or 3 antagonist, a neuropeptide (NP) Y antagonist, a NPY1, 2, or 3, or 5 antagonist, a substance P antagonist, a corticotrophin-releasing hormone (CRH or CRF) antagonist, a CRH (or CRF)-1 antagonist, a glucocorticoid receptor agonist or partial agonist, a glucocorticoid receptor antagonist, a glucocorticoid receptor type II antagonist, an anti-convulsant, a GABA modulator, a GABA inverse agonist or partial agonist, a GABA receptor antagonist, a GABA channel antagonist, a GABA reuptake inhibitor, a glutamate modulator, an mGluR receptor modulator, agonist or antagonist, an mGluR2/3 agonist, an mGluR5 antagonist, an estrogen receptor agonist or antagonist, a melatonin receptor agonist or antagonist, a glycine transporter inhibitor, an alpha-1 receptor agonist, an alpha-1 receptor antagonist, an alpha-2 receptor agonist, an alpha-2 receptor antagonist, a vasopressin-1B (V1B) agonist or antagonist, an NMDA receptor modulator (i.e., a partial agonist, agonist, or antagonist), an ampakine modulating agent, an opioid antagonist, an opioid partial agonist, a benzodiazepine, an anti-psychotic, a dopamine receptor agonist or analog, a wakefulness promoting agent, an anti-manic agent, a mood modulating (i.e., stabilizing) agent, a cholinesterase inhibitor, an anti-amyloid agent, an anti-aggregant, a beta-secretase inhibitor, a beta-amyloid antagonist, a monoamine oxidase inhibitor, an anti-migraine agent, a melanocyte inhibiting factor, or a combination of the foregoing.

Weight-loss drugs include, but are not limited to, lipase inhibitors. Non-limiting examples of weight loss drugs include orlistat.

Anti-diabetes drugs include, but are not limited to, hypoglycemic agents. Non-limiting examples include acarbose, chlorpromide, exenatide, gliclazide, glimepiride, glipizide, glyburide, insulin, metformin, miglitol, nateglinide, pioglitazone, pramlintide, repaglinide, rosiglitazone, and tolazamide.

Anti-psychotics include atypical anti-psychotics. Non-limiting examples of anti-psychotics include clozapine, olanzapine, risperidone, aripiprazole, quetiapine, paliperidone, ziprasidone, and amisulpride.

Anti-convulsants include, but are not limited to, anti-epileptics and anti-seizure medications. Non-limiting examples of anti-convulsants include topiramate, lamotrigine, pregabalin, tiagabine, and zonisamide.

Selective serotonin reuptake inhibitors include, but are not limited to, citalopram, escitalopram, femoxetine, fluoxetine, fluvoxamine, paroxetine, sertraline, and zimeldine.

Serotonin partial agonists include, but are not limited to, pindolol, gepirone, and flesinoxan.

Selective serotonin norepinephrine reuptake inhibitors include, but are not limited to, duloxetine, venlafaxine, desvenlafaxine, milnacipran, and clovoxamine.

Norepephrine reuptake inhibitors include, but are not limited to, atomoxetine and reboxetine.

Serotonin-2 antagonist reuptake inhibitors include, but are not limited to, trazodone.

Alpha-2 antagonist/serotonin 5HT2-3 receptor antagonists include, but are not limited to, mirtazapine.

Norepinephrine dopamine reuptake inhibitors include, but are not limited to bupropion.

Tricyclic antidepressants include, but are not limited to, doxepin, amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, and trimipramine.

Benzodiazepines include but are not limited to, alprazolam, clonazepam, diazepam, lorazepam, flurazepam, and bentazepam.

Anti-manics include, but are not limited to, carbamazepine, valproic acid and lithium.

Alpha-2 receptor agonists include but are not limited to guanfacine and clonidine.

Wakefulness promoting agents include but are not limited to modafinil and armodafinil.

Neurokinin-1 antagonists include but are not limited to casopitant.

Neurokinin-2 antagonists include but are not limited to saredutant.

Beta-3 adrenoreceptor agonists include but are not limited to amibegron.

CRF1 antagonists include but are not limited to pexacerfont.

An anti-obesity agent may include a cannaboid receptor ligand, antagonist, or inverse agonist; a fatty acid amide hydrolase inhibitor; a peptide YY; a serotonin 5-HT2c antagonist; an adipocyte 11B-hydroxysteroid dehydrogenase type 1 antagonist; an amylase inhibitor; an anti-angiogenesis inhibitor; an agouti-related peptide analog, agonist, or antagonist; a carboxypeptidase inhibitor; a ciliary neurotrophic factor; a cholecystokinin (CCK) analog, agonist or inhibitor; a corticotrophin relating hormone modulator, agonist, or antagonist; a CKGGRAKDC peptide; a dehydroepiandrosterone analog; a fatty acid synthesis inhibitor; a fat-targeted peptide; a G-protein coupled receptor (GCPR) modulator; a gastrointestinal lipase inhibitor; a ghrelin modulator, agonist or antagonist; a human growth hormone (HGH) analog or fragment; a growth harmone secrectogue receptor (GHS—R) modulator, agonist or antagonist; a lipase inhibitor; a leptin analog, transport and/or receptor promoter; a melanocortin (MC) receptor agonist or antagonist; an M4 receptor agonist or antagonist; a melanin concentrating hormone (MCHR) agonist or antagonist; a melanocyte stimulating hormone analog; a neuropeptide Y modulator, agonist or antagonist; a thyroid hormone;

a thyroid receptor agonist; an orexin modulator, agonist or antagonist; a peptide YY or related analog or stimulator; a phytostanol analog; a pro-opiomelanocortin (POMC) stimulator; a somatostatin agonist; or a TNF-alpha antagonist.

An anti-diabetes agent may include a glucose-lowering (i.e., hypoglycemic) agent; an alpha-glucosidase inhibitor; an amylin analog; a biguanide; an incretin mimetic or analog; a glucagon-like peptide-1 (GLP-1) agonist or analog; a dipeptidyl peptidase (DPP) inhibitor; a DPP-IV inhibitor; a glucose-dependent insulinotropic peptide (GIP) agonist or analog; a gastric inhibitory peptide analog; a form of insulin (ie, injectable or inhaled); a fructose 1,6 biphosphatase (FBPase) inhibitor; a meglitinide; a peroxysome proliferators activated receptor (PPAR) modulator, agonist or antagonist; a PPAR-gamma agonist or antagonist; a protein-tyrosine phosphatase (PTP) 1B modulator, agonist or antagonist; a sodium-dependent glucose transporter (SGLT) inhibitor; a sulfonylurea; or a thiazolidinedione (ie, a "glitazone").

The invention includes combination methods of treatment in which an amphetamine prodrug, such as lisdexamfetamine dimesylate, a methylphenidate prodrug, or a methylphenidate analog is provided together with a Norepinephrine/Dopamine Reuptake Inhibitor, a Serotonin Reuptake Inhibitor, a Selective Serotonin Norepinephrine Reuptake Inhibitor, a Norepinephrine Reuptake Inhibitor, or an Anticonvulsant. For example the invention includes combination methods in which the amphetamine prodrug (e.g. lisdexamfetamine dimesylate) or methylphenidate prodrug is provided in combination with one or more of bupropion HCl, venlafaxine, paroxetine, mirtazapine, duloxetine, citalopram, escitalopram, fluoxetine, sertraline, atomoxetine, topiramate, zonisamide, lamotrigine, gabapentin, tiagabine, or pregabalin.

When treating binge eating the following active agents are particularly useful in combination with a methylphenidate prodrug or amphetamine prodrug: orlistat, bupropion, memantine, naltrexone, acamprosate, topiramate, zonisamide, sibutramine. Sibutramine may not be suitable for all patients because of its tendency to elevate pulse and blood pressure. Zonisamide is effective for treatment of binge eating but is not always well tolerated.

When treating depression the following active agents are particularly useful in combination with a methylphenidate prodrug or amphetamine prodrug: excitalopram, sertraline, fluoxetine, citalopram, bupropion, venlafaxine, and duloxetine.

Articles of Manufacture

The invention includes articles of manufacture, which comprise an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog in a container and labeling stating that the amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog is effective for treating certain central nervous system disorders; including treating binge eating disorders, obesity resulting from binge eating behavior, and depression. The labeling may also state that the amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog is effective for treating certain co-morbidities in ADHD and ADD patients; for example the invention includes methods of treating generalized anxiety disorder, obsessional and ruminative thought disorders, and obsessive/compulsive behavior in ADHD and ADD patients. The amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog present in this article of manufacture may be lisdexamfetamine dimesylate or some other amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog. The article of manufacture may comprise the amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog as the only active agent or may include one or more additional active agents. Additional active agents may be combined in a single dosage form with the amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog or may be packaged as separate dosage forms.

The article of manufacture may comprise packaging material and a dosage form of an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog contained within the packaging material, wherein the packaging material comprises a label approved by a regulatory agency for the product. In certain embodiments the labeling is labeling approved by the United States FDA.

An example of an article of manufacture provided by the invention is a packaged pharmaceutical compositions comprising an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog in a container and printed labeling stating that the amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog is useful for treating a binge eating disorder or associated symptoms, obesity resulting from binge eating behavior, or depression.

When an article of manufacture of this invention comprises lisdexamfetamine dimesylate, the labeling may advise administering 2.5 mg to 250 mg, 2.5 mg to 12.5 mg, 2.5 to 15 mg, 10 to 100 mg per day, 20 to 70 mg per day, or about 50 mg per day lisdexamfetamine dimesylate. The labeling may advise that lisdexamfetamine dimesylate is to be administered once daily, but there may be clinical value in some patients for up to two times per day.

Pharmaceutical Preparations

An amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog alone or in combination with one or more other active agent(s) can be administered as the neat chemical, but is preferably administered as a pharmaceutical composition or formulation. Accordingly, the invention provides pharmaceutical formulations comprising an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog alone or in combination with one or more other active agents together with one or more pharmaceutically acceptable carriers. Pharmaceutical formulations comprising lisdexamfetamine dimesylate have been previously described in U.S. Pat. No. 7,105,486, which is hereby incorporated by reference at cols. 13 to 17 for its teachings regarding amphetamine prodrug formulations including lisdexamfetamine dimesylate formulations.

An amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog alone or in combination with one or more other active agent(s) may be administered orally, topically, parenterally, by inhalation or spray, sublingually, transdermally, via buccal administration, or by other means, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, excipients, adjuvants, and vehicles. Oral dosages forms such as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs are preferred. Oral administration is preferred for lisdexamfetamine dimesylate administration. In some embodiments solid oral dosage forms are preferred. Tablets, capsules, and inhalable (e.g. intranasal) preparations are preferred. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents, such as sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide pharmaceutically elegant and palatable preparations.

Oral formulations contain between 0.1 and 99%, at least about 5% (weight %), 25% to about 50% or from 5% to 75% of an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog alone or in combination with one or more other active agent(s) and usually at least about 5% (weight %) of a compound of the present invention.

In addition to the amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog alone or in combination with one or more other active agent(s), the compositions of the invention may contain a pharmaceutically acceptable carrier, one or more compatible solid or liquid filler diluents or encapsulating substances, which are suitable for administration to an animal. Carriers must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal being treated. The carrier can be inert or it can possess pharmaceutical benefits of its own. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound.

The pharmaceutical dosage forms may contain an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog as the only active agent or may be combined with one or more additional active agents in the same dosage form. Active agents suitable for combination with an amphetamine prodrug, methylphenidate prodrug or methylphenidate analog in a single dosage form have been listed above in the section titled "Combination Methods." Particularly useful combination dosage forms include lisdexamfetamine in combination with at least one of the following in a single dosage form: orlistat, memantine, naltrexone, acamprosate, topiramate, zonisamide, sibutramine, escitalopram, sertraline, fluoxetine, citalopram, bupropion, venlafaxine, and duloxetine.

Tablets and Capsules

Tablets typically comprise conventional pharmaceutically compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules (including time release and sustained release formulations) typically comprise one or more solid diluents disclosed above. The selection of carrier components often depends on secondary considerations like taste, cost, and shelf stability. Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methylcellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

The invention includes amphetamine prodrug capsule formulations, particularly lisdexamfetamine dimesylate capsule formulations,

2.5 mg to 250 mg, 2.5 mg to 12.5 mg, 2.5 to 15 mg, 10 to 100 mg per day, 20 to 70 mg per day, or about 50 mg per day lisdexamfetamine dimesylate together with one or more of microcrystalline cellulose, croscarmellose sodium, and magnesium stearate in a gelatin capsule. The invention also includes methylphenidate tablets comprising 2.5 to 200 mg

methylphenidate prodrug together with lactose, magnesium stearate, polyethylene glycol, starch, sucrose, talc, and gum tragacanth.

EXAMPLES

The following examples describe patients with binge eating disorder or associated symptoms, a history of major depressive episodes, obsessive compulsive behavior, generalized anxiety disorder, or attention deficit hyperactivity disorder whose symptoms were poorly managed with psychopharmacologic interventions. In the cases where binge eating and depression were present, binge eating behavior significantly lessened following treatment with the amphetamine prodrug, lisdexamfetamine dimesylate; in one of these cases, it was thought that binge eating symptoms were due to antidepressant medication and the addition of amphetamine prodrug lisdexamfetamine dimesylate decreased binging behavior. Additionally, patients treated with lisdexamfetamine dimesylate, either as a monotherapy or as an adjunct to existing therapies, experienced remission of their depressive symptoms. The examples demonstrate the effectiveness of an amphetamine prodrug as a monotherapy or in combination with one or more other therapeutic agents for treating a range of psychological symptoms, including binge eating and depression.

These case reports suggest the clinical efficacy of an amphetamine prodrug, methylphenidate prodrug, or methylphenidate analog in the treatment of binge eating disorder or associated symptoms (in two cases thought to worsen from antidepressant agents), obesity resulting from binge eating behavior, and depressive disorders, as either a monotherapy or as an adjunct to existing antidepressant pharmacotherapy. In addition these cases also demonstrate that an amphetamine prodrug, a methylphenidate prodrug, or methylphenidate analog may offer significant clinical value in treatment of anxiety spectrum symptoms, include generalized anxiety disorder and obsessive compulsive behavior.

Example 1

Treatment of a Patient with Major Depressive Disorders and Binge Eating Disorder Using the Amphetamine Prodrug Lisdexamfetamine Dimesylate

Patient 1 is an adult, non-geriatric patient with a history of a major depressive disorder, attention deficit hyperactivity disorder, and binge eating disorder. Throughout Patient 1's entire adult life, there were reportedly periodic depressive episodes and symptoms. Patient 1 also indicated a history of binge eating disorder for approximately one year, characterized by eating unusually large amounts of junk food, often until feeling nauseated, and then feeling very guilty about the binging behavior. Such symptoms, though intermittently present for the past two decades, had escalated to an average of nearly every other day for about 12 months. During this time Patient 1 was being treated with PAXIL (paroxetine) and then ZOLOFT (sertraline) daily. Patient 1 participated in group therapy to address mood and eating symptoms. However, group therapy did not prove helpful for managing the binging behavior; the number of episodes as well as the number of days binging continued on average every other day. Following group therapy, Patient 1 began to experience a worsening depressed mood, poor concentration, and excessive feelings of guilt, fatigue, and feelings of hopelessness. Prior treatments for this patient's major depressive disorder included PROZAC (fluoxetine), LEXAPRO (escitalopram), EFFEXOR (venlafaxine HCl), and WELLBUTRIN (bupropion Hal). Lisdexamfetamine dimesylate was added to Patient 1's 100 mg ZOLOFT (sertraline) therapy as this patient met criteria of attention deficit hyperactivity disorder, with both inattention and hyperactivity symptoms present since childhood, though this diagnosis was not previously made for Patient 1. The dose of lisdexamfetamine dimesylate was titrated from 30 mg, to 50 mg, to 70 mg, in three successive weeks, respectively. Patient 1 reported significant improvement in the prior symptoms of inattention, forgetfulness, procrastination and physical restlessness, among others, by the time Patient 1 was taking 70 mg of lisdexamfetamine dimesylate daily. Patient 1 was maintained on that dose for an ensuing 8 weeks, along with 100 mg ZOLOFT (sertraline), and reported having no more than 3 or 4 binging episodes in total and no more than 3 binging days for the 8 weeks that Patient 1 was maintained at 70 mg lisdexamfetamine dimesylate daily.

Patient 1 experienced a reduction from approximately 12 or more binge eating days per month, present for approximately one year, to no more than 3 per month while taking the amphetamine prodrug lisdexamfetamine dimesylate, an approximately 75% reduction of binging eating days per month. Patient 1 also noted full remission of depressive symptoms for the 8 weeks of maintenance on 70 mg lisdexamfetamine dimesylate in addition to 100 mg ZOLOFT (sertraline) noting significant improvement in depressed mood, concentration, feelings of guilt, fatigue and no longer experienced any sense of hopelessness.

Example 2

Treatment of a Patient with Binge Eating Disorder and Major Depressive Disorders Using Lisdexamfetamine Dimesylate

Patient 2 is a non-geriatric adult with a history of attention-deficit hyperactivity disorder, polysubstance dependence, major depressive disorder, generalized anxiety disorder, and binge eating disorder. The patient has been treated in the past with multiple medication trials, either alone or in combination, including: WELLBUTRIN (bupropion HCl), EFFEXOR (venlafaxine HCl), CELEXA (citalopram), LAMICTAL (lamotrigine), RISPERDAL (risperidone), NEURONTIN (gabapentin), KLONOPIN (clonazepam), STRATTERA (atomoxetine) CONCERTA (methylphenidate), RITALIN SR (methylphenidate), ADDERAL XR (dextroamphetamine+amphetamine), and PROVIGIL (modafinil). The patient also was previously treated with intensive psychotherapy and received various forms of substance abuse counseling in the past. Lisdexamfetamine dimesylate was initiated for treatment of the patient's ADHD to address 'wear off' effects from ADDERALL XR in the later afternoons and early evenings. While the patient experienced an underlying mild depressive disorder, such "wear off" effects correlated with worsening of an already mildly depressed mood, further lowered overall energy level, even poorer concentration and unsettled sleep. The patient also indicated hinging behavior in the evenings, typically characterized by rapidly devouring large amounts of "sweet" foods, while alone, and until feeling bloated. While the patient struggled with binging behavior for the past two decades, the binge eating symptoms intensified in the 6 months prior to starting lisdexamfetamine dimesylate treatment, occurring at least two days per week, and causing an approximately 30 pound weight gain. Lisdexamfetamine dimesylate treatment

was initiated, primarily for treatment of Patient 2's attention deficit hyperactivity disorder to provide greater coverage into the evening, with a dosing schedule of 30 mg on day 1, 50 mg on day 2, and 70 mg on day 3; the patient had been taking Adderall XR 30 mg per day, which was discontinued on day 1 of starting lisdexamfetamine dimesylate. The patient was maintained on lisdexamfetamine dimesylate for about 10 weeks.

Patient 2 noted an overall improvement in depressive symptoms, including depressed mood, general interest level in activities especially in the evenings, sleep quality, and physical fatigue. Patient 2 also noted a marked reduction in binging episodes, both in terms of the total number and total days of binges; such binging episodes occurred only once in the first 2 weeks of treatment and stopped entirely in the subsequent 8 weeks of treatment with lisdexamfetamine dimesylate. The patient, considered obese prior to starting lisdexamfetamine dimesylate, lost approximately 7% of total body weight while taking the amphetamine prodrug. Interestingly, triglyceride levels present prior to taking lisdexamfetamine dimesylate were 271 mg/dL and reduced to 160 mg/dL by the end of 5 weeks of treatment with lisdexamfetamine dimesylate.

This case report exemplifies the utility of an amphetamine prodrug as a monotherapy for depression treatment, as demonstrated in this patient with an underlying depressive disorder, untreated with antidepressant medication at the time of initiating lisdexamfetamine dimesylate, who showed significant improvement across all the patient's depressive symptoms. The effectiveness of lisdexamfetamine dimesylate monotherapy in treating the patient's treatment resistant depression is particularly remarkable in view of Patient 2's number of failed treatments of recurrent major depressive disorder. Prior treatments failed due to poor treatment response and medication side effect intolerability. It should be noted that Patient 2's ADHD symptoms were not at issue at the time lisdexamfetamine dimesylate monotherapy was begun. The patient's ADHD symptoms were adequately addressed with ADDERALL XR treatment. Lisdexamfetamine dimesylate monotherapy was started to address the adverse effects Patient 2 had experienced from ADDERALL XR treatment. Lisdexamfetamine dimesylate proved as effective as ADDERALL XR in addressing the patient's ADHD symptoms, demonstrated sustained and full day antidepressant efficacy, and functioned as an antidepressant in addition to alleviating ADHD symptoms.

Example 3

Treatment of a Patient with ADHD, Generalized Anxiety Disorder, and Obsessive-Compulsive Behavior Using Lisdexamfetamine Dimesylate

The patient is a non-geriatric adult diagnosed with a history of ADHD, inattentive type, and comorbid Generalized Anxiety Disorder, though had no prior treatment. Presenting ADHD symptoms included difficulty sustaining attention and attending to details, difficulty organizing tasks with tendencies toward avoidance, distractibility, and problems finishing tasks that have been initiated. Symptoms of Generalized Anxiety Disorder included frequent and intense ruminative worrying, feeling overly fatigued, muscle tension and intermittent problems with sleep. History suggests that a perseverative pattern of thinking and compulsive worrying may have evolved from deficits in attention and information processing. The patient was started on VYVANSE 30 mg in the morning, along with TRAZODONE 50 mg at bedtime. VYVANSE was maintained at 30 mg once daily in the morning for one week, followed by one week at 50 mg per day, and then 70 mg per day, taken in the morning. The patient experienced a positive effect across all ADHD and Generalized Anxiety Disorder symptoms within the first week, with more dramatic improvement as the dose of VYVANSE was increased. The patient maintained treatment on VYVANSE at 70 mg per day for 10 weeks; TRAZODONE 50 mg at bedtime was discontinued after 4 weeks as sleep patterns had sufficiently normalized. While maintained on VYVANSE at 70 mg per day, the patient noted significantly enhanced ability to sustain attention and attend to details, organize and finish projects, and process information as compared to previous baseline function, with clear and evident improvements in work function. The patient found, surprisingly, a highly significant improvement on compulsive ruminating and worrying. The patient previously felt little or no control around such worrying, ruminative behavior and speculated that it caused significant mental and even physical fatigue. After 10 weeks of treatment with VYVANSE at 70 mg per day, the patient reported being only mildly affected by inattention symptoms and preoccupied primarily with 'realistic kinds of worries' that were generally well-managed.

This case demonstrates the use of an amphetamine prodrug lisdexamfetamine dimesylate as monotherapy for comorbid ADHD and anxiety spectrum symptoms, most notably generalized anxiety (in this case Generalized Anxiety Disorder) that took on a perseverative and 'compulsive worrying' quality along with physical symptoms of fatigue and muscle tension. Stimulant medications have traditionally been associated with causing or worsening anxiety symptoms (for instance, being 'anxiogenic'). It is thus surprising that an amphetamine prodrug proved useful for treating the Generalized Anxiety Disorder symptoms for the duration of the day, with no problematic 'wear off'.

Example 4

Treatment of Patient with Comorbid Depressive Disorders and Binge Eating Behavior with Lisdexamfetamine Dimesylate

The patient is a non-geriatric adult with a history of intermittent major depressive disorder, dysthymic disorder, and binge eating behavior. The patient also endorsed symptoms of ADHD, inattentive type, primarily around problems with organizing tasks, procrastination of work activities, and problems completing projects, though such 'inattention' symptoms were considered as clinically less detrimental than feeling chronically depressed, lacking motivation or interest in work or social activities, feeling fatigued and sometimes guilty, and having gained weight over several years due to 'emotional eating' behavior. The patient had received therapy in the past to address depressive episodes and associated life stressors, with modest benefit. The patient also described a history of 'emotional eating' that could occur at any time of day though more often in the late afternoons or early evenings. Such 'emotional eating' was often triggered by stressful situations or events, accompanied by an urge to eat, and would typically lead to excess consumption of carbohydrate-based foods. In recent years, the patient reported having gained over 10% body weight and noted a general trend toward increasing emotional eating and binging behavior. More severe binges occurred at least several times per month over a stretch of several years, though were much less common than 'emotional eating' that was milder in nature and occurred nearly daily. Medication treatment was initiated

with VYVANSE at 30 mg per day for two weeks and the dose was increased to 50 mg per day, without any adverse effects. The patient was maintained on VYVANSE for 10 weeks at 50 mg per day. The patient reported a rather abrupt and sustained cessation of emotional eating behavior in the afternoon while taking 50 mg VYVANSE daily. Symptoms of emotional eating were improved in the evenings as well, with less than one per week on average as compared to most evenings previously. There were no reported major binges reported at any point while taking VYVANSE and the patient lost approximately 6-7 pounds over 2½ months of treatment. The patient also noted significant amelioration of depressive symptoms, of feeling chronically low, and felt sufficiently motivated and invested in work and social activities in a way that was not present for some time. The organization and execution of work-related tasks improved during the course of treatment as well.

The case report demonstrates successful treatment of a comorbid depressive disorder (both major depressive disorder and dysthymic disorder) and binge-eating behavior with the amphetamine prodrug lisdexamfetamine dimesylate. The patient also began a trend of weight loss on account of decreased emotional eating and binging. The patient's ADHD was also clinically relevant, which is the primary reason VYVANSE was chosen as the initial medication treatment, though it was not the reason for which evaluation and treatment was sought and of secondary importance with regard to symptoms causing the patient difficulty and concern. Clinical improvement on depressive symptoms was present, most notably improved interest in daily activities and overall mood. Binge-eating behavior, largely taking the form of 'self-soothing' eating activity with potentially serious risks in this patient insofar as it was causing steady increased weight gain to the point of obesity), responded remarkably well to treatment with VYVANSE. The patient's symptoms of ADHD, inattentive type, also demonstrated improvement and enhanced an overall sense of improved well being, effectiveness, and confidence.

Example 5

Treatment of Binge Eating Disorder, Medication-Induced Cognitive Problems, and Fatigue with Lisdexamfetamine Dimesylate

The patient is a non-geriatric adult with a history of recurrent major depressive disorder with comorbid anxiety symptoms and severe binge eating disorder. The patient previously has been treated with therapy and has had multiple prior medication trials, either discontinued due to lack of efficacy or side effects, including ZOLOFT (sertraline), CELEXA (citalopram), PROZAC (fluoxetine), LEXAPRO (escitalopram), WELLBUTRIN SR (bupropion HCl), NORTRIPTYLINE, ATIVAN (lorazepam), ABILIFY (aripiprazole), RISPERDAL (risperidone), SEROQUEL (quetiapine), LYRICA (pregabalin), and RITALIN (methylphenidate). Selective serotonin reuptake inhibitors exacerbated binge eating symptoms and caused problematic weight gain. For treatment of depression with comorbid anxiety, binge-eating, and weight-gain related to binge eating symptoms, the patient was maintained on a medication regimen that included TOPAMAX (topiramate) 175 mg in the morning and 200 mg at night, LAMICTAL (lamotrigine) 200 mg in the morning, CYTOMEL (liothyronine) 25 mcg per day, KLONOPIN (clonazepam) 0.25 mg at bed time, and NEURONTIN (gabapentin) 600 mg at bedtime. However, symptoms of depressed mood, hopelessness, amotivation, problems with concentration (possibly worsened with the use of TOPAMAX though prior attempts to decrease the dose exacerbated binge-eating symptoms), significant fatigue, and tendency toward emotional eating and binging significantly increased from baseline. Given prior poor response to a number of different classes of medication trials, off-label use of VYVANSE was initiated at 30 mg each morning to target a constellation of symptoms, including symptoms of major depression, binge-eating disorder, fatigue, and concentration problems. VYVANSE was maintained at 30 mg each morning for weeks before being discontinued due to adverse effects. These side effects were excessive appetite suppression and visual blurring. However, during the time of treatment, the patient indicated a notably reduced urge to binge, fewer absolute binges per week, fewer binge-eating days per week, and improvement in both fatigue and concentration throughout the day. However, there appeared to be no benefit on the patient's depressed mood, amotivation, and feelings of hopelessness.

This case exemplifies the clinical benefit of lisdexamfetamine dimesylate on binge-eating symptoms and potentially on weight-gain related to binging (body weight was not obtained), though longer-term treatment was cut short by adverse effects at the 30 mg dosage form. Given the number of failed prior trials, off-label use of VYVANSE was clinically indicated, especially given the severity of binge eating behavior. Though TOPAMAX helped reduce binge eating behavior, it was clinically insufficient to fully address binge eating behavior, as it was poorly tolerated at higher doses due to cognitive side effects, and may have had a contributory role in cognitive slowing and fatigue at the maintenance dose.

Example 6

Treatment of a Patient with Comorbid Generalized Anxiety Disorder, Major Depression, and ADHD with Lisdexamfetamine Dimesylate

Patient 6 is a non-geriatric adult with a history of Generalized Anxiety Disorder and Major Depressive Disorder. The patient was maintained on PAXIL (paroxetine) 30 mg per day following a significant comorbid major depressive episode associated with anxiety symptoms, and a history consistent with Generalized Anxiety Disorder. Treatment with PAXIL had rapidly stabilized both depressive and anxiety symptoms and for approximately 2 years the patient was maintained at 30 mg per day with no change in dose. Over this time, the patient had gained approximately 10% of their body weight. It was periodically addressed that the patient may have experienced previous academic difficulties due to ADHD, inattentive type, though during the course of treatment with PAXIL, the patient was generally able to adapt to work pressures and developed compensatory strategies to deal with organizational difficulties, auditory inattention and forgetfulness, and feeling poorly engaged. However, after beginning a new job with more challenging responsibilities, the patient was unable to compensate for such deficits and a pattern of obsessive ruminations emerged, often involving work. In addition to perseverative and obsessive thinking, the patient experienced heightened anxiety and mild depressive symptoms, including fatigue, low mood, and amotivation, especially while at work. After discussing medication options and side effect concerns, VYVANSE was initiated to address underlying ADHD symptoms, which were felt to drive the patient's perseverative thinking, anxious ruminations, and low mood. VYVANSE was initiated at 30 mg per day for one week, and then titrated to 50 mg per day, without adverse effect. PAXIL was maintained at 30 mg per day. Over the course of the

ensuing 9 weeks, the patient reported improvement across ADHD, Generalized Anxiety Disorder, and Major Depressive Disorder symptoms. Work function began to feel 'easier', with better ability to attend to tasks and more efficient performance, improved attention to detail, and feeling internally less restless. The patient reported a substantial reduction in worrying, an approximate 4-5% weight loss over 2 months of treatment, and improved mood, motivation and energy.

The case report exemplifies the use of the amphetamine prodrug lisdexamfetamine dimesylate to address multiple clinical issues, the most unexpected one being the alleviation in generalized anxiety symptoms, perseverative thinking, and obsessive ruminations. The patient's initial presenting symptoms in past treatment have been within the class of Anxiety Disorders, mainly of Generalized Anxiety Disorder but also possibly Obsessive-Compulsive Disorder, as well as within the class of Depressive Disorders, mainly Major Depressive Disorder. While the patient may have exhibited ADHD symptoms in the past, they were considered clinically of a secondary nature, such that pharmacologic treatment had been initiated with the selective serotonin reuptake inhibitor (SSRI) PAXIL (paroxetine) to target both depressive and anxiety spectrum symptoms. The use of the amphetamine prodrug VYVANSE was able to accomplish a number of clinically very important objectives, with full-day duration effects, including augmentation of the mood-enhancing effect of the antidepressant PAXIL, alleviation of anxiety spectrum symptoms (including worrying and obsessive/compulsive mental behavior), and reduction of ADHD symptoms.

What is claimed is:

1. A method of treating Binge Eating Disorder, comprising diagnosing a patient as having Binge Eating Disorder, wherein the patient exhibits Binge Eating Disorder as defined in the DSM-IV-TR and administering a therapeutically effective amount of lisdexamfetamine dimesylate to the patient, wherein the lisdexamfetamine dimesylate is the only active agent administered or is administered together with one or more additional active agents.

2. The method of claim **1**, wherein 15 to 70 mg lisdexamfetamine dimesylate is administered daily.

3. The method of claim **1** wherein the lisdexamfetamine dimesylate is administered together with one or more other active agent(s).

4. The method of claim **3**, wherein the one or more other active agent(s) is an appetite suppressant, a weight loss drug, an anti-obesity agent, an anti-diabetes agent, a selective serotonin reuptake inhibitor, a serotonin 5HT receptor partial agonist or antagonist, a norepinephrine dopamine reuptake inhibitor, a serotonin norepinephrine dopamine reuptake inhibitor, a serotonin norepinephrine reuptake inhibitor, a nicotinic acetylcholine receptor agonist or antagonist, an anti-convulsant, a glutamate modulator, an opioid antagonist, or a combination of the foregoing.

5. The method of claim **4**, wherein the other active agent is orlistat, sibutramine, phentermine, rimonabant, acamprosate, adiponectin, benzphetamine, butabinide, cetilistat, cholecystokinin, diethylpropion, d-cycloserine, lorcaserin, naltrexone, 6-beta-naltrexol, buprenorphine, octreotide, oleoyl-estrone, oxytocin, phenylpropanolamine, phendimetrazine, phentermine, sodium oxybate, tesofensine, thyroxine, acarbose, acipimox, chlorpropamide, diazoxide, exenatide, gliclazide, glimepiride, glipizide, glucagon, glyburide, liraglutide, metformin, miglitol, nateglinide, pioglitazone, pramlintide, repaglinide, rosiglitazone, saxagliptin, sitagliptin, tolazamide, vildagliptin, dapagliflozin, sergliflozin, clovoxamine, femoxetine, flesinoxan, citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, duloxetine, desvenlafaxine, venlafaxine, atomoxetine, reboxetine, thionisoxetine, bupropion, mianserin, buspirone, amantadine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, ropinirole, vanoxerine, amisulpride, lamotrigine, levetiracetam, topiramate, zonisamide, modafinil, armodafinil, varenicline, galantanaine, memantine, or pharmaceutically active salts thereof, or a combination of the foregoing.

6. The method of claim **5**, wherein the other active agent is orlistat, naltrexone, or zonisamide, or a pharmaceutically acceptable salt or hydrate of any of the foregoing.

7. The method of claim **6**, wherein the other active agent is naltrexone.

8. A method of treating Binge Eating Disorder, comprising diagnosing a patient as having Binge Eating Disorder, wherein the patient exhibits Binge Eating Disorder as defined in the DSM-IV-TR and administering a therapeutically effective amount of lisdexamfetamine dimesylate to the patient wherein the lisdexamfetamine dimesylate is the only active agent administered.

9. The method of claim **8** wherein from 2.5 to 200 mg of lisdexamfetamine dimesylate is administered daily.

10. The method of claim **8**, wherein 15 to 100 mg lisdexamfetamine dimesylate is administered once per day.

11. The method of claim **8**, wherein the effective amount is an amount effective to decrease the number of binge eating episodes per month or decrease the number of days in a month in which the patient experiences a binge eating episode.

12. The method of claim **8**, wherein 15 to 70 mg lisdexamfetamine dimesylate is administered daily.

13. A method of treating Binge Eating Disorder as defined in the DSM-IV-TR, comprising administering a therapeutically effective amount of lisdexamfetamine dimesylate to a patient in need thereof, wherein the lisdexamfetamine dimesylate is the only active agent administered or is administered together with one or more additional active agents.

* * * * *

CONFIDENTIAL DISCLOSURE AGREEMENT

This Confidential Disclosure Agreement (the "Agreement") made and effective this 24th day of October 2013 (the "Effective Date") between Shire LLC, a company organized and existing under the laws of the commonwealth of Kentucky ("Shire") and LCS Group, LLC a company formed and existing under the laws of the state of Connecticut ("LCS"). Each of Shire and LCS is sometimes referred to individually herein as a "Party" and collectively as the "Parties."

In order to facilitate the Parties' discussions regarding a potential business opportunity involving U.S. Patent No. 8,318,813 and related patent applications (the "Business Opportunity"), Shire and/or LCS (as the "Disclosing Party") may disclose certain "Highly Proprietary and Confidential Information" (as defined below) to the other Party (as the "Receiving Party") for the limited purpose of each Parties' evaluation of the Business Opportunity.

In consideration of such disclosure, the Parties hereby agree as follows:

1. **Definitions.** **"Highly Proprietary and Confidential Information"** shall mean, any and all information disclosed by the Disclosing Party, including, without limitation, information relating to the Disclosing Party's business or interests, including without limitation, inventions (whether or not patentable), know-how, ideas, clinical data, non-clinical studies, forecasts, strategies, pharmaceutical formulations, processes, chemical syntheses, methodologies, schematics, specifications, testing procedures, internal documentation, and other details of its products, services, and operations, as well as technical, business, financial, marketing, customer and product development plans, and names and expertise of employees, consultants, customers and prospects, as well as the terms, conditions and existence of this Agreement, all of which, regardless of whether such information is: (i) specifically marked or designated as "confidential" or "proprietary;" (ii) patentable, copyrightable or protected by law; or (iii) furnished verbally, in writing, in electronic, or an other form. In addition, "Highly Proprietary and Confidential Information" includes, but is not limited to, any and all notes, memoranda, analyses, compilations, studies or other documents (whether in hard copy or electronic media or otherwise) prepared by the Receiving Party which contain or otherwise reflect such information, any and all copies, extracts or other reproductions of any of the same.

2. **Confidentiality.**

a) The Receiving Party acknowledges and understands that the Highly Proprietary and Confidential Information of the Disclosing Party is confidential, and is of great value and importance to the success of the Disclosing Party's business. The Receiving Party agrees to safeguard the Highly Proprietary and Confidential Information and to use its best efforts (i.e., not less than that employed by it to protect its own highly proprietary and confidential information) to prevent the unauthorized, negligent or inadvertent disclosure thereof.

b) The Receiving Party shall use the Highly Proprietary and Confidential Information of the Disclosing Party solely for the limited purpose of evaluating the Business Opportunity. The Receiving Party shall not disclose or use such Highly Proprietary and Confidential Information for any other purpose whatsoever.

c) The Receiving Party shall not, without the prior written approval of an officer of the Disclosing Party, directly or indirectly, disclose the Highly Proprietary and Confidential Information of the Disclosing Party to any person other than persons employed by or consultants working on behalf of the Receiving Party (and its agents and necessary support staff) that: (i) have a need to know such Highly Proprietary and Confidential Information for the purpose of evaluating the Business Opportunity; and (ii) have been advised of the confidential nature of the Highly Proprietary and Confidential Information and agree to comply with this Agreement.

d) The Receiving Party shall promptly notify the Disclosing Party in writing of any unauthorized, negligent or inadvertent use or disclosure of the Highly Proprietary and Confidential Information of the Disclosing Party. The Receiving Party shall be liable under this Agreement to the Disclosing Party for any use or disclosure in violation of this Agreement by the Receiving Party or its employees, consultants or agents.

e) The fact that the Parties have entered into negotiations of the Business Opportunity, and any and all discussions and exchanges of Highly Proprietary and Confidential Information between the Parties shall, in addition to the obligations and rights set forth in this Agreement, also be subject to Rule 408 of the Federal Rules of Evidence.

3. **Duty To Return.** Upon the earlier of: (i) completion or other termination of discussions with respect to the Business Opportunity; (ii) termination of this Agreement; or (iii)

demand by the Disclosing Party, the Receiving Party shall promptly: (a) return to the Disclosing Party any and all Highly Proprietary and Confidential Information of the Disclosing Party in tangible form together with all copies or reproductions thereof; and (b) destroy any notes, memoranda or other documents (including electronic documents such as email) concerning the Highly Proprietary and Confidential Information of the Disclosing Party and provide a certificate issued by the Receiving Party certifying to the Disclosing Party that such items have been destroyed.

4. **Remedies.** The Receiving Party acknowledges and understands that the use or disclosure of the Highly Proprietary and Confidential Information of the Disclosing Party in any manner inconsistent with this Agreement will cause the Disclosing Party irreparable damage. The Disclosing Party shall have the right to: (a) equitable and injunctive relief to prevent such unauthorized, negligent or inadvertent use or disclosure; and (b) recover the amount of all such damage (including reasonable attorneys' fees and expenses) to the Disclosing Party in connection with such use or disclosure. Nothing in this Agreement shall be construed to prohibit the Disclosing Party from pursuing any other available remedies for breach or threatened breach of this Agreement, including the recovery of damages. No failure or delay by the Disclosing Party in exercising any right, power or privilege under this Agreement shall operate as a waiver thereof, nor shall any single or partial exercise thereof preclude the exercise of any other right, power or privilege hereunder.

5. **Exclusions.** The Receiving Party shall not have any obligations under this Agreement with respect to any information that, as evidenced by the Receiving Party's contemporaneously prepared written records, is:

a) already known to it at the time of the disclosure;

b) publicly known at the time of the disclosure or becomes publicly known after the time of disclosure through no wrongful act or failure of the Receiving Party ; or

c) subsequently disclosed to the Receiving Party on a non-confidential basis by a third party not having a confidential relationship with the Disclosing Party and which rightfully acquired such information.

6. **Judicial Requests for Disclosure.** In the event the Receiving Party receives a request or is required by applicable law to disclose all or any part of the Highly Proprietary and Confidential Information of the Disclosing Party, the Receiving Party shall promptly notify the Disclosing Party of the request or requirement, and shall to the extent requested, consult with and assist the Disclosing Party in seeking a protective order or other appropriate protective remedy. If such order or other remedy is not obtained or the Disclosing Party waives compliance with the terms hereof, the Receiving Party shall disclose only that portion of the Disclosing Party's Highly Proprietary and Confidential Information which, in the reasonable and good-faith opinion of its counsel, is legally required to be disclosed, and shall exercise their respective best efforts to assure that confidential treatment will be accorded such Highly Proprietary and Confidential Information by the persons or entities receiving it. The Receiving Party shall be given a reasonable opportunity to review the Highly Proprietary and Confidential Information before its disclosure.

7. **Publicity.** In addition to the confidentiality obligations set forth in this Agreement, each Party hereby agrees, during the term of this Agreement and for a period of three (3) months after termination of this Agreement, not to discuss publically or with any third party that: (i) it is has entered into this Agreement; (ii) it is has been, or will be, negotiating an agreement with the other Party related to the Business Opportunity; or (iii) except pursuant to a duly executed agreement with confidentiality provisions at least as restrictive as those set forth in this Agreement, U.S. Patent No. 8,318,813 includes claims that could relate to the use of lisdexamfetamine dimesylate or Vyvanse®.. The foregoing notwithstanding, in response to direct inquiries from stockholders, investors or financial analysts Shire shall be permitted to disclose that is in the process of negotiating an agreement with LCS related to the Business Opportunity. Each Party hereby agrees and acknowledges that the other Party is making an investment of time and money in pursuing the Business Opportunity in consideration and on reliance of the obligations and conditions set forth in this Paragraph 7.

8. **Assignment.** This Agreement shall not be assignable by any Party without the prior express written consent of the other Party. Any assignment or attempt at the same in the absence of such prior written consent shall be void and without effect.

9. **Termination.** This Agreement shall remain in effect until such time as the Highly Proprietary and Confidential Information is returned or destroyed pursuant to Paragraph 3 above. The Receiving Party's obligations of confidentiality pursuant to Paragraphs 2 thru 6, and the obligation set forth in Paragraph 7 shall survive the termination of this Agreement. Any Party may terminate this Agreement by giving the other Party forty eight (48) hours written notice. The rights and obligations of the Parties hereunder with respect to any Highly Proprietary and Confidential Information disclosed or obtained prior to termination, shall survive any termination of this Agreement or any return of Highly Proprietary and Confidential Information.

10. **General.**

a) Neither Party makes any representation or warranty, express or implied, as to the accuracy or completeness of any Highly Proprietary and Confidential Information, nor shall the Disclosing Party have any liability to the Receiving Party, or to any other person resulting from the Receiving Party's use of or reliance on the Disclosing Party's Highly Proprietary and Confidential Information. The provisions of this Agreement shall be binding upon each Party's successors and permitted assigns and shall be governed by and construed in accordance with the laws of the State of New York, including its conflict of laws provisions. The Parties irrevocably agree that the United States District Court for the Southern District of New York shall have exclusive jurisdiction to deal with any disputes arising out of or in connection with this Agreement and that, accordingly, any proceedings arising out of or in connection with this Agreement shall be brought in the United States District Court for the Southern District of New York. Notwithstanding the foregoing, if there is any dispute for which the United States District Court for the Southern District of New York does not have subject matter jurisdiction, the state courts in the state and county of New York shall have jurisdiction. In connection with any dispute arising out of or in connection with this Agreement, each Party (i) hereby expressly consents and submits to the personal jurisdiction of the federal and state courts in the state and county of New York and (ii) hereby irrevocably waives any right to a trial by jury.

b) This Agreement grants no licenses, express or implied.

c) Nothing in this Agreement shall be construed as requiring either Party to disclose any Highly Proprietary and Confidential Information or any other information or materials to the

other Party. The Disclosing Party is free to provide its Highly Proprietary and Confidential Information with certain portions and elements redacted.

11. **Authority.** Each Party represents and warrants that it has the complete authority and has all rights necessary to negotiate and execute a final binding agreement related to the Business Opportunity.

12. **No Other Agreement.** This Agreement constitutes the entire understanding between the Parties relating to the subject matter hereof and no amendment or modification to this Agreement shall be valid or binding upon the Parties unless made in writing and signed by each Party.

13. **Amendments.** This Agreement may not be amended, supplemented, or modified in any manner, orally, or otherwise, except by an instrument in writing referencing the Agreement signed by a duly authorized representative of each Party.

14. **Severability.** If one or more of the provisions of the Agreement is held invalid, illegal, or unenforceable, the remaining provisions shall not in any way be affected or impaired. In the event any such provision is held invalid, illegal, or unenforceable, the Parties shall use reasonable efforts to substitute a valid, legal, and enforceable provision, which, insofar as is practical, implements the purposes of the section held to be invalid, illegal, or unenforceable.

15. **Jointly Drafted.** The Parties and their counsel have reviewed and contributed to the drafting of the Agreement, and the rule of construction providing that any ambiguities are to be resolved against the drafting Party shall not be employed in the interpretations of the Agreement.

16. **Counterparts and Electronic Execution.** This Agreement may be executed in one or more counterparts or by facsimile or by email, each of which when executed and delivered shall be an original, and all of which when executed shall constitute one and the same instrument.

[Signature Page to Confidential Disclosure Agreement]

SHIRE LLC

Date: 10-29-2013

By: _____

Name: JAMES J. Harrington

Title: MANAGER

James J. Harrington
Shire LLC
Manager

LCS GROUP, LLC

Date: 10/25/13

By: _____

Name: LOUIS SANFILIPPO

Title: CEO

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SHIRE DEVELOPMENT LLC
Petitioner
v.
LCS GROUP, LLC
Patent Owner

U.S. Patent No. 8,318,813 to Sanfilippo
Issue Date: November 27, 2012
Title: Method of Treating Binge Eating Disorder

Inter Partes Review

Petition for *Inter Partes* Review for U.S. Patent No. 8,318,813 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

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LIST OF EXHIBITS

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1001	U.S. Patent No. 8,318,813 to Sanfilippo. ("'813 patent")
1002	Prosecution History of U.S. Patent No. 8,318,813 (certified) obtained from the U.S. Patent and Trademark Office. ("'813 PH")
1003	July 21, 2011 Office Action for U.S. Application Serial No. 12/666,460. ("July 2011 OA")
1004	January 23, 2012 Response to Office Action for U.S. Application Serial No. 12/666,460. ("Jan. 2012 Resp.")
1005	April 18, 2012 Final Office Action for U.S. Application Serial No. 12/666,460. ("Apr. 2012 OA")
1006	June 18, 2012 Response to Final Office Action for U.S. Application Serial No. 12/666,460. ("June 2012 Resp.")
1007	June 21, 2012 Examiner-Initiated Interview Summary for U.S. Application Serial No. 12/666,460. ("June 2012 Int. Sum.")
1008	July 20, 2012 Notice of Allowance for U.S. Application Serial No. 12/666,460. ("July 2012 NOA")
1009	Dr. Timothy D. Brewerton's Declaration. ("Brewerton Dec.")
1010	American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association: 2000; 583-595, 785-787. ("DSM-IV-TR")
1011	Ioannides-Demos LL., et al., Pharmacotherapy for Obesity. *Drugs*. 2005; 65(10): 1391-1418. ("Ioannides-Demos")
1012	Jimerson DC, et al., Low Serotonin and Dopamine Metabolite Concentrations in Cerebrospinal Fluid From Bulimic Patients With Frequent Binge Episodes. *Arch. Gen. Psychiatry*. 1992; 49(2): 132-138. ("Jimerson")
1013	Epstein LH, et al., Dopamine Transporter Genotype as a Risk Factor for Obesity in African-American Smokers. *Obes. Res*. 2002; 10(12): 1232-1240. ("Epstein")
1014	Samanin R, et al., Neurochemical Mechanism of Action of Anorectic Drugs. *Pharmacol. Toxicol*. 1993; 73(2): 63-68. ("Samanin")

Exhibit Number	Exhibit Name
1015	Blundell JE, et al., Serotonin and Appetite Regulation: Implications for the Pharmacological Treatment of Obesity. *CNS Drugs*. 1998; 9(6): 473-495. ("Blundell")
1016	Drimmer EJ, Stimulant Treatment of Bulimia Nervosa With and Without Attention-Deficit Disorder: Three Case Reports. *Nutrition*. 2003; 19(1): 76-77. ("Drimmer")
1017	Ong YL, Suppression of Bulimic Symptoms with Methylamphetamine. *Brit. J. Psychiatry*. 1983; 143: 288-293. ("Ong")
1018	Sokol MS, et al., Methylphenidate Treatment for Bulimia Nervosa Associated with a Cluster B Personality Disorder. *Int. J. Eat. Disord*. 1999; 25(2): 233-237. ("Sokol")
1019	Dukarm CP, Bulimia Nervosa and Attention Deficit Hyperactivity Disorder: A Possible Role for Stimulant Medication. *J. Womens Health*. 2005; 14(4): 345-350. ("Dukarm")
1020	Appolinario JC, et al., Pharmacological Approaches in the Treatment of Binge Eating Disorder. *Curr. Drug Targets*. 2004; 5(3): 301-307. ("Appolinario")
1021	Appolinario JC, et al., An Open-Label Trial of Sibutramine in Obese Patients with Binge-Eating Disorder. *J. Clin. Psychiatry*. 2002; 63(1): 28-30. ("Appolinario 2002")
1022	Milano W, et al., Use of Sibutramine, an Inhibitor of the Reuptake of Serotonin and Noradrenaline, in the Treatment of Binge Eating Disorder: A Placebo-Controlled Study. *Adv. Ther*. 2005; 22(1): 25-31. ("Milano")
1023	U.S. Publication No. 2007/0042955 to Mickle et al. ("Mickle")
1024	Marrazzi MA, et al., Binge Eating Disorder: Response to Naltrexone. *Int. J. Obes*. 1995; 19(2): 143-145. ("Marrazzi")
1025	Grilo CM, et al., Reliability of the Eating Disorder Examination in Patients with Binge Eating Disorder. *Int. J. Eat. Disord*. 2004; 35(1): 80-85. ("Grilo")
1026	American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association: 1994; 545-550, 729-731. ("DSM-IV")

Exhibit Number	Exhibit Name
1027	Fairburn CG, et al., The Natural Course of Bulimia Nervosa and Binge Eating Disorder in Young Women. *Arch. Gen. Psychiatry*. 2000; 57(7): 659-665. ("Fairburn 2000")
1028	Fairburn CG, et al., Cognitive Behaviour Therapy for Eating Disorders: a "Transdiagnostic" Theory and Treatment. *Behav. Res. Ther.* 2003; 41: 509-528. ("Fairburn 2003")
1029	Grilo CM, et al., Efficacy of Cognitive Behavioral Therapy and Fluoxetine for the Treatment of Binge Eating Disorder: A Randomized Double-Blind Placebo-Controlled Comparison. *Biol. Psychiatry*. 2005; 57(3): 301-309. ("Grilo 2005")
1030	Arnold LM, et al., A Placebo-Controlled, Randomized Trial of Fluoxetine in the Treatment of Binge-Eating Disorder. *J. Clin. Psychiatry*. 2002; 63(11): 1028-1033. ("Arnold")
1031	American Psychiatric Association, *Practice Guideline for the Treatment of Patients with Eating Disorders, Third Ed.* 2006. ("Practice Guideline")
1032	National Institute for Clinical Excellence, *Eating Disorders: Core Interventions in the Treatment and Management of Anorexia Nervosa, Bulimia Nervosa, and Related Eating Disorders*. January 2004. ("NICE")
1033	Shire Press Release, 2007 Guidance Upgraded as Revenue Growth Accelerates. July 26, 2007. ("Shire PR")
1034	Dr. Timothy D. Brewerton's Curriculum Vitae. ("Brewerton CV")
1035	McCarthy LP, et al., Revising Psychiatry's Charter Document DSM-IV. *Written Communication*. 1994; 11(2): 147-192. ("McCarthy")
1036	American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*. Washington, DC: American Psychiatric Association. 1980; 67-71. ("DSM-III")
1037	Brewerton TD, Binge Eating Disorder: Diagnosis and Treatment Options. *CNS Drugs*. 1999; 11(5): 351-361. ("Brewerton")

Exhibit Number	Exhibit Name
1038	American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised*. Washington, DC: American Psychiatric Association: 1987; 65-71. ("DSM-III-R")
1039	Russell G, Bulimia Nervosa: An Ominous Variant of Anorexia Nervosa. *Psychol. Med.* 1979; 9(3): 429-448. ("Russell")
1040	Stunkard A, Eating Patterns and Obesity, *The Psychiatry Quarterly*. 1959; 33(1): 284-295. ("Stunkard 1959")
1041	Messner E, Methylphenidate Treatment of Bulimia Nervosa After Surgery. *Can. J. Psychiatry*. 1989; 34(8): 824-826. ("Messner")
1042	Schweickert LA, et al., Efficacy of Methylphenidate in Bulimia Nervosa Comorbid with Attention-Deficit Hyperactivity Disorder: A Case Report. *Int. J. Eat. Disord.* 1997; 21(3): 299-301. ("Schweickert")
1043	Hudson JI, et al., The Prevalence and Correlates of Eating Disorders in the National Comorbidity Survey Replication. *Biol. Psychiatry*. 2007; 61(3): 348-358. ("Hudson")
1044	Stunkard A, et al., d-Fenfluramine Treatment of Binge Eating Disorder. *Am. J. Psychiatry*. 1996; 153(11): 1455-1459. ("Stunkard 1996").
1045	Wilfley DE, et al., Efficacy of Sibutramine for the Treatment of Binge Eating Disorder: A Randomized Multicenter Placebo-Controlled Double-Blind Study. *Am. J. Psychiatry*. 2008; 165(1): 51-58. ("Wilfley")
1046	Appolinario JC, et al., A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the Treatment of Binge-Eating Disorder. *Arch. Gen. Psychiatry*. 2003; 60(11): 1109-1116. ("Appolinario 2003")
1047	Devlin MJ, et al., Open Treatment of Overweight Binge Eaters with Phentermine and Fluoxetine as an Adjunct to Cognitive-Behavioral Therapy. *Int. J. Eat. Disord.* 2000;28(3):325-332. ("Devlin")
1048	McCann UD, et al., Successful Treatment of Nonpurging Bulimia Nervosa With Desipramine: A Double-Blind, Placebo-Controlled Study. *Am. J. Psychiatry*. 1990; 147(11): 1509-1513. ("McCann")

Exhibit Number	Exhibit Name
1049	Malhotra S, et al., Venlafaxine Treatment of Binge-Eating Disorder Associated With Obesity: A Series of 35 Patients. J. *Clin. Psychiatry*. 2002; 63(9): 802-806. ("Malhotra")
1050	Schepers RJF, et al., Methamphetamine and Amphetamine Pharmacokinetics in Oral Fluid and Plasma after Controlled Oral Methamphetamine Administration to Human Volunteers. *Clin. Chem*. 2003; 49(1): 121-132. ("Schepers")
1051	Sulzer, D. Mechanisms of Neurotransmitter Release by Amphetamines: A Review. *Prog. Neurobiol*. 2005; 75(6): 406-433. ("Sulzer")
1052	Fleckenstein AE, New Insights into the Mechanism of Action of Amphetamines. *Annu. Rev. Pharmacol. Toxicol*. 2007; 47: 681-698. ("Fleckenstein")
1053	June 10, 2011 Response to Office Action for U.S. Application Serial No. 12/666,460. ("June 2011 Resp.")
1054	Carter WP, et al., Pharmacologic Treatment of Binge Eating Disorder. *Int. J. Eat. Disord*. 2003; 34 Suppl: S74-S88. ("Carter")
1055	Cortese S, et al., Attention-Deficit/Hyperactivity Disorder (ADHD) and Binge Eating. *Nutr. Rev*. 2007;65(9):404-411. ("Cortese")
1056	Corstorphine E, et al., Trauma and Multi-impulsivity in the Eating Disorders. *Eat. Behav*. 2007; 8: 23-30. ("Corstorphine")
1057	Nasser JA, et al., Impulsivity and Test Meal Intake in Obese Binge Eating Women. *Appetite*. 2004; 43(3): 303-307. ("Nasser")

Shire Development LLC ("Petitioner") petitions the United States Patent and Trademark Office ("USPTO") for *Inter Partes* Review ("IPR") under 35 U.S.C. § 311 *et seq.* and 37 C.F.R. § 42.1 *et seq.* of claims 1-13 of U.S. Patent No. 8,318,813 ("the '813 patent") (Ex.1001). As explained below, there is a reasonable likelihood that Petitioner will prevail with respect to at least one of the claims challenged in this Petition.

I. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(a)(1)

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Petitioner, Shire Development LLC, is the real party-in-interest.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Petitioner is not aware of any other judicial or administrative matter that would affect, or be affected by, a decision in this proceeding.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Petitioner provides the following designation of counsel.

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D. Service Information

Please address all correspondence and service to counsel at the address provided in Section I.C. Petitioner also consents to electronic service by email at shire.ipr.813@flhlaw.com.

II. PAYMENT OF FEES UNDER 37 C.F.R. § 42.103

Petitioner provides herewith payment of the required fees in accordance with 37 C.F.R. §§ 42.103 and 42.15(a). If any additional fees are required, the USPTO is authorized to charge such fees to Deposit Account No. 50-0320.

III. GROUNDS FOR STANDING UNDER 37 C.F.R. § 42.104(a)

Petitioner certifies that the '813 patent is eligible for IPR and that Petitioner is not barred or estopped from requesting IPR.

IV. CHALLENGE UNDER 37 C.F.R. § 42.104(b) AND RELIEF REQUESTED

Petitioner requests IPR of claims 1-13 of the '813 patent on the grounds set forth in the table below and requests cancellation of the claims as unpatentable.

An explanation of how claims 1-13 are unpatentable under the statutory grounds identified below, including the identification of where each element can be found in the cited prior art and relevance of that prior art, is provided in the form of text and detailed claim charts.

Grounds	Claims	Prior Art
1	1-5, 8-10, 12, and 13	Appolinario (Ex.1020) in view of Mickle (Ex.1023)
2	6 and 7	Appolinario (Ex.1020) in view of Mickle (Ex.1023) in view of Marrazzi (Ex.1024)
3	11	Appolinario (Ex.1020) in view of Mickle (Ex.1023) in view of Grilo (Ex.1025)
4	1-5, 8-10, 12, and 13	Ong (Ex.1017) in view of Mickle (Ex.1023) in view of DSM-IV-TR (Ex.1010)
5	6 and 7	Ong (Ex.1017) in view of Mickle (Ex.1023) in view of DSM-IV-TR (Ex.1010) in view of Marrazzi (Ex.1024)
6	11	Ong (Ex.1017) in view of Mickle (Ex.1023) in view of DSM-IV-TR (Ex.1010) in view of Grilo (Ex.1025)
7	1-5, 8-10, 12, and 13	Dukarm (Ex.1019) in view of Mickle (Ex.1023) in view of DSM-IV-TR (Ex.1010)
8	6 and 7	Dukarm (Ex.1019) in view of Mickle (Ex.1023) in view of DSM-IV-TR (Ex.1010) in view of Marrazzi (Ex.1024)
9	11	Dukarm (Ex.1019) in view of Mickle (Ex.1023) in view of DSM-IV-TR (Ex.1010) in view of Grilo (Ex.1025)

V. SUMMARY OF THE '813 PATENT

A. Brief Description

The claims of the '813 patent are directed to a method of treating binge eating disorder ("BED") with lisdexamfetamine dimesylate ("LDX dimesylate").

The '813 patent further claims methods in which the LDX dimesylate is combined with another active agent. The '813 patent discloses examples of six patients who were administered LDX dimesylate for treatment of BED and/or other disorders. (Ex.1001, '813 patent, col.19, l.5-col.25, l.30). The examples report that the patients who suffered from BED experienced a reduction in the number of binging episodes and/or the number of days in which binging occurred. (*Id.*).

B. Summary of the Prosecution History of the '813 Patent

The '813 patent issued on Nov. 27, 2012, from U.S. application Serial No. 12/666,460, which claims priority to U.S. provisional application Serial No. 60/972,046 filed on Sept. 13, 2007. (*Id.* at col.1, ll.4-7).

In a Nonfinal Office Action the claims, which were directed to a method of treating binge eating disorder with amphetamine prodrugs, were generally rejected under 35 U.S.C. § 103(a) as unpatentable over Dukarm as evidenced by The American Heritage Medical Dictionary in view of U.S. Publication No. 2005/0038121 ("Mickle 2005"). (*See* Ex.1003, July 2011 OA, p.5). According to the Examiner, "Dukarm teaches a method of treating binge eating in patients with bulimia nervosa" by administering dextroamphetamine sulfate. (*Id.*) Although Dukarm discusses treatment of bulimia nervosa ("BN"), the Examiner stated that it was relevant to the pending claims for two reasons: (1) the claims were not limited to BED but also encompassed BN; and (2) a person of ordinary skill in the art

("POSA") would extend to BED the teachings of Dukarm regarding stimulant medication and decreased desire to binge. (*See id.* at 5-6). The Examiner relied on Mickle 2005 for the disclosure of abuse-resistant amphetamine prodrugs. (*See id.* at 6-7). Applicant responded by amending the claims to limit them to BED, and to recite the specific amphetamine prodrug, LDX dimesylate. (Ex.1004, Jan. 2012 Resp., pp.2-5). Applicant argued that there was no motivation to apply the teachings of Dukarm to the treatment of BED, and no reasonable expectation of success that the teachings of Dukarm were applicable to BED. (*See id.* at 8-12).

In a Final Office Action the Examiner withdrew the previous 35 U.S.C. § 103(a) rejections "in view of Applicant's amendments" and introduced new grounds of rejection under 35 U.S.C. § 103(a). (*See* Ex.1005, Apr. 2012 OA, p.4-8). Applicant's response included arguments that LDX dimesylate shows unexpected efficacy in treating BED, and that there has been a long-felt and unmet need for a BED treatment. (Ex.1006, June 2012 Resp., pp.8-14). This evidence of secondary considerations was found persuasive and the application was then allowed (*see* Ex.1007, June 2012 Int. Sum.; Ex.1008, July 2012 NOA).

VI. STATE OF THE ART

At least since the 1950s, clinicians have identified, characterized, and treated abnormal eating behaviors. (*See, e.g.*, Ex.1009, Brewerton Dec. ¶¶ 30-50). BN and BED are separate conditions that have as a central diagnostic criterion

recurrent episodes of binge eating. (*See id.* ¶ 36). According to The Diagnostic and Statistical Manual of Mental Disorders (DSM)—psychiatry's preeminent diagnostic manual of mental disorders (*see id.* ¶¶ 30, 120)—a recurrent episode of binge eating is the same in both BN and BED, namely an uncontrolled consumption of a definitely large amount of food in a short period of time associated with a feeling of loss of control. (*Compare* Ex.1010, DSM-IV-TR, p.14 *with id.* at 18; *see also* Ex.1009, Brewerton Dec. ¶¶ 37, 99).

Extensive research has mapped out a neurobiochemical explanation for the etiology of binge eating. (*See* Ex.1009, Brewerton Dec. ¶¶ 51-53). Dysfunction of the serotonin (5-HT), dopamine (DA), and norepinephrine (NE) neurotransmitter systems in the brain have been implicated in the underlying cause of eating disorders. (*See* Ex.1011, Ioannides-Demos, p.5). Specifically, decreased levels of these NTs play a central role in the binge eating cycle. (Ex.1012, Jimerson, p.5). This is not surprising since DA is fundamental to the regulation of food uptake (*see* Ex.1013, Epstein, p.1), and stimulation of certain of these NT receptors leads to suppression of eating (*see* Ex.1014, Samanin, p.4; Ex.1015, Blundell, p.13). The finding that patients diagnosed with binge eating had decreased levels of NTs and metabolites in their cerebrospinal fluid clinically corroborated the role of NTs in this disorder. (*See* Ex.1016, Drimmer, p.3; Ex.1012, Jimerson, pp.3-5).

At least since the 1980s, psychostimulants (also referred to as stimulants) have been shown over and over again to be effective in treating the symptom of binge eating in patients with BN. (*See, e.g.*, Ex.1009, Brewerton Dec. ¶¶ 39-45, 160). The efficacy was not limited to a particular agent, but rather was associated with stimulants as a class, given the positive results obtained with methylamphetamine (*see, e.g.,* Ex.1017, Ong, pp.3-6), methylphenidate (*see, e.g.,* Ex.1018, Sokol, pp.4-6), mixed amphetamine salts (*see, e.g.,* Ex.1016, Drimmer, pp.2-3), and d-amphetamine (*see, e.g.,* Ex.1019, Dukarm, pp.3-6). Such stimulants have been shown to increase NE levels and block DA reuptake (*see* Ex.1011, Ioannides-Demos, p.6; *see also* Ex.1009, Brewerton Dec. ¶ 56). Stimulants therefore address low NT levels in the brain, which is a central cause of binge eating. (*See also* Ex.1009, Brewerton Dec. ¶ 51).

Anti-obesity agents have been shown to be effective in the treatment of BED, two of which are the centrally acting compounds d-fenfluramine and sibutramine. (*See* Ex.1020, Appolinario, p.3; *see also* Ex.1009, Brewerton Dec. ¶¶ 46-48). These anti-obesity agents modulate NT levels, and therefore address the decreased NT levels in patients with BED. (*See* Ex.1009, Brewerton Dec. ¶¶ 57-58). For example, d-fenfluramine increases levels of 5-HT (Ex.1014, Samanin, p.2) while sibutramine increases levels of both 5-HT and NE. (*See* Ex.1021, Appolinario 2002, p.2; *see also* Ex.1022, Milano, p.3).

Despite the success in suppressing binge eating in BN with stimulants and in BED with centrally acting obesity agents, their use was not ideal. Although stimulants (e.g., d-amphetamine) were highly efficacious (*see, e.g.*, Ex.1019, Dukarm, p.2, Abstract), the risk of abuse in a patient population already susceptible to substance abuse remained a concern (*see, e.g.*, *id.*, p.6; *see also* Ex.1009, Brewerton Dec. ¶ 125). As for anti-obesity agents (e.g., d-fenfluramine, sibutramine), the desired balance between safety and efficacy had not yet been struck. (*See* Ex.1020, Appolinario, p.3; Ex.1009, Brewerton Dec. ¶¶ 79-81).

Mickle describes LDX dimesylate, a new drug that demonstrates properties ideal for the treatment of binge eating, including BED. (*See, e.g.*, Ex.1009, Brewerton Dec. ¶¶ 83, 102-104, 126-127, 169-172). LDX dimesylate is an amino acid prodrug of d-amphetamine. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0085], [0098], [0123]). Upon oral administration this prodrug releases the standard, naturally occurring amino acid L-lysine and the stimulant d-amphetamine (*See id.* ¶¶ [0107], [0123]). A preferred indication for LDX dimesylate is as an anti-obesity agent. (*See id.* ¶ [0124]). Significantly, clinical studies have shown LDX dimesylate to have reduced abuse potential compared to d-amphetamine. (*See, e.g.*, *id.* ¶¶ [0355]-[0360]).

VII. PERSON OF ORDINARY SKILL IN THE ART

An underlying factual inquiry in an obviousness analysis includes the level of ordinary skill in the art. A POSA is "a hypothetical person who is presumed to have known the relevant art at the time of the invention." *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). Several key factors may be considered in determining the level of ordinary skill in the art: "(1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007). The USPTO applies this analysis when making determinations of a POSA. *See* MPEP § 2141(II)(C).

Petitioner submits that a POSA with respect to the '813 patent would be a medical doctor (M.D.) specializing in psychiatry. This POSA would have clinical experience in the diagnosis and psychopharmacology of eating disorders, specifically BED. (*See* Ex.1009, Brewerton Dec., ¶¶ 26-28).

VIII. CLAIM CONSTRUCTION

In an IPR a claim term is given its "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b). For purposes of this Petition, Petitioner sets forth the interpretation of the claim term

"therapeutically effective amount." At this time, the other claim limitations should be given their plain and ordinary meanings.

The term "therapeutically effective amount" appears in independent claims 1, 8, and 13. This term is properly construed as "an amount effective to decrease the symptoms of BED or an amount sufficient to significantly reduce the frequency and severity of binge eating behavior." (*See* Ex.1009, Brewerton Dec., ¶ 71). This interpretation is consistent with the specification of the '813 patent, which provides a definition of the term:

> **The term 'therapeutically effective amount'** or 'effective amount' **means** an amount effective, when administered to a human or non-human patient, to provide any therapeutic benefit. A therapeutic benefit may be an amelioration of symptoms, e.g., **an amount effective to decrease the symptoms of binge-eating disorder** or a major depressive disorder. In certain circumstances a patient may not present symptoms of a condition for which the patient is being treated. Thus a therapeutically effective amount of a compound is **also** an amount sufficient to provide a significant positive effect on any indicia of a disease, disorder or condition e.g. **an amount sufficient to significantly reduce the frequency and severity of binge eating behavior** or depressive symptoms.

(Ex. 1001, '813 patent, col.8 ll.48-61) (emphasis added). This quotation provides a definition of "therapeutically effective amount" with respect to the treatment of both BED and major depressive disorder. Because the claims of the '813 patent are directed to the treatment of BED, the bolded portions of the quotation, which relate specifically to BED, should be used for the interpretation of this claim term.

The prosecution history of the '813 patent confirms this interpretation of "therapeutically effective amount." The term was added to claim 1 during prosecution, and Applicant asserted that support for the amendment could be found in the above-quoted paragraph. (*See* Ex.1004, Jan. 2012 Resp., p.2, 6).

IX. MANNER OF APPLYING CITED PRIOR ART TO EVERY CLAIM FOR WHICH IPR IS REQUESTED

In this Section, Petitioner proposes various grounds for canceling claims 1-13, and thus explains the justification for IPR. Petitioner presents the following arguments and claim charts demonstrating that the claims are unpatentable under the statutory grounds identified in Section IV above.

A. The Cited References Qualify as Prior Art

The references relied on in the statutory grounds all qualify as prior art as laid out below.

1. Appolinario (Ex.1020)

Appolinario was publicly available in 2004 and thus qualifies as prior art to the '813 patent under 35 U.S.C. § 102(b). It does not appear to have been considered during prosecution of the '813 patent.

2. Mickle (Ex.1023)

Mickle was filed on April 10, 2006 and published on February 22, 2007. The application as filed qualifies as prior art to the '813 patent under 35 U.S.C. § 102(e) and the publication qualifies as prior art under both §§ 102(a) and (e). Mickle does not appear to have been considered during prosecution of the '813 patent. However, during prosecution the Examiner relied on Mickle 2005 and U.S. Patent No. 7,678,770, which both claim priority to a common provisional application as Mickle.

3. Marrazzi (Ex.1024)

Marrazzi was publicly available in 1995 and thus qualifies as prior art to the '813 patent under 35 U.S.C. § 102(b). Marrazzi does not appear to have been considered during prosecution of the '813 patent.

4. Grilo (Ex.1025)

Grilo was publicly available at least since 2004 and thus qualifies as prior art to the '813 patent under 35 U.S.C. § 102(b). Grilo does not appear to have been considered during prosecution of the '813 patent.

5. Ong (Ex.1017)

Ong was published in 1983 and thus qualifies as prior art to the '813 patent under 35 U.S.C. § 102(b). Ong was before the USPTO during prosecution of the '813 patent but was not relied on for a rejection.

6. DSM-IV-TR (Ex.1010)

DSM-IV-TR was published in 2000 and thus qualifies as prior art to the '813 patent under 35 U.S.C. § 102(b). DSM-IV-TR was before the USPTO during prosecution of the '813 patent but was not relied on for a rejection.

7. Dukarm (Ex.1019)

Dukarm was publically available in 2005 and thus qualifies as prior art to the '813 patent under 35 U.S.C. § 102(b). Dukarm was relied on in a rejection during prosecution of the '813 patent, after which Applicant amended the claims and set forth counterarguments. (*See supra* Section V.B). The Examiner then withdrew the rejection. The details of the relevant positions of Applicant and the Examiner with respect to Dukarm are discussed and analyzed below. (*See infra* Section X).

B. Ground 1: Claims 1-5, 8-10, 12, and 13 Are Unpatentable Under 35 U.S.C. § 103(a) over Appolinario in View of Mickle

1. Appolinario Teaches that Centrally Acting Anti-Obesity Agents Can Be Used to Treat BED Diagnosed According to DSM-IV-TR

Appolinario describes the diagnostic criteria for BED as recited in DSM-IV. (Ex.1020, Appolinario, p.1). Appolinario further teaches the diagnosis of BED

according to such criteria. (*Id.* at 4). Although claim 1 of the '813 patent refers to DSM-IV-TR, which is a text revision of DSM-IV, the diagnostic features and research criteria for BED are the same in both. (*Compare* Ex.1026, DSM-IV, pp.9-11 *with* Ex.1010, DSM-IV-TR, pp.16-18; *see also* Ex.1009, Brewerton Dec., ¶ 35). Thus, a POSA would have understood that Appolinario discloses diagnosing BED as defined in DSM-IV-TR. (*See* Ex.1009, Brewerton Dec. ¶ 78, n.1).

Appolinario also describes three classes of drugs that have been studied in humans for the treatment of BED, one such class being anti-obesity agents. (*See* Ex.1020, Appolinario, p.1, Abstract). In particular, two anti-obesity agents that were successfully used in the treatment of BED were identified: d-fenfluramine and sibutramine. (*Id.* at 3). Regarding d-fenfluramine, it "was found to promote binge eating suppression in 22 patients with BED and obesity," which resulted in a high rate of remission (i.e., 80%) of binge eating. (*Id.*). For sibutramine, in a randomized controlled trial (RCT) sibutramine was found to improve binge eating frequency, reduce body weight, and decrease depressive symptoms. (*Id.*). A 52% rate of remission of binge eating was reported. (*See id.* at 5).

After reading Appolinario, a POSA would have recognized that d-fenfluramine and sibutramine can be used to successfully treat BED. Because they both act on the central nervous system by impacting NTs that are responsible for

hunger and satiety (*see supra* Section VI; *see also* Ex.1009, Brewerton Dec. ¶¶ 57-58), a POSA would have reasonably expected other centrally acting anti-obesity agents to be useful in the treatment of BED. (*See* Ex.1009, Brewerton Dec. ¶ 80). Therefore, from Appolinario, a POSA would have learned to diagnose a patient with BED as defined in DSM-IV-TR and administer a centrally acting anti-obesity agent to the patient to treat BED. (*See id.*).

Notwithstanding the positive results of d-fenfluramine and sibutramine, a POSA also would have been aware of their limitations. As noted in Appolinario, d-fenfluramine was withdrawn from the market due to cardiopulmonary risks. (Ex.1020, Appolinario, p.3). In the sibutramine RCT, while the sibutramine cohort had a 52% remission from binge eating, the placebo group had a 32% remission. (*Id.* at 5). Therefore, the net difference in the percentage of patients with remission from binge eating at the end of the trial was only 20%. (*Id.*; *see also* Ex.1009, Brewerton Dec. ¶ 81).

Hence, a POSA would have been motivated to identify another centrally acting anti-obesity agent with positive properties for the treatment of BED. (Ex.1009, Brewerton Dec. ¶ 82).

2. Mickle Discloses LDX Dimesylate as a Centrally Acting Anti-obesity Agent Having Desirable Properties

Mickle discloses abuse-resistant amphetamine prodrugs, the preferred amphetamine prodrug being LDX dimesylate. (*See* Ex.1023, Mickle, Abstract, ¶

[0098]). Following oral administration of LDX dimesylate, d-amphetamine—a central nervous system stimulant—is released. (*See e.g., id.* ¶¶ [0003], [0085], [0096], [0358]). Mickle also teaches methods for treating a patient by administering a therapeutically effective amount of an amphetamine prodrug, e.g., LDX dimesylate, that is sufficient to prevent, ameliorate, and/or eliminate the symptoms of a disease. (*See id.* ¶ [0124]). In particular, Mickle lists obesity as a preferred indication for treatment with the amphetamine prodrugs of the invention, e.g., LDX dimesylate. (*See id.*).

The POSA further would have appreciated the benefits afforded by LDX dimesylate. According to Mickle, LDX dimesylate demonstrates reduced abuse potential (*see, e.g., id.* ¶¶ [0355]-[0361]), a desirable property in a population of patients that are prone to substance abuse (*see* Ex.1020, Appolinario, p.1). In addition, LDX dimesylate exhibits sustained release properties. (*See, e.g.*, Ex.1023, Mickle, ¶¶ [0226]-[0227]). A POSA also would have known that d-amphetamine increases NE and DA levels in the brain, which would address what is believed to be the main dysfunction in BED, namely, low levels of NTs. (*See* Ex.1009, Brewerton Dec. ¶ 56; *see also supra* Section VI).

3. Appolinario in View of Mickle Renders the Treatment of BED with LDX Dimesylate Obvious

As described above, Appolinario teaches the diagnosis of BED as per the criteria provided by DSM-IV-TR, and the successful use of centrally acting anti-

obesity agents in the treatment of BED. Yet a POSA also would have learned from Appolinario that the disclosed anti-obesity agents, although exhibiting positive results, presented potential limitations to their use. Thus, a POSA would have been motivated to find alternative centrally acting anti-obesity agents, and therefore would have turned to Mickle's disclosure of LDX dimesylate. As a result of the teachings and directives of Appolinario, in view of the disclosures in Mickle, a POSA would have used LDX dimesylate to treat BED with a reasonable expectation of success, making such a treatment obvious and unpatentable. (*See* Ex.1009, Brewerton Dec., ¶¶ 78-84).

The combination of Appolinario and Mickle renders claims 1-5, 8-10, 12, and 13 of the '813 patent obvious under 35 U.S.C. § 103(a). A claim chart for claim 1 is provided below.

Claim 1	**Appolinario in view of Mickle**
A method of treating Binge Eating Disorder, comprising	"Medications studied in the treatment of BED or similar conditions include . . . anti-obesity agents . . . ." (Ex.1020, Appolinario, p.2). The anti-obesity agent d-fenfluramine "was found to promote binge-eating suppression in 22 patients with BED and obesity . . . ." (*Id.* at 3). "Sibutramine is an anti-obesity agent that has also been shown effective in BED. It reduces binge eating behavior, promotes marked weight loss, and significantly reduces depressive symptoms." (*Id.* at 6).
diagnosing a patient as having Binge Eating	"More recent drug trials have used subjects with BED diagnosed according to DSM-IV criteria . . . ." (*Id.* at 4).

Claim 1	Appolinario in view of Mickle
Disorder, wherein the patient exhibits Binge Eating Disorder as defined in DSM-IV-TR	Appolinario summarizes the criteria for BED provided in DSM-IV. (*See id.* at 1). The criteria for BED in DSM-IV are identical to the criteria for BED in DSM-IV-TR. (*Compare* Ex.1026, DSM-IV, pp.9-11 *with* Ex.1010, DSM-IV-TR, pp.16-18; *see also* Ex.1009, Brewerton Dec., ¶ 35).
and administering a therapeutically effective amount of lisdexamfetamine dimesylate to the patient	LDX dimesylate is a prodrug of amphetamine. (*See* Ex.1023, Mickle ¶ [0098]). Following oral administration of LDX dimesylate, d-amphetamine is released. (*See, e.g., id.* ¶¶ [0085], [0358]). "Amphetamines stimulate the central nervous system." (*Id.* ¶¶ [0003], *see also id.* ¶ [0096]). Mickle provides that a preferred indication for the amphetamine prodrugs of the invention is obesity. (*See id.* ¶ [0124]). "In one embodiment, the invention provides methods for treating a patient comprising administering a therapeutically effective amount of an amphetamine prodrug, i.e., an amount sufficient to prevent, ameliorate, and/or eliminate the symptoms of a disease." (*Id.*).
wherein the lisdexamfetamine dimesylate is the only active agent administered or is administered together with one or more additional active agents.	Mickle discloses administering LDX dimesylate alone. (*See id.* ¶¶ [0202]-[0211]). "The methods of treatment include combination therapies which further comprise administering one or more therapeutic agents in addition to administering an amphetamine prodrug." (*Id.* ¶ [0125]).

Claim 2 depends from claim 1[1] and further requires that 15 to 70 mg of LDX dimesylate be administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in a daily dose of about 10 mg to about 100 mg. (*See id.* ¶ [0153]). Thus, the combination of Appolinario in view of Mickle renders claim 2 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 85).

Claim 2	**Appolinario in view of Mickle**
The method of claim 1, wherein 15 to 70 mg lisdexamfetamine dimesylate is administered daily.	"Tablets and other dosage forms provided in discrete units can contain a **daily dose** . . . . The dosage form can contain a dose of about 2.5 mg to about 500 mg, about 10 mg to about 250 mg, **about 10 mg to about 100 mg, about 25 mg to about 75 mg**, or increments therein of one or more of the amphetamine prodrugs. In a preferred embodiment, the dosage form contains 30 mg, 50 mg, or 70 mg of an amphetamine prodrug." (Ex.1023, Mickle ¶ [0153]) (emphasis added). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g., id.* ¶¶ [0348], [0353]).

Claim 3 depends from claim 1 and further requires that the LDX dimesylate be administered together with one or more other active agent(s). Mickle teaches methods of treatment that comprise a combination of one or more therapeutic agents in addition to an amphetamine prodrug, e.g., LDX dimesylate. (*See id.*

[1] For all dependent claims, Petitioner incorporates by reference its arguments and analyses set forth for all claims from which they depend.

¶ [0125]). Thus, the combination of Appolinario in view of Mickle renders claim 3 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 86).

Claim 3	Appolinario in view of Mickle
The method of claim 1 wherein the lisdexamfetamine dimesylate is administered together with one or more other active agent(s).	"The methods of treatment include combination therapies which further comprise administering one or more therapeutic agents in addition to administering an amphetamine prodrug." (Mickle ¶ [0125]).

Claim 4 depends from claim 3 and further requires that the one or more other active agent(s) be of a drug class recited in the claim. The claim includes selective serotonin reuptake inhibitors ("SSRI"). Appolinario teaches that BED is frequently associated with depression and identifies antidepressants (such as SSRIs) as useful for the treatment of BED. (Ex.1020, Appolinario, p.2). Further, Mickle teaches the combination of an amphetamine prodrug, such as LDX dimesylate, with antidepressants, including SSRIs. (*See* Ex.1023, Mickle ¶ [0125], Table 1). Thus, the combination of Appolinario in view of Mickle renders claim 4 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 87).

Claim 4	Appolinario in view of Mickle
The method of claim 3, wherein the one or more other active agent(s) is . . . a selective serotonin reuptake inhibitor, ...	"[P]atients and persons from the community with BED display a high prevalence of a lifetime diagnosis of major depressive disorder . . . ." (Ex.1020, Appolinario, p.2). "At present, antidepressants are the best studied class of agents in BED, and SSRIs represent the best studied class of antidepressants in this condition." (*Id.* at 6).

Claim 4	Appolinario in view of Mickle
	Mickle discloses that "[e]xemplary drug therapies contemplated for use in combination with an amphetamine prodrug" include "Antidepressant (SSRI . . . .)." (Ex.1023, Mickle ¶ [0125], Table 1).

Claim 5 depends from claim 4 and further recites that the other active agent can be citalopram, fluoxetine, fluvoxamine, or sertraline, among others. Appolinario teaches that BED is frequently associated with depression and identifies the above antidepressant SSRIs as useful for the treatment of BED. (Ex.1020, Appolinario, p.2). Further, Mickle teaches the combination of an amphetamine prodrug, such as LDX dimesylate, with the antidepressants fluoxetine and sertraline. (*See* Ex.1023, Mickle ¶ [0125]). Thus, the combination of Appolinario in view of Mickle renders claim 5 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 88).

Claim 5	Appolinario in view of Mickle
The method of claim 4, wherein the other active agent is . . . citalopram, . . . fluoxetine, fluvoxamine, sertraline	"[P]atients and persons from the community with BED display a high prevalence of a lifetime diagnosis of major depressive disorder . . . ." (Ex.1020, Appolinario, p.2). Appolinario identifies four double-blind placebo controlled trials for BED involving the use of fluvoxamine, sertraline, fluoxetine, and citalopram and states that these trials "confirmed the effectiveness of SSRIs in BED[.]" (*Id.*). Mickle discloses that "[e]xemplary drug therapies contemplated for use in combination with an amphetamine prodrug" includes the following: "Fluoxetine (e.g., Prozac®), Zoloft® [sertraline] . . . ." (Ex.1023, Mickle ¶ [0125], Table 1).

Independent claim 8 is identical to claim 1 except that claim 8 does not encompass the administration of LDX dimesylate together with one or more additional active agents. Instead, claim 8 is limited to the administration of LDX dimesylate as the only active agent administered. Thus, for the reasons outlined above for claim 1, the combination of Appolinario in view of Mickle renders claim 8 obvious under 35 U.S.C. § 103(a). (*See* Ex.1009, Brewerton Dec. ¶ 89).

Claim 9 depends from claim 8 and further requires that from 2.5 to 200 mg of LDX dimesylate be administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in a daily dose of about 2.5 mg to about 500 mg, or about 10 mg to about 250 mg. (*See* Ex.1023, Mickle ¶ [0153]). Thus, the combination of Appolinario in view of Mickle renders claim 9 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 90).

Claim 9	**Appolinario in view of Mickle**
The method of claim 8 wherein from 2.5 to 200 mg of lisdexamfetamine dimesylate is administered daily.	"Tablets and other dosage forms provided in discrete units can contain a **daily dose** . . . . The dosage form can contain a dose of **about 2.5 mg to about 500 mg, about 10 mg to about 250 mg**, about 10 mg to about 100 mg, about 25 mg to about 75 mg, or increments therein of one or more of the amphetamine prodrugs. In a preferred embodiment, the dosage form contains 30 mg, 50 mg, or 70 mg of an amphetamine prodrug." (Ex.1023, Mickle ¶ [0153]) (emphasis added). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g., id.* ¶¶ [0348], [0353]).

Claim 10 depends from claim 8 and further requires that from 15 to 100 mg of LDX dimesylate be administered once per day. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in a dose of about 10 mg to about 100 mg, administered once daily. (*See id.* ¶ [0153]). Thus, the combination of Appolinario in view of Mickle renders claim 10 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 91).

Claim 10	**Appolinario in view of Mickle**
The method of claim 8, wherein 15 to 100 mg lisdexamfetamine dimesylate is administered once per day.	"The dosage form can contain a dose of about 2.5 mg to about 500 mg, about 10 mg to about 250 mg, **about 10 mg to about 100 mg**, about 25 mg to about 75 mg, or increments therein of one or more of the amphetamine prodrugs. In a preferred embodiment, the dosage form contains 30 mg, 50 mg, or 70 mg of an amphetamine prodrug." (Ex.1023, Mickle ¶ [0153]) (emphasis added). "Preferably, a single dose is administered **once daily**." (*Id.* ¶ [0155]) (emphasis added). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g., id.* ¶¶ [0348], [0353]).

Claim 12 depends from claim 8 and further requires that 15 to 70 mg of LDX dimesylate be administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in a daily dose of about 10 mg to about 100 mg. (*See id.* ¶ [0153]). Thus, the combination of Appolinario in view of Mickle renders claim 12 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 92).

Claim 12	Appolinario in view of Mickle
The method of claim 8, wherein 15 to 70 mg lisdexamfetamine dimesylate is administered daily.	"Tablets and other dosage forms provided in discrete units can contain a **daily dose** . . . . The dosage form can contain a dose of about 2.5 mg to about 500 mg, about 10 mg to about 250 mg, **about 10 mg to about 100 mg**, about 25 mg to about 75 mg, or increments therein of one or more of the amphetamine prodrugs. In a preferred embodiment, the dosage form contains 30 mg, 50 mg, or 70 mg of an amphetamine prodrug." (Ex.1023, Mickle ¶ [0153]) (emphasis added). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g., id.* ¶¶ [0348], [0353]).

Independent claim 13 is identical to claim 1 except there is no requirement for diagnosing a patient as having BED. Thus, for the reasons outlined above for claim 1, the combination of Appolinario in view of Mickle renders claim 13 obvious under 35 U.S.C. § 103(a). (*See* Ex.1009, Brewerton Dec. ¶ 93).

C. Ground 2: Claims 6 and 7 Are Unpatentable Under 35 U.S.C. § 103(a) over Appolinario in View of Mickle and Marrazzi

Claim 6 depends from claim 5 and further requires that the other active agent administered together with LDX dimesylate be orlistat, naltrexone, or zonisamide, while claim 7 depends from claim 6 and further requires that the other active agent administered together with LDX dimesylate be naltrexone. Marrazzi provides that naltrexone was administered to a patient having BED, yielding positive results. (*See* Ex.1024, Marrazzi, p.2, Abstract). Additionally, Mickle teaches the combination of an amphetamine prodrug, such as LDX dimesylate, with another

therapeutic agent. (*See* Ex.1023, Mickle ¶ [0125]). As such, a POSA would have had a reasonable expectation of success that LDX dimesylate administered with a known BED agent, naltrexone, would treat BED. (*See* Ex.1009, Brewerton Dec. ¶ 94). Thus, the combination of Appolinario in view of Mickle and Marrazzi renders claims 6 and 7 obvious. (*See id.*).

Claims 6 and 7	Appolinario in view of Mickle and Marrazzi
6. The method of claim 5, wherein the other active agent is . . . naltrexone	"We report here a response to naltrexone in a subject with BED . . . . Symptoms were reduced in the naltrexone compared to placebo period." (Ex.1024, Marazzi, p.2, Abstract).
7. The method of claim 6, wherein the other active agent is naltrexone.	"The methods of treatment include combination therapies which further comprise administering one or more therapeutic agents in addition to administering an amphetamine prodrug." (Ex.1023, Mickle ¶ [0125]).

D. Ground 3: Claim 11 Is Unpatentable Under 35 U.S.C. § 103(a) over Appolinario in View of Mickle and Grilo

Claim 11 depends from claim 8 and further requires that the effective amount be an amount effective to decrease the number of binge eating episodes per month or decrease the number of days in a month in which the patient experiences a binge eating episode. Grilo describes that the Eating Disorder Examination ("EDE") is a reliable examination for patients with BED that involves assessing the number of large binge episodes as well as the number of days during which large binge episodes occurred. (*See* Ex.1025, Grilo, p.1, Abstract). The EDE focuses on 28-day durations of examinations. (*See id.* at 3, 5; *see also* Ex.1009,

Brewerton Dec., ¶ 95). Given the teachings of Grilo, a POSA would have understood that a reliable analysis for studying BED would involve assessing the number of large binge episodes and the number of days during which large binge episodes occurred, focusing on intervals of 28 days, i.e., about a month. (*See* Ex.1009, Brewerton Dec., ¶ 95). Thus, the combination of Appolinario in view of Mickle and Grilo renders claim 11 obvious. (*See id.*).

Claim 11	Appolinario in view of Mickle and Grilo
The method of claim 8, wherein the effective amount is an amount effective to decrease the number of binge eating episodes per month or decrease the number of days in a month in which the patient experiences a binge eating episode.	"These findings support the reliability of the EDE for patients with BED. The EDE has utility for assessing the number of large binge episodes (objective bulimic episodes), as well as the number of days during which large binge episodes occurred." (Ex.1025, Grilo, p.1, Abstract). "The EDE focuses on the previous 28 days . . . ." (*Id.* at 3; *see also id.* at 5).

E. Ground 4: Claims 1-5, 8-10, 12, and 13 Are Unpatentable Under 35 U.S.C. § 103(a) over Ong in View of DSM-IV-TR and Mickle

1. The Combination of Ong and DSM-IV-TR Teaches the Diagnosis of BED and Its Treatment Using Stimulants

Ong reports on the effects of the stimulant methylamphetamine on patients diagnosed with BN, and focuses on the symptom of "bulimia." (*See* Ex.1017, Ong, p.1, Abstract). Ong defines an episode of bulimia as "overeating," (*id.* at p.1), and characterizes it as "rapid, excessive and distressing eating" (*id.* at

Abstract). "Bulimia" is thereby regarded as a symptom of BN that is distinct from the inappropriate compensatory behavior also associated with BN. (*See* Ex.1009, Brewerton Dec. ¶ 97). The episodes of bulimia experienced by the patients were recurring, i.e., daily, weekly, monthly (*see* Ex.1017, Ong, p.2, Table 1), and in a typical episode the patients "experienced a loss of control of their eating behavior" (*id.* at 5). The "most important" finding reported in the study was that the symptom of bulimia was suppressed by methylamphetamine. (*Id.*).

At the time of the invention, a POSA would have regarded DSM-IV-TR as the gold standard for diagnosing mental disorders, including eating disorders (*see supra* Section IV; *see also* Ex.1009, Brewerton Dec. ¶ 30), and would have recognized that the symptom of bulimia defined in Ong displays many overlapping characteristics with the criteria for binge eating in DSM-IV-TR for both BN and BED (*see* Ex.1009, Brewerton Dec. ¶ 99). For example, DSM-IV-TR teaches that an essential diagnostic feature of BN and BED is recurrent episodes of binge eating (eating a definitely large amount of food in a short period of time) associated with indicators of impaired control over, and significant distress about, the binge eating. (Ex.1010, DSM-IV-TR, pp.14, 18; *see also* Ex.1009, Brewerton Dec. ¶ 99).

Therefore, in light of the teachings in DSM-IV-TR, a POSA would have understood that the characteristics of "bulimia" of the patients treated in Ong closely resemble the symptom of binge eating for BED. (*See* Ex.1009, Brewerton

Dec. ¶ 99). Since Ong discloses that methylamphetamine administered to these patients resulted in suppression of the bulimic or binge eating symptoms, a POSA would have had a reasonable expectation of success in treating BED with methylamphetamine. (*See id.* ¶ 100). Further, at the time of the invention numerous studies had already shown that stimulants as a class were effective in suppressing binge eating. (*See supra* Section VI; *see also* Ex.1009, Brewerton Dec. ¶¶ 39-45, 100). Hence, from Ong and DSM-IV-TR, a POSA would have learned to treat BED by diagnosing the patient based upon DSM-IV-TR and administering methylamphetamine to the patient. (*See* Ex.1009, Brewerton Dec. ¶ 100).

2. Ong Motivates the POSA to Search for an Improved Stimulant, and Mickle Provides the Solution

Ong cautions that "drugs with stimulant and euphoric effects carry the dangers of dependence and drug induced psychosis . . . ." (Ex.1017, Ong, p.5.). Given these precautions, the POSA seeking a treatment for BED would have been motivated to identify a stimulant with the beneficial pharmacological properties of methylamphetamine but without the associated abuse liability. (*See* Ex.1009, Brewerton Dec. ¶ 101. Mickle provides the solution. (*See id.*).

Specifically, Mickle discloses amphetamine prodrugs that reduce the euphoric effects associated with amphetamine abuse. (Ex.1023, Mickle, ¶¶ [0114], [0355]-[0360]. The preferred amphetamine prodrug disclosed is LDX dimesylate

(*see id.* ¶ [0098]), which following oral administration releases d-amphetamine (*see id.* ¶¶ [0085], [0358]). Like methylamphetamine, d-amphetamine is a known central nervous system stimulant (*see id.* ¶¶ [0003], [0096]), and both methylamphetamine and d-amphetamine share similar neurobiological mechanisms of action and also affect the same neurotransmitters, in particular dopamine. (*See* Ex.1009, Brewerton Dec. ¶ 103). Mickle also teaches methods for treating a patient by administering a therapeutically effective amount of an amphetamine prodrug, e.g., LDX dimesylate, that is sufficient to prevent, ameliorate, and/or eliminate the symptoms of a disease. (*See* Ex.1023, Mickle ¶ [0124]).

3. Ong in View of DSM-IV-TR and Mickle Renders the Treatment of BED with LDX Dimesylate Obvious

At the time of the invention a POSA would have had a reasonable expectation of success in treating BED with methylamphetamine. However, in light of the teachings in Ong regarding the risk associated with stimulants, a POSA would have been motivated to replace methylamphetamine with LDX dimesylate, given that LDX dimesylate was designed to have a lower potential for abuse, but would have common psychopharmacological effects as methylamphetamine. (*See* Ex.1009, Brewerton Dec. ¶ 105). Therefore, because of the teachings of Ong, DSM-IV-TR, and Mickle, it would have been obvious at the time of the invention

for a POSA to diagnose BED based upon DSM-IV-TR and to treat BED with the stimulant LDX dimesylate. (*See id.* ¶ 106).

The combination of Ong, DSM-IV-TR, and Mickle renders claims 1-5, 8-10, 12, and 13 of the '813 patent obvious under 35 U.S.C. § 103(a). A claim chart for claim 1 is provided below.

Claim 1	**Ong in view of DSM-IV-TR and Mickle**
A method of treating Binge Eating Disorder, comprising	Ong reports "an experimental study of the effects of methylamphetamine on patients with bulimia nervosa . . . ." (Ex.1017, Ong, p.1). The "most important finding is that bulimia as defined in [Ong's] report, is suppressed by methylamphetamine." (*Id.* at 5). The bulimia in Ong is defined as "**overeating**" and "**rapid**, **excessive** and **distressing** eating." (*Id.* at 1, Abstract) (emphasis added). The episodes of overeating were **recurring**, i.e., daily, weekly, monthly. (*See id.* at 2, Table 1). The patients "experienced a **loss of control** of their eating behaviour . . . ." (*Id.* at 5) (emphasis added). DSM-IV-TR teaches that the essential diagnostic features of BED "are **recurrent** episodes of binge eating associated with subjective and behavioral indicators of **impaired control** over, and significant **distress** about, the binge eating . . . ." (Ex.1010, DSM-IV-TR, p.16) (emphasis added). An episode of binge eating is characterized as "eating, in a **discrete period of time** . . . an amount of food that is definitely **larger** than most people would eat . . . under similar circumstances." (*Id.* at 18) (emphasis added).
diagnosing a patient as having Binge Eating Disorder, wherein the patient	The patients in the Ong study "satistifed criteria for the **diagnosis** of bulimia nervosa . . . ." (Ex.1017, Ong, p.1) (emphasis added)

Claim 1	Ong in view of DSM-IV-TR and Mickle
exhibits Binge Eating Disorder as defined in DSM-IV-TR	The bulimia in Ong is defined as "**overeating**" and "**rapid**, **excessive** and **distressing** eating." (*Id.* at 1, Abstract) (emphasis added). The episodes of overeating were **recurring**, i.e., daily, weekly, monthly. (*See id.* at 2, Table 1). The patients "experienced a **loss of control** of their eating behaviour . . . ." (*Id.* at 5) (emphasis added). DSM-IV-TR teaches that the essential diagnostic features of BED "are **recurrent** episodes of binge eating associated with subjective and behavioral indicators of **impaired control** over, and significant **distress** about, the binge eating . . . ." (Ex.1010, DSM-IV-TR, p.16) (emphasis added). An episode of binge eating is characterized as "eating, in a **discrete period of time** . . . an amount of food that is definitely **larger** than most people would eat . . . under similar circumstances." (*Id.* at 18) (emphasis added).
and administering a therapeutically effective amount of lisdexamfetamine dimesylate to the patient	"[D]rugs with stimulant and euphoric effects carry the dangers of dependence and drug induced psychosis . . . ." (Ex.1017, Ong, p.5). LDX dimesylate is a prodrug of amphetaminewith reduced abuse potential. (*See, e.g.,* Ex.1023, Mickle, ¶¶ [0098], [0355]-[0360]). Following oral administration of LDX dimesylate, d-amphetamine is released. (*See id.* ¶¶ [0085]. [0358]). "Amphetamines stimulate the central nervous system." (*Id.* ¶ [0003]; *see also id.* ¶ [0096]). "In one embodiment, the invention provides methods for treating a patient comprising administering a therapeutically effective amount of an amphetamine prodrug, i.e., an amount sufficient to prevent, ameliorate, and/or eliminate the symptoms of a disease." (*Id.* ¶ [0124]).

Claim 1	Ong in view of DSM-IV-TR and Mickle
wherein the lisdexamfetamine dimesylate is the only active agent administered or is administered together with one or more additional active agents.	Mickle discloses administering LDX dimesylate alone. (*See id.* ¶¶ [0202]-[0211]). "The methods of treatment include combination therapies which further comprise administering one or more therapeutic agents in addition to administering an amphetamine prodrug." (*Id.* ¶ [0125]).

Claim 2 depends from claim 1 and further requires that 15 to 70 mg of LDX dimesylate be administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in a daily dose of about 10 mg to about 100 mg. (*See id.* ¶ [0153]). Thus, the combination of Ong in view of DSM-IV-TR and Mickle renders claim 2 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 107).

Claim 2	Ong in view of DSM-IV-TR and Mickle
The method of claim 1, wherein 15 to 70 mg lisdexamfetamine dimesylate is administered daily.	"Tablets and other dosage forms provided in discrete units can contain a **daily dose** . . . . The dosage form can contain a dose of about 2.5 mg to about 500 mg, about 10 mg to about 250 mg, **about 10 mg to about 100 mg, about 25 mg to about 75 mg**, or increments therein of one or more of the amphetamine prodrugs. In a preferred embodiment, the dosage form contains 30 mg, 50 mg, or 70 mg of an amphetamine prodrug." (Ex.1023, Mickle ¶ [0153]) (emphasis added). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g., id.* ¶¶ [0348], [0353]).

Claim 3 depends from claim 1 and further requires that the LDX dimesylate be administered together with one or more other active agent(s). Mickle teaches

methods of treatment that comprise a combination of one or more therapeutic agents in addition to an amphetamine prodrug, e.g., LDX dimesylate. (*See id.* ¶ [0125]). Thus, the combination of Ong in view of DSM-IV-TR and Mickle renders claim 3 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 108).

Claim 3	**Ong in view of DSM-IV-TR and Mickle**
The method of claim 1 wherein the lisdexamfetamine dimesylate is administered together with one or more other active agent(s).	"The methods of treatment include combination therapies which further comprise administering one or more therapeutic agents in addition to administering an amphetamine prodrug." (Ex.1023, Mickle ¶ [0125]).

Claim 4 depends from claim 3 and further requires that the one or more other active agent(s) be of a drug class recited in the claim. The claim includes SSRIs, which can often be used as antidepressants. (*See* Ex.1009, Brewerton Dec. ¶ 109). DSM-IV-TR states that "[s]ome individuals report that binge eating is triggered by dysphoric moods, such as depression and anxiety" (Ex.1010, DSM-IV-TR, p.17), which suggests the need for combination drug therapy with antidepressants. (*See* Ex.1009, Brewerton Dec. ¶ 109). Further, Mickle teaches the combination of an amphetamine prodrug, such as LDX dimesylate, with antidepressants, including SSRIs. (*See* Ex.1023, Mickle ¶ [0125], Table 1). Thus, the combination of Ong in view of DSM-IV-TR Mickle renders claim 4 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 109).

Claim 4	Ong in view of DSM-IV-TR and Mickle
The method of claim 3, wherein the one or more other active agent(s) is . . . a selective serotonin reuptake inhibitor, ...	"Some individuals report that binge eating is triggered by dysphoric moods, such as depression and anxiety." (Ex.1010, DSM-IV-TR, p.17). Mickle discloses that "[e]xemplary drug therapies contemplated for use in combination with an amphetamine prodrug" include "Antidepressant (SSRI . . . .)." (Ex.1023, Mickle ¶ [0125], Table 1).

Claim 5 depends from claim 4 and further recites that the other active agent can be fluoxetine or sertraline, among others. DSM-IV-TR states that "[s]ome individuals report that binge eating is triggered by dysphoric moods, such as depression and anxiety" (Ex.1010, DSM-IV-TR, p.17), which suggests the need for combination drug therapy with antidepressants. (*See* Ex.1009, Brewerton Dec. ¶ 110). Further, Mickle teaches the combination of an amphetamine prodrug, such as LDX dimesylate, with the antidepressants fluoxetine and sertraline. (*See* Ex.1023, Mickle ¶ [0125], Table 1). Thus, the combination of Ong in view of DSM-IV-TR and Mickle renders claim 5 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 110).

Claim 5	Ong in view of DSM-IV-TR and Mickle
The method of claim 4, wherein the other active agent is . . . fluoxetine, . . . sertraline, ..."	"Some individuals report that binge eating is triggered by dysphoric moods, such as depression and anxiety." (Ex.1010, DSM-IV-TR, p.17). Mickle discloses that "[e]xemplary drug therapies contemplated for use in combination with an amphetamine prodrug" includes the following: "Fluoxetine (e.g., Prozac®), Zoloft® [sertraline] . . . ." (Ex.1023, Mickle ¶ [0125], Table 1).

Independent claim 8 is identical to claim 1 except that claim 8 does not encompass the administration of LDX dimesylae together with one or more additional active agents. Instead, claim 8 is limited to the administration of LDX dimesylate as the only active agent administered. Thus, for the reasons outlined above for claim 1, the combination of Ong in view of DSM-IV-TR and Mickle renders claim 8 obvious under 35 U.S.C. § 103(a). (*See* Ex.1009, Brewerton Dec. ¶ 111).

Claim 9 depends from claim 8 and further requires that from 2.5 to 200 mg of LDX dimesylate be administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in a daily dose of about 2.5 mg to about 500 mg, or about 10 mg to about 250 mg. (*See* Ex.1023, Mickle ¶ [0153]). Thus, the combination of Ong in view of DSM-IV-TR and Mickle renders claim 9 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 112).

Claim 9	**Ong in view of DSM-IV-TR and Mickle**
The method of claim 8 wherein from 2.5 to 200 mg of lisdexamfetamine dimesylate is administered daily.	"Tablets and other dosage forms provided in discrete units can contain a **daily dose** . . . . The dosage form can contain a dose of **about 2.5 mg to about 500 mg, about 10 mg to about 250 mg**, about 10 mg to about 100 mg, about 25 mg to about 75 mg, or increments therein of one or more of the amphetamine prodrugs. In a preferred embodiment, the dosage form contains 30 mg, 50 mg, or 70 mg of an amphetamine prodrug." (Ex.1023, Mickle ¶ [0153]) (emphasis added). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g., id.* ¶¶ [0348], [0353]).

Claim 10 depends from claim 8 and further requires that from 15 to 100 mg of LDX dimesylate be administered once per day. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in a dose of about 10 mg to about 100 mg, administered once daily. (*See id.* ¶ [0153]). Thus, the combination of Ong in view of DSM-IV-TR and Mickle renders claim 10 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 113).

Claim 10	**Ong in view of DSM-IV-TR and Mickle**
The method of claim 8, wherein 15 to 100 mg lisdexamfetamine dimesylate is administered once per day.	"The dosage form can contain a dose of about 2.5 mg to about 500 mg, about 10 mg to about 250 mg, **about 10 mg to about 100 mg**, about 25 mg to about 75 mg, or increments therein of one or more of the amphetamine prodrugs. In a preferred embodiment, the dosage form contains 30 mg, 50 mg, or 70 mg of an amphetamine prodrug." (Ex.1023, Mickle ¶ [0153]) (emphasis added). "Preferably, a single dose is administered **once daily**." (*Id.* ¶ [0155]) (emphasis added). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g., id.* ¶¶ [0348], [0353]).

Claim 12 depends from claim 8 and further requires that 15 to 70 mg of LDX dimesylate be administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in a daily dose of about 10 mg to about 100 mg. (*See id.* ¶ [0153]). Thus, the combination of Ong in view of DSM-IV-TR and Mickle renders claim 12 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 114).

Claim 12	Ong in view of DSM-IV-TR and Mickle
The method of claim 8, wherein 15 to 70 mg lisdexamfetamine dimesylate is administered daily.	"Tablets and other dosage forms provided in discrete units can contain a **daily dose** . . . . The dosage form can contain a dose of about 2.5 mg to about 500 mg, about 10 mg to about 250 mg, **about 10 mg to about 100 mg**, about 25 mg to about 75 mg, or increments therein of one or more of the amphetamine prodrugs. In a preferred embodiment, the dosage form contains 30 mg, 50 mg, or 70 mg of an amphetamine prodrug." (Ex.1023, Mickle ¶ [0153]) (emphasis added). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g., id.* ¶¶ [0348], [0353]).

Independent claim 13 is identical to claim 1 except there is no requirement for diagnosing a patient as having BED. Thus, for the reasons outlined above for claim 1, the combination of Ong in view of DSM-IV-TR and Mickle renders claim 13 obvious under 35 U.S.C. § 103(a). (*See* Ex.1009, Brewerton Dec. ¶ 115).

F. Ground 5: Claims 6 and 7 Are Unpatentable Under 35 U.S.C. § 103(a) over Ong in View of DSM-IV-TR, Mickle, and Marrazzi

Claim 6 depends from claim 5 and further requires that the other active agent administered together with LDX dimesylate be orlistat, naltrexone, zonisamide, or pharmaceutically acceptable salts thereof, while claim 7 depends from claim 6 and further requires that the other active agent administered together with LDX dimesylate be naltrexone. Marrazzi provides that naltrexone was administered to a patient having BED, yielding positive results. (*See* Ex.1024, Marrazzi, p.2, Abstract). Additionally, Mickle teaches the combination of an amphetamine

prodrug, such as LDX dimesylate, with another therapeutic agent. (*See* Ex.1023, Mickle ¶ [0125]). As such, a POSA would have had a reasonable expectation of success that LDX dimesylate administered with a known BED agent, naltrexone, would treat BED. (*See* Ex.1009, Brewerton Dec. ¶ 116). Thus, the combination of Ong in view of DSM-IV-TR, Mickle, and Marrazzi renders claims 6 and 7 obvious. (*See id.*).

Claims 6 and 7	**Ong in view of DSM-IV-TR, Mickle, and Marrazzi**
6. The method of claim 5, wherein the other active agent is . . . naltrexone	"We report here a response to naltrexone in a subject with BED . . . . Symptoms were reduced in the naltrexone compared to placebo period." (Ex.1024, Marazzi, p.2, Abstract).
7. The method of claim 6, wherein the other active agent is naltrexone.	"The methods of treatment include combination therapies which further comprise administering one or more therapeutic agents in addition to administering an amphetamine prodrug." (Ex.1023, Mickle ¶ [0125]).

G. Ground 6: Claim 11 is Unpatentable Under 35 U.S.C. § 103(a) over Ong in View of DSM-IV-TR, Mickle, and Grilo.

Claim 11 depends from claim 8 and further requires that the effective amount be an amount effective to decrease the number of binge eating episodes per month or decrease the number of days in a month in which the patient experiences a binge eating episode. Grilo describes that the EDE is a reliable examination for patients with BED that involves assessing the number of large binge episodes as well as the number of days during which large binge episodes occurred. (*See* Ex.1025, Grilo, p.1, Abstract). The EDE focuses on 28-day durations of

examinations. (*See id.* at 3, 5; *see also* Ex. 1009, Brewerton Dec., ¶ 117). Given the teachings of Grilo, a POSA would have understood that a reliable analysis for studying BED would involve assessing the number of large binge episodes and the number of days during which large binge episodes occurred, focusing on intervals of 28 days, i.e., about a month. (*See* Ex.1009, Brewerton Dec., ¶ 117). Thus, the combination of Ong in view of DSM-IV-TR, Mickle, and Grilo renders claim 11 obvious. (*See id.*).

Claim 11	Ong in view of DSM-IV-TR, Mickle, and Grilo
The method of claim 8, wherein the effective amount is an amount effective to decrease the number of binge eating episodes per month or decrease the number of days in a month in which the patient experiences a binge eating episode.	"These findings support the reliability of the EDE for patients with BED. The EDE has utility for assessing the number of large binge episodes (objective bulimic episodes), as well as the number of days during which large binge episodes occurred." (Ex.1025, Grilo, p.1, Abstract). "The EDE focuses on the previous 28 days . . . ." (*Id.* at 3; *see also id.* at 5).

H. Ground 7: Claims 1-5, 8-10, 12, and 13 Are Unpatentable Under 35 U.S.C. § 103(a) over Dukarm in View of DSM-IV-TR and Mickle

1. The Combination of Dukarm and DSM-IV-TR Teaches the Diagnosis of BED and Its Treatment Using d-Amphetamine

Dukarm presents case reports on the use of the stimulant dextroamphetamine (commonly referred to as "d-amphetamine") on six patients diagnosed with BN

and comorbid with ADHD, who experienced recurring binge eating. (*See* Ex.1019, Dukarm, pp.2-5). After administration of d-amphetamine "all of the 6 patients described reported complete abstinence from binge eating . . . ." (*Id.* at 5). Dukarm thus concluded that "these cases suggest the potential role of psychostimulants in the management of BN because of the **high rate of abstinence from bulimic symptoms** and the low rate of adverse side effects." (*Id.* at 6) (emphasis added).

At the time of the invention, and as described above, a POSA would have routinely relied on DSM-IV-TR, the charter document of the guidelines on mental disorders, for diagnosing a patient with BED. (*See supra* Section VI; Ex.1009, Brewerton Dec. ¶¶ 30, 120). DSM-IV-TR teaches that an essential feature of both BN and BED is "recurrent episodes of binge eating" (Ex.1010, DSM-IV-TR, pp.14, 18) and provides the same characterization of a binge eating episode with respect to the diagnosis of both BN and BED (*compare id.* at 14 *with id.* at 18). In fact, in the discussion of the "Diagnostic Features" of BED, DSM-IV-TR refers the reader to the section on BN: "[t]he characteristics of a binge episode are discussed in the text for Bulimia Nervosa . . . ." (*Id.* at 16).

Given the teachings of DSM-IV-TR, a POSA would have understood that the characteristics of binge eating episodes in BN and BED are essentially the same. (*See* Ex.1009, Brewerton Dec. ¶ 124). Further, since Dukarm discloses that

d-amphetamine administered to patients with BN resulted in abstinence from binge eating, a POSA would have had a reasonable expectation of success in treating BED with d-amphetamine. (*See id.*). Further, Dukarm highlights numerous studies that had already shown stimulants as a class to be effective in suppressing binge eating. (*See* Ex.1019, Dukarm, p.3; *see also* Ex.1009, Brewerton Dec. ¶¶ 39-45, 160-62). Thus, from Dukarm and DSM-IV-TR, a POSA would have learned to treat BED by diagnosing the patient according to DSM-IV-TR and administering d-amphetamine to the patient. (*See id.* ¶ 124).

2. Mickle Addresses the Specific Problem Raised by Dukarm Regarding the Use of d-Amphetamine

In considering the use of stimulants, Dukarm raises concerns about the "possible side effects of the medications and the risk of abuse of the medication," particularly in the context of a patient population already at "increased risk for substance abuse." (Ex.1019, Dukarm, p.6). Mickle solves this problem with the disclosure of amphetamine prodrugs that reduce the euphoric effects associated with amphetamine abuse. (Mickle, Ex.1023, ¶¶ [0114], [0355]-[0360]; *see also* Ex.1009 Brewerton Dec. ¶ 125).

Mickle teaches that the preferred amphetamine prodrug is LDX dimesylate. (*See* Ex.1023, Mickle ¶ [0098]). Following oral administration of LDX dimesylate, d-amphetamine—the same active ingredient shown by Dukarm to reduce binge eating—is released. (*See id.* ¶¶ [0085], [0358]). Mickle also teaches

methods for treating a patient including the administration of a therapeutically effective amount of an amphetamine prodrug, e.g., LDX dimesylate, sufficient to prevent, ameliorate, and/or eliminate the symptoms of a disease. (*See id.* ¶ [0124]).

3. Dukarm in View of DSM-IV-TR and Mickle Renders the Treatment of BED with LDX Dimesylate Obvious

Since Dukarm teaches that d-amphetamine successfully treated the binge eating of BN, and DSM-IV-TR provides that BN and BED share the common essential feature of binge eating, a POSA would have had a reasonable expectation of success in treating BED with d-amphetamine. But given the warning in Dukarm of the risk of stimulant abuse in a susceptible patient population, a POSA would have been motivated instead to use LDX dimesylate, a prodrug with reduced abuse potential that releases the same active agent used in Dukarm, namely d-amphetamine. (*See* Ex.1009, Brewerton Dec. ¶ 128). In light of the teachings of Dukarm, DSM-IV-TR, and Mickle, it would have been obvious at the time of the invention for a POSA to diagnose BED according to DSM-IV-TR and treat BED with LDX dimesylate. (*Id.* ¶ 129).

The combination of Dukarm, DSM-IV-TR, and Mickle renders claims 1-5, 8-10, 12, and 13 of the '813 patent obvious under 35 U.S.C. § 103(a). A claim chart for claim 1 is provided below.

Claim 1	Dukarm in view of DSM-IV-TR and Mickle
A method of treating Binge Eating Disorder, comprising	Dukarm reports a study of "6 patients with comorbid BN and ADHD who were treated with the stimulant medication, dextroamphetamine." (Ex.1019, Dukarm, p.3). "[A]ll of the 6 patients described reported complete abstinence from binge eating and purging following treatment with psychostimulants." (*Id.* at 5). "[T]hese cases suggest the potential role of psychostimulants in the management of BN because of the **high rate of abstinence from bulimic symptoms** and the low rate of adverse side effects." (*Id.* at 6) (emphasis added). DSM-IV-TR teaches that an "essential feature" of both BN and BED is "recurrent episodes of binge eating" (Ex.1010, DSM-IV-TR, pp.9, 14, 16, 18) and provides the same characterization of a binge eating episode with respect to the diagnosis of both BN and BED (*compare id.* at 14 *with id.* at 18). In the "Diagnostic Features" section for BED, DSM-IV-TR refers the reader to the section on BN: "[t]he characteristics of a binge episode are discussed in the text for Bulimia Nervosa . . . ." (*Id.* at 16).
diagnosing a patient as having Binge Eating Disorder, wherein the patient exhibits Binge Eating Disorder as defined in DSM-IV-TR	Six patients were diagnosed "with comorbid BN and ADHD . . . ." (Ex.1019, Dukarm, p.3). DSM-IV-TR provides diagnostic criteria for BED. (Ex.1010, DSM-IV-TR, pp.16-18).
and administering a therapeutically effective amount of lisdexamfetamine dimesylate to the patient	Dukarm notes "the risk of abuse" of stimulants and states that "[p]racticioners need to be aware of the potential for misuse of stimulant medication by individuals with eating disorders in an attempt at further weight loss." (*Id.* at 6). LDX dimesylate is a prodrug of amphetamine with reduced abuse potential. (*See, e.g.*, Ex.1023, Mickle,

Claim 1	Dukarm in view of DSM-IV-TR and Mickle
	¶¶ [0098], [0355]-[0360]). Following oral administration of LDX dimesylate, d-amphetamine is released. (*See id.* ¶¶ [0085], [0358]). "Amphetamines stimulate the central nervous system." (*Id.* ¶ [0003]; *see also id.* ¶ [0096]). "In one embodiment, the invention provides methods for treating a patient comprising administering a therapeutically effective amount of an amphetamine prodrug, i.e., an amount sufficient to prevent, ameliorate, and/or eliminate the symptoms of a disease." (*Id.* ¶ [0124]).
wherein the lisdexamfetamine dimesylate is the only active agent administered or is administered together with one or more additional active agents.	Mickle discloses administering LDX dimesylate alone. (*See id.* ¶¶ [0202]–[0211]). "The methods of treatment include combination therapies which further comprise administering one or more therapeutic agents in addition to administering an amphetamine prodrug." (*Id.* ¶ [0125]).

Claim 2 depends from claim 1 and further requires that 15 to 70 mg of LDX dimesylate be administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in a daily dose of about 10 mg to about 100 mg. (*See id.* ¶ [0153]). Thus, the combination of Dukarm in view of DSM-IV-TR and Mickle renders claim 2 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 130).

Claim 2	Dukarm in view of DSM-IV-TR and Mickle
The method of claim 1, wherein 15 to 70 mg lisdexamfetamine	"Tablets and other dosage forms provided in discrete units can contain a **daily dose** . . . . The dosage form can contain a dose of about 2.5 mg to about 500 mg, about 10 mg to about 250 mg, **about 10 mg to about 100 mg,**

Claim 2	Dukarm in view of DSM-IV-TR and Mickle
dimesylate is administered daily.	**about 25 mg to about 75 mg**, or increments therein of one or more of the amphetamine prodrugs. In a preferred embodiment, the dosage form contains 30 mg, 50 mg, or 70 mg of an amphetamine prodrug." (Ex.1023, Mickle ¶ [0153]) (emphasis added). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g., id.* ¶¶ [0348], [0353]).

Claim 3 depends from claim 1 and further requires that the LDX dimesylate be administered together with one or more other active agent(s). Mickle teaches methods of treatment that comprise a combination of one or more therapeutic agents in addition to an amphetamine prodrug, e.g., LDX dimesylate. (*See id.* ¶ [0125]). Thus, the combination of Dukarm in view of DSM-IV-TR and Mickle renders claim 3 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 131).

Claim 3	Dukarm in view of DSM-IV-TR and Mickle
The method of claim 1 wherein the lisdexamfetamine dimesylate is administered together with one or more other active agent(s).	"The methods of treatment include combination therapies which further comprise administering one or more therapeutic agents in addition to administering an amphetamine prodrug." (Ex.1023, Mickle ¶ [0125]).

Claim 4 depends from claim 3 and further requires that the one or more other active agent(s) be of a drug class recited in the claim. The claim includes SSRIs, which can often be used as antidepressants. (*See* Ex.1009, Brewerton Dec. ¶ 132). DSM-IV-TR states that "[s]ome individuals report that binge eating is

triggered by dysphoric moods, such as depression and anxiety" (Ex.1010, DSM-IV-TR, p.17), which suggests the need for combination drug therapy with antidepressants. (*See* Ex.1009, Brewerton Dec. ¶ 132). Further, Mickle teaches the combination of an amphetamine prodrug, such as LDX dimesylate, with antidepressants, including SSRIs. (*See* Ex.1023, Mickle ¶ [0125], Table 1). Thus, the combination of Dukarm in view of DSM-IV-TR Mickle renders claim 4 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 132).

Claim 4	**Dukarm in view of DSM-IV-TR and Mickle**
The method of claim 3, wherein the one or more other active agent(s) is . . . a selective serotonin reuptake inhibitor, ...	"Some individuals report that binge eating is triggered by dysphoric moods, such as depression and anxiety." (Ex.1010, DSM-IV-TR, p.17). Mickle discloses that "[e]xemplary drug therapies contemplated for use in combination with an amphetamine prodrug" include "Antidepressant (SSRI . . . .)" (Ex.1023, Mickle ¶ [0125], Table 1).

Claim 5 depends from claim 4 and further requires that the other active agent can be fluoxetine or sertraline, among others. DSM-IV-TR states that "[s]ome individuals report that binge eating is triggered by dysphoric moods, such as depression and anxiety" (Ex.1010, DSM-IV-TR, p.17), which suggests the need for combination drug therapy with antidepressants. (*See* Ex.1009, Brewerton Dec. ¶ 133). Further, Mickle teaches the combination of an amphetamine prodrug, such as LDX dimesylate, with the antidepressants fluoxetine and sertraline. (*See* Ex.1023, Mickle ¶ [0125], Table 1). Thus, the combination of Dukarm in view of

DSM-IV-TR and Mickle renders claim 5 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 133).

Claim 5	Dukarm in view of DSM-IV-TR and Mickle
The method of claim 4, wherein the other active agent is . . . fluoxetine, . . . sertraline, . . . reboxetine, . . . bupropion, . . . amisulpride, ...	"Some individuals report that binge eating is triggered by dysphoric moods, such as depression and anxiety." (Ex.101, DSM-IV-TR, p.17). Mickle discloses that "[e]xemplary drug therapies contemplated for use in combination with an amphetamine prodrug" includes the following: "Fluoxetine (e.g., Prozac®), Zoloft® [sertraline] . . . ." (Ex.1023, Mickle ¶ [0125], Table 1).

Independent claim 8 is identical to claim 1 except that claim 8 does not encompass the administration of LDX dimesylate together with one or more additional active agents. Instead, claim 8 is limited to the administration of LDX dimesylate as the only active agent administered. Thus, for the reasons outlined above for claim 1, the combination of Dukarm in view of DSM-IV-TR and Mickle renders claim 8 obvious under 35 U.S.C. § 103(a). (*See* Ex.1009, Brewerton Dec. ¶ 134).

Claim 9 depends from claim 8 and further requires that from 2.5 to 200 mg of LDX dimesylate be administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in a daily dose of about 2.5 mg to about 500 mg, or about 10 mg to about 250 mg. (*See* Ex.1023, Mickle ¶ [0153]). Thus, the combination of Dukarm in view of DSM-IV-TR and Mickle renders claim 9 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 135).

Claim 9	Dukarm in view of DSM-IV-TR and Mickle
The method of claim 8 wherein from 2.5 to 200 mg of lisdexamfetamine dimesylate is administered daily.	"Tablets and other dosage forms provided in discrete units can contain a **daily dose** . . . . The dosage form can contain a dose of **about 2.5 mg to about 500 mg, about 10 mg to about 250 mg**, about 10 mg to about 100 mg, about 25 mg to about 75 mg, or increments therein of one or more of the amphetamine prodrugs. In a preferred embodiment, the dosage form contains 30 mg, 50 mg, or 70 mg of an amphetamine prodrug." (Ex.1023, Mickle ¶ [0153]) (emphasis added). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g., id.* ¶¶ [0348], [0353]).

Claim 10 depends from claim 8 and further requires that from 15 to 100 mg of LDX dimesylate be administered once per day. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in a dose of about 10 mg to about 100 mg, administered once daily. (*See id.* ¶ [0153]). Thus, the combination of Dukarm in view of DSM-IV-TR and Mickle renders claim 10 obvious. (*See* Ex.1009, Brewerton Dec. ¶ 136).

Claim 10	Dukarm in view of DSM-IV-TR and Mickle
The method of claim 8, wherein 15 to 100 mg lisdexamfetamine dimesylate is administered once per day.	"The dosage form can contain a dose of about 2.5 mg to about 500 mg, about 10 mg to about 250 mg, **about 10 mg to about 100 mg**, about 25 mg to about 75 mg, or increments therein of one or more of the amphetamine prodrugs. In a preferred embodiment, the dosage form contains 30 mg, 50 mg, or 70 mg of an amphetamine prodrug." (Ex.1023, Mickle ¶ [0153]) (emphasis added). "Preferably, a single dose is administered **once daily**." (*Id.* ¶ [0155]) (emphasis added). Mickle also provides for administration of LDX

Claim 10	Dukarm in view of DSM-IV-TR and Mickle
	dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g., id.* ¶¶ [0348], [0353]).

Claim 12 depends from claim 8 and further requires that 15 to 70 mg of LDX dimesylate be administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in a daily dose of about 10 mg to about 100 mg. (*See id.* ¶ [0153]). Thus, the combination of Dukarm in view of DSM-IV-TR and Mickle renders claim 12 obvious. (See Ex.1009, Brewerton Dec. ¶ 137).

Claim 12	Dukarm in view of DSM-IV-TR and Mickle
The method of claim 8, wherein 15 to 70 mg lisdexamfetamine dimesylate is administered daily.	"Tablets and other dosage forms provided in discrete units can contain a **daily dose** . . . . The dosage form can contain a dose of about 2.5 mg to about 500 mg, about 10 mg to about 250 mg, **about 10 mg to about 100 mg**, about 25 mg to about 75 mg, or increments therein of one or more of the amphetamine prodrugs. In a preferred embodiment, the dosage form contains 30 mg, 50 mg, or 70 mg of an amphetamine prodrug." (Ex.1023, Mickle ¶ [0153]) (emphasis added). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g., id.* ¶¶ [0348], [0353]).

Independent claim 13 is identical to claim 1 except there is no requirement for diagnosing a patient as having BED. Thus, for the reasons outlined above for claim 1, the combination of Dukarm in view of DSM-IV-TR and Mickle renders claim 13 obvious under 35 U.S.C. § 103(a). (*See* Ex.1009, Brewerton Dec. ¶ 138).

I. Ground 8: Claims 6 and 7 Are Unpatentable Under 35 U.S.C. § 103(a) over Dukarm in View of DSM-IV-TR, Mickle, and Marrazzi

Claim 6 depends from claim 5 and further requires that the other active agent administered together with LDX dimesylate be orlistat, naltrexone, zonisamide, or pharmaceutically acceptable salts thereof, while claim 7 depends from claim 6 and further requires that the other active agent administered together with LDX dimesylate be naltrexone. Marrazzi provides that naltrexone was administered to a patient having BED, yielding positive results. (*See* Ex.1024, Marrazzi, p.2, Abstract). Additionally, Mickle teaches the combination of an amphetamine prodrug, such as LDX dimesylate, with another therapeutic agent. (*See* Ex.1023, Mickle ¶ [0125]). As such, a POSA would have had a reasonable expectation of success that LDX dimesylate administered with a known BED agent, naltrexone, would treat BED. (*See* Ex.1009, Brewerton Dec., ¶ 139). Thus, the combination of Dukarm in view of DSM-IV-TR, Mickle, and Marrazzi renders claims 6 and 7 obvious. (*See id.*).

Claims 6 and 7	Dukarm in view of DSM-IV-TR, Mickle, and Marrazzi
6. The method of claim 5, wherein the other active agent is . . . naltrexone	"We report here a response to naltrexone in a subject with BED . . . . Symptoms were reduced in the naltrexone compared to placebo period." (Ex.1024, Marazzi, p.2, Abstract).
7. The method of claim 6, wherein the other active	"The methods of treatment include combination therapies which further comprise administering one or more therapeutic agents in addition to administering an

Claims 6 and 7	Dukarm in view of DSM-IV-TR, Mickle, and Marrazzi
agent is naltrexone.	amphetamine prodrug." (Ex.1023, Mickle ¶ [0125]).

J. Ground 9: Claim 11 Is Unpatentable Under 35 U.S.C. § 103(a) over Dukarm in View of DSM-IV-TR, Mickle, and Grilo

Claim 11 depends from claim 8 and further requires that the effective amount be an amount effective to decrease the number of binge eating episodes per month or decrease the number of days in a month in which the patient experiences a binge eating episode. Grilo describes that the EDE is a reliable examination for patients with BED that involves assessing the number of large binge episodes as well as the number of days during which large binge episodes occurred. (*See* Ex.1025, Grilo, p.1, Abstract). The EDE focuses on 28-day durations of examinations. (*See id.* at 3, 5; *see also* Ex.1009, Brewerton Dec., ¶ 140). Given the teachings of Grilo, a POSA would have understood that a reliable analysis for studying BED would involve assessing the number of large binge episodes and the number of days during which large binge episodes occurred, focusing on intervals of 28 days, i.e., about a month. (*See* Ex.1009, Brewerton Dec., ¶ 140). Thus, the combination of Dukarm in view of DSM-IV-TR, Mickle, and Grilo renders claim 11 obvious. (*See id.*).

Claim 11	Dukarm in view of DSM-IV-TR, Mickle, and Grilo
The method of claim 8, wherein the effective	"These findings support the reliability of the [EDE] for patients with BED. The EDE has utility for assessing the number of large binge episodes (objective bulimic

Claim 11	Dukarm in view of DSM-IV-TR, Mickle, and Grilo
amount is an amount effective to decrease the number of binge eating episodes per month or decrease the number of days in a month in which the patient experiences a binge eating episode.	episodes), as well as the number of days during which large binge episodes occurred." (Ex.1025, Grilo, p.1, Abstract). "The EDE focuses on the previous 28 days . . . ." (*Id.* at 3; *see also id.* at 5).

X. APPLICANT'S ARGUMENTS DURING PROSECUTION DO NOT DEMONSTRATE NONOBVIOUSNESS OF THE CLAIMS

Petitioner's Grounds 7-9 allege obviousness of claims 1-13 based primarily upon Dukarm in view of Mickle. During prosecution, the Examiner also relied on Dukarm when rejecting as obvious an earlier set of claims similar to the issued claims. (*See* Ex.1003, July 2011 OA, pp.5-6). However, the Examiner did not rely on Mickle; rather the Examiner relied on Mickle 2005 (which is a related patent publication, *see supra* Section IX.A.2).

The Examiner stated that Dukarm's teaching of treating the binge eating in BN with d-amphetamine could be applied to treating BED, while also noting Dukarm's caution that stimulants have abuse potential. (*See* Ex.1003, July 2011 OA, pp.5-6). The Examiner then relied on Mickle 2005 for teaching abuse-resistant amphetamine prodrugs that release d-amphetamine, concluding that it would have been obvious to modify the teachings of Dukarm by providing LDX to

a patient diagnosed with BED. (*Id*). Applicant made claim amendments and rebutted the rejection on multiple grounds (*see* Ex.1004, Jan. 2012 Resp., p.6-12), and the rejection was withdrawn (*see* Ex.1005, Apr. 2012 OA, p.4). Presented below are reasons why Applicant's arguments do not detract from Petitioner's Grounds 7-9 that rely on Dukarm in view of Mickle to demonstrate obviousness of the claims. (*See also* 1009, Brewerton Dec. ¶¶ 145-65).

A. A POSA Would Have Extended Dukarm's Teachings of the Use of Stimulants in the Treatment of BN to the Treatment of BED

In dismissing Dukarm, Applicant alleged that because BN and BED are separate disorders with different courses and outcomes, a POSA would not have been motivated to extend Dukarm's teachings about BN to BED. (*See* Ex.1004, Jan. 2012 Resp., pp.8-9). However, as discussed in detail above, the binge eating symptom of BN and BED is strikingly similar, so much so that DSM-IV-TR provides the same diagnostic criteria for the binge eating of both disorders. (*See supra* Section VI, pp.5-6, Section IX.H.1, pp.39-40, Ex.1009, Brewerton Dec. ¶¶ 36-38). Accordingly, a POSA would have had a reasonable expectation of success in applying Dukarm's teachings to the treatment of BED. (*See* Ex.1009, Brewerton Dec. ¶ 124).

In support of its position Applicant raised an article, Fairburn 2000 (Ex.1027). (*See id.*). But Applicant's reliance on Fairburn 2000 is misplaced. (*See id.* ¶¶ 147-151). Although Fairburn 2000 concludes that BN and BED have

different courses and outcomes, it does not suggest that different treatments are needed. (Ex.1027, Fairburn 2000, p.6). In fact, a subsequent publication, Fairburn 2003, discusses that common mechanisms are involved in the persistence of eating disorders (including BN and atypical eating disorders such as BED) and thus, "[t]he patient's specific eating disorder disagnosis is not relevant to the treatment." (Ex.1028, Fairburn 2003, p.14).

Applicant also argued that because the patients in Dukarm had both ADHD and BN, it was impossible to know which disorder was being treated, thereby dissuading a POSA from applying the results of Dukarm to BED. (*See* Ex.1004, Jan. 2012 Resp., pp.9-10). This argument is unpersuasive, particularly because **Dukarm itself** lays out a chronological summary of the prior successful use of stimulants in the treatment of binge eating, in both comorbid patients and those presenting with only BN. (*See* Ex.1019, Dukarm, p.3). In reading Dukarm, a POSA would have viewed its unequivocal, positive results in light of the prior successful use of stimulants in treating binge eating. (*See* Ex.1009, Brewerton Dec. ¶¶ 160-61). Notably, during prosecution, Dukarm's chronology of the prior successful use of stimulants for binge eating was not considered. For at least these reasons, the comorbidity of the patients in Dukarm would not have deterred a POSA from extending the results of Dukarm to BED. (*See id.* ¶¶154-59).

Finally, Applicant took the position that, in general, drugs useful for treating BN are not necessarily effective for treating BED. (*See* Ex.1004, Jan. 2012 Resp., pp.10-11). This argument was based solely on a single publication (Grilo 2005), which concluded that fluoxetine was not superior to placebo in the treatment of BED. (*See id.*). The Applicant compared these results to an unrelated study that reported efficacy of fluoxetine in the treatment of BN. (*See id.*) Despite the findings in Grilo 2005, a POSA would have been aware of countervailing data demonstrating positive results for fluoxetine in the treatment of BED. (*See e.g.*, Ex.1030, Arnold, p.2, Abstract; *see also* Ex.1009, Brewerton Dec. ¶ 163). A POSA would have also been aware of treatment guidelines suggesting the use of antidepressants, particularly SSRIs such as fluoxetine, for the treatment of BED. (*See* Ex.1031, Practice Guideline, pp.21, 56, 86; Ex.1032, NICE, p.20). Thus, the Applicant's argument that treatments for BN, such as Dukarm's use of d-amphetamine, cannot be applied with any reasonable expectation of success to the treatment of BED is unfounded. (*See* Ex.1009, Brewerton Dec. ¶¶ 163-65).

B. Given the Positive Attributes of LDX Dimesylate, a POSA Would Have Been Motivated to Use It to Treat BED

As stated above, while Petitioner's Grounds 7-9 rely on Mickle, during prosecution of the '813 patent the Examiner relied on a related patent publication, Mickle 2005. The Examiner used Mickle 2005 for its disclosure of abuse-resistant amphetamine prodrugs, specifically LDX. (*See* Ex.1003, July 2011 OA, p.7). The

Examiner noted that Mickle 2005 discloses the pharmacokinetics of the amphetamine prodrugs, which "provide[] a therapeutically bioequivalent area under the curve (AUC) but do[] not provide a maximal concentration which results in euphoria (paragraph [0034] and [0179])." (*Id.*).

In response, Applicant argued that a POSA would not have reasonably expected the LDX dimesylate of Mickle 2005 to provide the same benefits as the d-amphetamine of Dukarm because: (1) LDX dimesylate is long-acting, with markedly different pharmacokinetic properties from short-acting d-amphetamine given three times daily; and (2) LDX dimesylate and d-amphetamine have different appetite-suppressant properties. (*See* Ex.1004, Jan. 2012 Resp., pp.11-12). Neither of these arguments regarding Mickle 2005 minimize Petitioner's grounds of obviousness relying on Mickle. (*See* Ex.1009, Brewerton Dec. ¶¶ 166-75).

As an initial matter, Applicant distinguished LDX dimesylate from the d-amphetamine of Dukarm by suggesting that the former is long-acting while the latter is short-acting. Yet a POSA would have recognized that administering a short-acting stimulant three times a day (Dukarm) does not necessarily result in markedly different pharmacokinetic properties as compared to a long-acting stimulant (Mickle). (*See* Ex.1023, Mickle ¶¶ [0226]-[0227]; *see also* Ex.1009, Brewerton Dec. ¶ 167). In addition, the overwhelmingly positive attributes of the pharmacokinetics of LDX dimesylate described by Mickle (e.g., bioequivalent

AUC, decreased Cmax, minimal food effect, no gender differences) would have motivated a POSA to use LDX dimesylate in place of d-amphetamine in the treatment of binge eating. (*See* Ex.1009, Brewerton Dec. ¶¶ 171-73).

Further, a POSA would not have viewed the different rates of appetite suppression of d-amphetamine and LDX dimesylate as a deterrent to the use of LDX dimesylate in BED. Rather, the report of decreased appetite in 39% of ADHD patients receiving LDX dimesylate, together with obesity being one of Mickle's preferred indications for this prodrug, would have provided a POSA with motivation and a reasonable expectation of success for the use of LDX dimesylate for the treatment of BED. (*See id.* ¶ 174).

XI. SECONDARY CONSIDERATIONS ARGUED BY APPLICANT DURING PROSECUTION DO NOT REFUTE OBVIOUSNESS

During prosecution of the application that led to the '813 patent, the Applicant alleged (i) surprising and unexpected results and (ii) long-felt but unmet need. (*See* Ex.1006, June 2012 Resp., pp.8-15). None of the evidence provided by the Applicant supports either argument.

A. Examples 1, 2, and 5 of the '813 Patent Do Not Demonstrate that LDX Dimesylate Shows Surprising and Unexpected Efficacy for Treating BED

A POSA would have expected LDX dimesylate to be an effective treatment for BED because it was well understood in the art that centrally acting stimulants successfully treat binge eating. (*See* Ex.1009, Brewerton Decl., ¶¶ 176-183). Any

clinical data demonstrating the efficacy of LDX dimesylate for BED thus would not have been surprising to a POSA.

By contrast, Applicant asserted that the data of Examples 1, 2, and 5 of the '813 patent demonstrated surprising and unexpected results. (*See* Ex.1006, June 2012 Resp., pp.8-10). Regarding Example 1, the patient presented with comorbid disorders, including BED. (Ex.1001, '813 patent, col.19-20, Example 1). The successful use of LDX dimesylate to treat the BED was far from surprising, given the numerous prior-art disclosures that demonstrate the effective treatment of binge eating with stimulants. (*See* Ex.1009, Brewerton ¶ 178).

The patient in example 2 of the '813 patent was administered LDX dimesylate to address the late-day "wear-off" effect of another stimulant, Adderall XR, which was given to treat ADHD. (Ex.1001, '813 patent,col.20, ll.52-55). Binge eating was occurring in the evening (i.e., during the "wear-off" period), and was not addressed by Adderall XR. (*See id.*, col.20, ll.59-60). Not surprisingly, LDX dimesylate, a long-acting stimulant, addressed both the daytime and evening symptoms of ADHD and BED. (*See* Ex.1009, Brewerton Dec., ¶ 180).

Finally, the patient in Example 5 was treated with 17 different medications, including a stimulant, before being given LDX dimesylate. (Ex.1001, '813 patent, col.23, ll.48-66). It is not surprising, particularly in such a complex case, that the

patient would be responsive to one stimulant and not another. (*See* Ex.1009, Brewerton Dec., ¶¶ 182-83).

In view of what a POSA would have known at the time of the invention, none of the Examples in the '813 patent demonstrate surprising and unexpected results.

B. Applicant's Arguments Regarding Long-Felt Need Do Not Support Nonobviousness

According to Applicant, there was a long-felt and unmet need for a BED treatment, because BED is the most common eating disorder and there were no FDA approved treatments. (*See* Ex.1006, June 2012 Resp., p.14). But there is difference between "no FDA-approved treatments" and "no treatments." (*See* Ex. 1009, Brewerton Dec. ¶¶ 185-187). At the time of the invention, and even before, there were "off-label" options for the treatment of BED. (*See id.*; *see also* Ex.1020, Appolinario, p.1, Abstract). In fact, the American Psychiatric Association promoted the off-label use of antidepressants as well as CBT for the treatment of BED. (*See* Ex.1031, Practice Guideline, pp.21, 56, 85-86).

But even assuming that there was a long-felt but unmet need for a treatment for BED, this evidence is entitled to little or no weight here. This is not a situation in which LDX dimesylate had been around for years and nobody thought to use it for treating BED. Rather, LDX dimesylate did not come to market until June 2007—only three months before the earliest claimed filing date of the '813 patent.

(*See* Ex.1033, Shire PR, p.9). Simply put, given the short timeframe between the launch of Vyvanse and the alleged invention of the '813 patent, "long-felt but unmet need" does not support nonobviousness here.

XII. CONCLUSION

Accordingly, Petitioner respectfully requests institution of IPR for claims 1-13 of the '813 patent on each of the grounds presented herein.

Respectfully submitted,
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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.8(e) and 42.105(b), the undersigned certifies that on May 9, 2014, a complete and entire copy of this Petition for Inter Partes Review and all supporting exhibits and any other motions or filings were provided via Federal Express, costs prepaid, to the Patent Owner by serving the correspondence address of record as follows:

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