



Therapeutic Class ReviewSM

Behavior Modification – lisdexamfetamine (VyvanseTM)

September 2007

New Product for Review:

Lisdexamfetamine (VyvanseTM) [Shire]

Dossier Provided by Manufacturer:

Dossier Evaluation: 2

- 1- dossier w/missing components
- 2- all components present, except pharmacoeconomic model
- 3- all components present (comprehensive)

Available Therapeutic Alternatives:

Preferred/Formulary	Non-Preferred/Non-Formulary
<i>Methylphenidate and derivatives</i>	
methylphenidate tablet, (Ritalin [®]) – generic	dexmethylphenidate (Focalin TM) [Novartis]
methylphenidate ER tablet (Ritalin SR [®]) – generic	dexmethylphenidate extended-release (Focalin TM XR) [Novartis]
methylphenidate ER capsules (Metadate [®] CD) [UCB]	methylphenidate ER capsules (Ritalin LA [®]) [Novartis]
	methylphenidate transdermal system (Daytrana TM) [Shire]
	methylphenidate chewable tabs, oral solution (Methylin [®]) [Alliant]
	methylphenidate extended release tablets (Concerta [®]) [McNeil]
<i>Amphetamines and derivatives</i>	
dextroamphetamine tablet (Dexedrine [®]) – generic	methamphetamine (Desoxyn [®]) [Ovation Pharma]
dextroamphetamine SR capsule (Dexedrine [®] Spansule [®]) – generic	lisdexamfetamine (Vyvanse TM) [Shire]
amphetamine/dextroamphetamine tablet (Adderall [®]) – generic	
amphetamine/dextroamphetamine SR Capsule (Adderall [®] XR) [Shire]	
<i>Other</i>	
	atomoxetine (Strattera [®]) [Eli Lilly]

* Covered with prior authorization

Executive Summary

- Lisdexamfetamine (Vyvanse) is a pro-drug of dextroamphetamine. Lisdexamfetamine (Vyvanse) has no demonstrable activity in either *in vitro* assays or *in vivo* animal data. ^[2,12]
- After oral administration, lisdexamfetamine (Vyvanse) is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine, which is responsible for the drug's activity. ^[2,12]
- In their clinical review for approval, the FDA noted the small number of patients exposed to lisdexamfetamine (Vyvanse) during the development program (n=272). ^[2,12]
 - The FDA considers lisdexamfetamine (Vyvanse) to be a prodrug for d-amphetamine, a compound which has a substantial safety history.
 - Approval was based on superior efficacy compared to placebo in the two randomized controlled trials (RCTs).
- Based on submitted pharmacokinetic trials, the FDA assessed lisdexamfetamine (Vyvanse) to have a similar time-concentration profile to amphetamine/dextroamphetamine SR (Adderall XR). ^[2,12]
 - The AUC and C_{max} for d-amphetamine from 75 mg of lisdexamfetamine (Vyvanse) was comparable to both d-amphetamine and l-amphetamine from 35 mg of amphetamine/dextroamphetamine SR (Adderall XR).
 - There has been no trials to help correlate differences in pharmacokinetic profiles with improved clinical effects.
- Both the FDA and DEA were unconvinced that lisdexamfetamine (Vyvanse) had lower abuse potential due to similarity to d-amphetamine in: ^[2,13]
 - Pharmacokinetic and adverse event profiles.
 - Similar “rewarding” effects.
 - Psychological dependence and tolerance.

Evidence

- There is no useful evidence to show an advantage of lisdexamfetamine (Vyvanse) over existing preferred/formulary treatment options for the management of patients with ADHD.
 - Efficacy and safety appears to be similar to dextroamphetamine.
 - Despite claims of reduced abuse potential, lisdexamfetamine (Vyvanse) was designated a schedule II controlled substance by the DEA, and no useful evidence was found to support a claim of reduced abuse potential.

Considerations in Subpopulations:³

- **Pediatrics:** Lisdexamfetamine (Vyvanse) is indicated for use in children aged 6 to 12 years.
- **Geriatrics:** Lisdexamfetamine (Vyvanse) has not been studied in the geriatric population.
- **Gender:** Systemic exposure to dextroamphetamine is similar for men and women given the same g/kg dose.
- **Race, ethnicity:** There is no information to indicate that the safety or efficacy of lisdexamfetamine differs between individuals due to race or ethnicity.

Product Value

Lisdexamfetamine (Vyvanse) offers another stimulant treatment option for the management of children aged 6 to 12 years with ADHD. However, there is no useful evidence that lisdexamfetamine (Vyvanse) offers any clinical advantages over preferred/formulary stimulant medications for the treatment of ADHD.

Conclusion

Lisdexamfetamine (Vyvanse) is non-preferred/non-formulary because there is no evidence that it offers superior safety or efficacy over currently available preferred/formulary d-amphetamine products.

Products

Drug Products ¹⁻³	FDA approval ^a	Patent Expiration(s) ^c	FDA approved indications	Usual Dose/Route	Cost ^b	Potential Off-label Uses ^c
dexamethylphenidate Focalin [®] Focalin XR [®]	11/2001 05/2005	12/2015 12/2019	- ADHD	5 mg PO BID 10 mg PO QD	\$59 \$118	- none listed – likely similar to methylphenidate
methylphenidate Methylin [®] Ritalin [®]	04/2003 12/1955		- ADHD - Narcolepsy	10 mg PO BID	\$9	- autism - bipolar disorder: adjunct - bulimia nervosa - cancer – fatigue, depression, pain, brain tumors - cerebral palsy – adjunct
methylphenidate extended release tablets Metadate ER Methylin ER Ritalin SR [®] Concerta [®]	10/1999 05/2000 03/1982 08/2000	04/2008	- ADHD - Narcolepsy (except for Concerta)	40 mg PO QD 36 mg PO QD	\$48 \$128	- cocaine dependence - dementia - depression - epilepsy - fatigue - hiccoughs, intractable - impaired cognition - paraphilia – adjunct - schizophrenia - traumatic brain injury
methylphenidate extended release capsules Metadate CD [®] Ritalin LA [®]	04/2001 06/2002	10/2020 11/2019	- ADHD	40 mg PO QD	\$154 \$107	
methylphenidate transdermal system Daytrana [®]	04/2006	9/2018	- ADHD	10 mg – 30 mg / 9 hrs QD	\$149	
amphetamine salt combo Adderall [®]	01/1960	N/A	- ADHD - Narcolepsy	10 mg PO BID	\$13	- cerebrovascular accident - hiccoughs
amphetamine salt combo extended release Adderall XR [®]	10/2001	01/2009	- ADHD - Narcolepsy	10 mg to 30 mg PO QD	\$128	
dextroamphetamine (Dexedrine [®] , Dextrostat [®])	05/1975	N/A	- ADHD - Narcolepsy	10 mg PO BID	\$15	- cocaine dependence - depression - mania - schizophrenia - sleep deprivation
dextroamphetamine sustained release Dexedrine Spansules	08/1976	N/A	- ADHD - Narcolepsy	20 mg PO QD	\$43	
methamphetamine Desoxyn [®]	12/1943	N/A	- ADHD - Exogenous Obesity	10 mg PO BID	\$343	- none listed
atomoxetine Strattera [®]	11/2002	11/2016	- ADHD	80 mg PO QD	\$161	- nocturnal enuresis
lisdexamfetamine Vyvanse [®]	6/2023		- ADHD	30 mg to 70 mg PO QD	\$128	- none listed

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b Cost estimate based on AWP (average wholesale price) listed in First Data Bank or MAC (maximum allowable cost) as of July 2007 for 1 month of therapy.

^c As listed in © 1974 - 2005 Thomson MICROMEDEX database or as referenced.

ADHD = Attention deficit disorders/Attention deficit hyperactivity disorder, QD = once daily, BID = twice daily

Product Indications And Release Patterns

Extended or Sustained Release Products	Indicated Patient Population		Release Profile (%IR/%SR)
	Pediatric	Adult	
methylphenidate ER tablet (Metadate ER, Methylin ER, Ritalin SR [®])	✓	✓	0/100
Metadate CD	✓	✓	30/70
Ritalin LA	✓		50/50
Concerta	✓		22/78
Daytrana	✓		0/100
Adderall XR	✓	✓	50/50
dextroamphetamine XR Capsules (Dexedrine XR, generic)	✓		0/100
Focalin XR	✓	✓	50/50
Vyvanse	✓		Not an SR dosage form.

References

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