Vyvanse®
(lisdexamfetamine dimesylate) capsules
30 • 50 • 70 mg

הפרו-דראג היחיד
לאיזון תסמיני ADHD[1]*

13hr[2]

20:00

07:00**

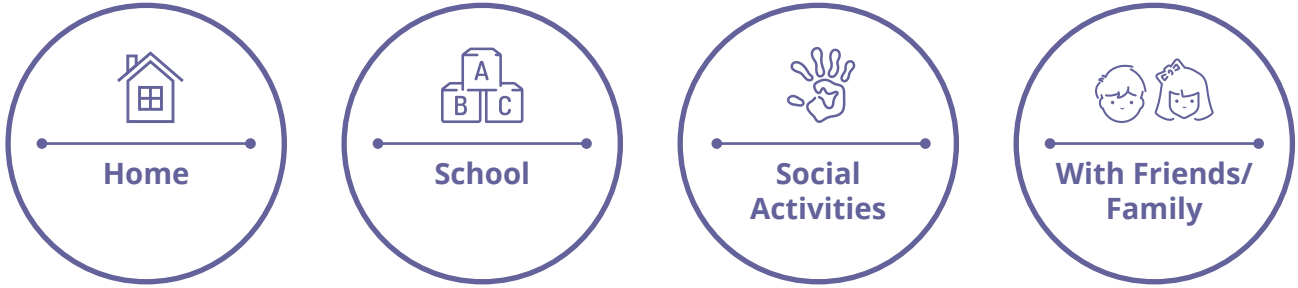
*Vyvanse controls ADHD (Attention Deficit Hyperactive Disorder) symptoms for up to 13 hours post-dose in children and up to 14 hours post-dose in adults ** Dose taken at 7:00
Indication: Vyvanse Is A Central Nervous System (CNS) Stimulant Indicated For The Treatment Of Attention Defiit Hyperactive Disorder (Adhd) In Patients Ages 6 Years And Above | For further information (including side effects) please read the PI as approved by the Israel MOH
Reference: 1. Goodman DW, Psychiatry (Edgmont). 2007 Aug; 4(8):39-45.

MEDISON
Delivering Innovative Healthcare

Shire

ADHD SYMPTOMS

MAY VARY DEPENDING ON THE CONTEXT OF A GIVEN SETTING[1]



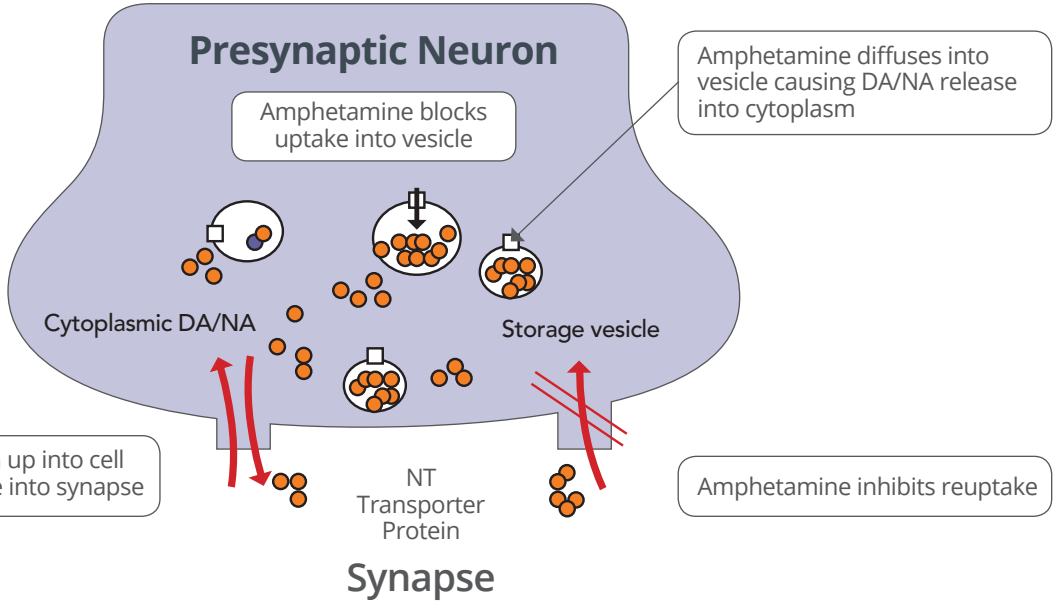
ADHD symptoms may be more evident in situations where a patient is not interested, engaged, or closely supervised[1]

▶ Several symptoms must be present in 2 or more settings

NOTE: These are not the complete diagnostic criteria. Diagnosis should be based on a complete history and evaluation of the patient by a trained ADHD specialist.

Reference:
1. American Psychiatric Association. Attention-deficit and disruptive behavior disorders. In: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5®). Arlington, VA: American Psychiatric Association; 2013:59-65.

AMPHETAMINES
MECHANISM OF ACTION

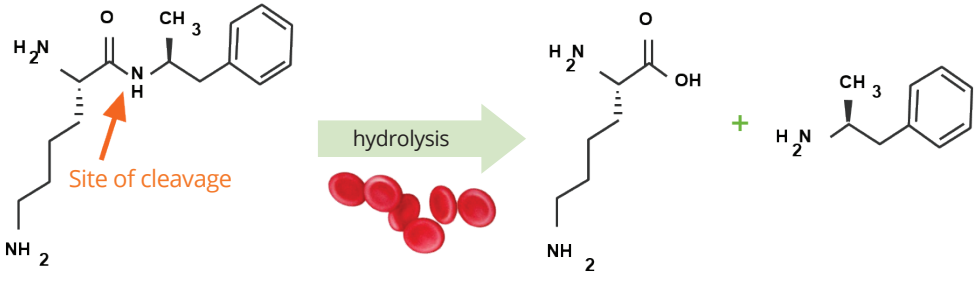


MPH=Methylphenidate
NT= Neurotransmitter
NA=Noradrenaline
DA= Dopamine
Adapted from Wilens & Spencer
Neurobehavioral Pharmacology 1998; 501-513

Reference:
1. Goodman DW, Psychiatry (Edgmont). 2007 Aug; 4(8):39-45

VYVANSE:
THE ONLY PRO-DRUG STIMULANT[1]

Vyvanse is a pharmacologically inactive prodrug, which is enzymatically converted in-vivo to the active stimulant d-amphetamine and l-lysine[2]



lisdexamfetamine dimesylate
Prodrug

/-lysine

d-amphetamine
Active Drug

Pro-drug technology was designed to enhance the attributes of the active drug, E.G.[3]:

- Enhanced solubility
- Increased/enhanced absorption and distribution
- Prolonged systemic availability

Reference:
1. Goodman DW, Psychiatry (Edgmont). 2007 Aug; 4(8):39-45.
2. Stanczak A, Ferra A. Pharmacol Rep 2006; 58: 599–613.
3. Ettmayer P et al. J Med Chem 2004; 47: 2393–2404.

VYVANSE:
SUSTAINED EFFICACY WITH CONVENIENT ADMINISTRATION

Efficient delivery of d-amfetamine

- Enzymatically controlled bioconversion to d-amfetamine in the blood[1]
- Rapid absorption, not pH-dependent[2-5]
- Low inter- and intra-patient variability in pharmacokinetic parameters[1,3]

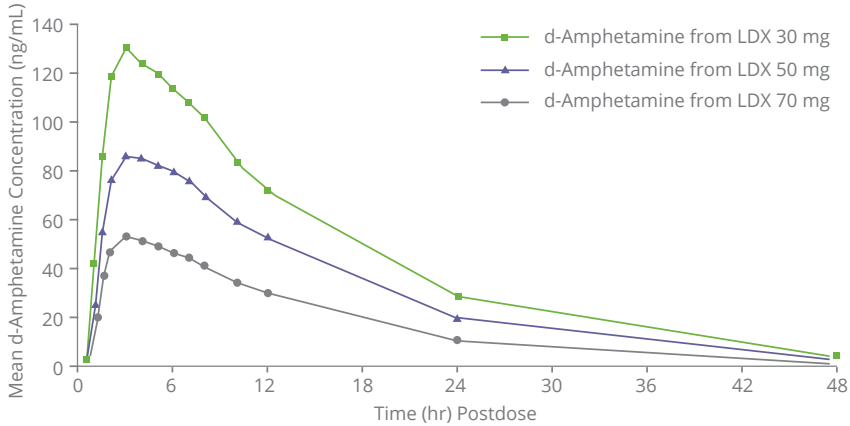
Low potential for drug-drug interaction[2]

- Vyvanse does not undergo CYP-450 mediated metabolism

Easy Administration[2]

- Once-daily dose. Vyvanse provides proven long duration of action (up to 13 post dose)
- Can be taken as whole or capsule can be opened and dissolved in water, orange juice or yogurt
- Not influenced by food intake

MEAN PLASMA CONCENTRATION TIME PROFLLES OF D-AMPHETAMINE



Reference:
1. Boellner SW et al. Clin Ther 2010; 32: 252–264.
2. Vyvanse Prescribing Information approved by MoH, 2014.
3. Ermer JC et al. J Clin Pharmacol 2010; 50: 1001–1010.
4. Krishnan SM et al. Clin Drug Invest 2008; 28(12): 745–755.
5. Shojaei A et al. Poster presented at the 2007 American Psychiatric Association Annual Meeting, San Diego, CA, USA, 19–24 May 2007.

THE ONLY PRODRUG THAT CONTROLS ADHD SYMPTOMS[1]

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Reference:
1. Goodman DW, Psychiatry (Edgmont). 2007 Aug; 4(8):39-45

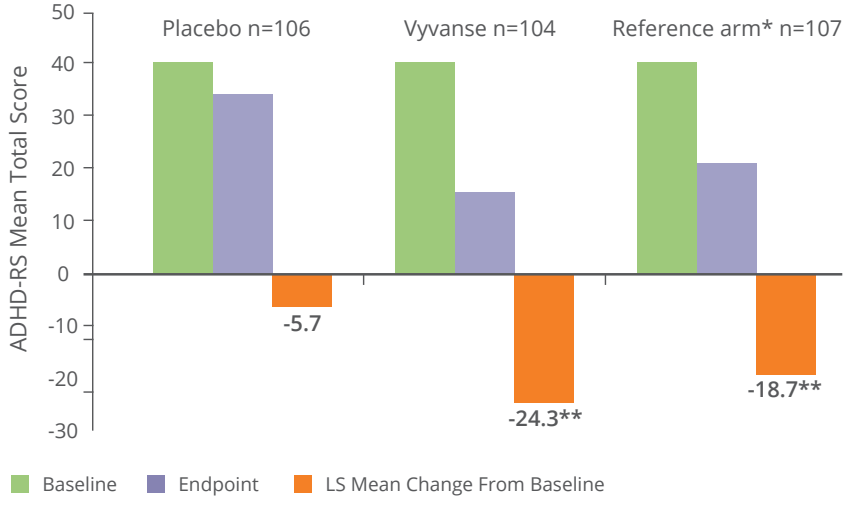
VYVANSE:

PEDIATRIC & ADOLESCENTS (AGED 6 TO 17)
PROVIDES SIGNIFICANTLY IMPROVED CORE ADHD SYMPTOM CONTROL VS. PLACEBO[1]

STUDY DESIGN[1]

- Randomized, double-blind, parallel-group, dose-optimized, placebo-controlled 7-week study of Vyvanse in 336 children aged 6-12 years & adolescents aged 13-17 years with ADHD based on DSM-IV-TR.
- Study objective was to evaluate the efficacy and safety of Vyvanse 30, 50 and 70mg/day compared with placebo. Osmotic-release oral system methylphenidate (OROS-MPH) 18, 36 and 54mg/day was included as a reference arm
- The primary efficacy measure was the change from baseline in the investigator-rated ADHD-RS-IV total score at endpoint
- The key secondary efficacy measure was the CGI-I rating
- CGI-I is a 7-point global measure of clinical and functional improvement ranging from 1 (very much improved) to 7 (very much worse)

ADHD-RS-IV MEAN TOTAL SCORES AT BASELINE AND ENDPOINT AND LS MEAN CHANGES FROM BASELINE



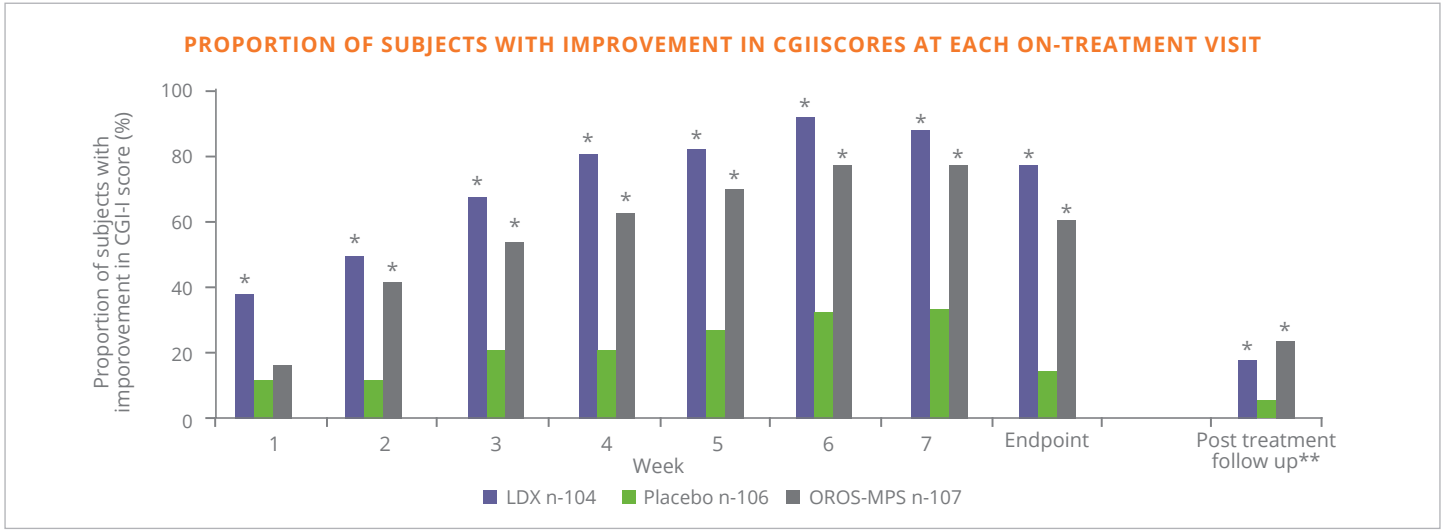
*OROS-MPH is a reference arm **p<0.001 FAS=full analysis set (n=317)

References:
1. Coghill D et al. European Neuropsychopharmacology(2013) 23, 1208–1218.

VYVANSE:

VYVANSE DEMONSTRATED CONSISTENT IMPROVEMENT AS ASSESSED USING THE CGI-I RATING[1]

The proportion of patients with an improved CGI-I rating was higher in the LDX group than in the placebo group at every on- treatment study visit, with 78% of participants reportedly 'very much improved' or 'much improved' (CGI-I score of 1 or 2) at study endpoint compared with 14% of patients in the placebo group.



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Reference:
1. Goodman DW, Psychiatry (Edgmont). 2007 Aug; 4(8):39-45

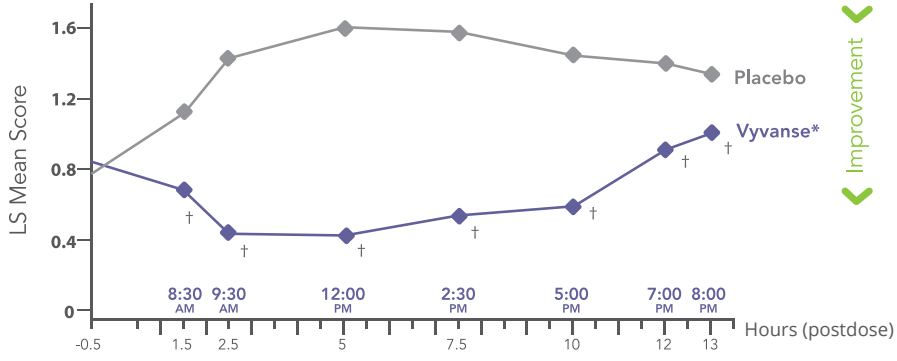
VYVANSE:

VYVANSE PROVIDES SUSTAINED SYMPTOMS CONTROL UP TO 13 HOURS POST DOSE[1]

STUDY DESIGN[1]

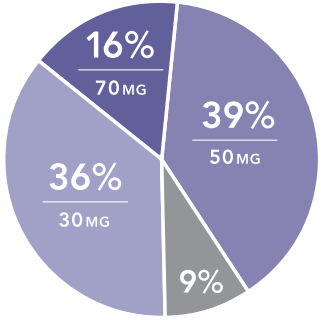
- Randomized, double-blind, placebo-controlled, crossover, analog classroom study of Vyvanse in 129 children aged 6-12 years with ADHD (as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th Ed, text revision [DSM-IV®-TR])
- The primary efficacy endpoint was time of onset of Vyvanse compared with placebo in the analog classroom setting, as measured by average SKAMP-D subscale scores[4,5]
- The key secondary efficacy endpoint was duration of efficacy of Vyvanse compared with placebo in the analog classroom setting, as measured by the average SKAMP-D subscale scores evaluated at 1.5, 2.5, 5, 7.5,10,12, and 13 hours postdose[3,4]
- SKAMP-D = Swanson, Kotkin, Agler, M-Flynn, and Pelham Deportment subscale

LEAST SQUARES (LS) MEAN SKAMP-D SCORE BY POSTDOSE TIMEPOINT[3,4]



• Dose given at 7AM • n=113 *Average for all doses tested

†P<.005 for Vyvanse vs placebo at all postdose timepoints assessed



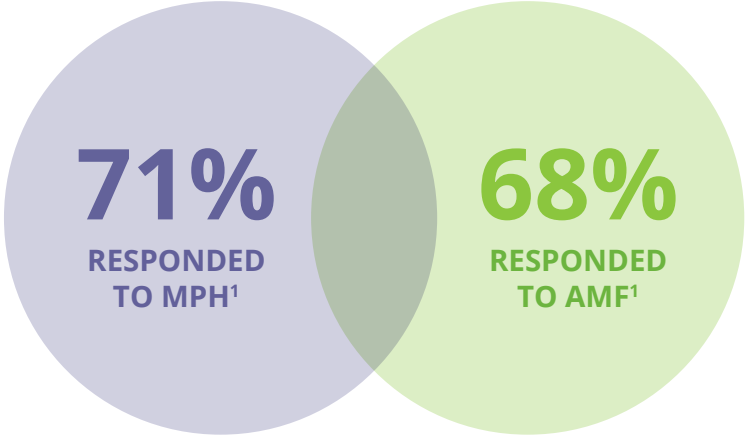
VYVANSE DOSE AT THE END OF THE DOSE-OPTIMIZATION PHASE[1]

References:

1. Wigal SB, et al. Child Adolesc Psychiatry Ment Health. 2009;3(1):17.

VYVANSE:
PATIENTS RESPOND DIFFERENTLY TO MADICATIONS

91% of patients responded to either drug[1]:



Because every case of ADHD is unique, and because patients may respond differently to medications, Shire provides a range of treatment options to optimise and individualise management and care.

A pooled analysis from 8 randomised studies was conducted to summarise responses to methylphenidate (MPH) or amfetamine (AMF) in children and adolescents with ADHD[1]

- These comprised 7 crossover studies and 1 parallel-group study (some overlap with studies included in the previous Arnold review)[1]
- A total of 318 patients were included in the analysis[1]
- Within each study, mean patient age ranged from 8 to 10.3 years[1]

References:
1. Hodgkins P et al. Eur Child Adolesc Psychiatry 2012; 21(9): 477-492.
MPH- Methylphenidate
AMP- Amphetamine

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VYVANSE:

PEDIATRIC (AGED 6 TO 12)

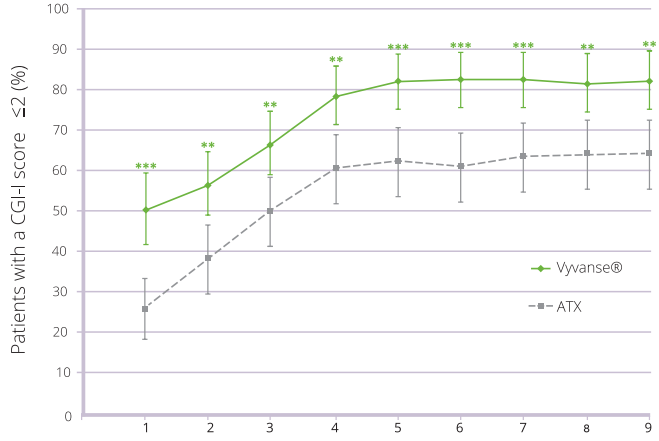
CONSISTENT SYMPTOM IMPROVEMENT BASED ON PARENT RATINGS (CPRS)[1]

STUDY DESIGN[1]

- 9-week, head-to-head, randomized, doubleblind, active-controlled study in patients (aged 6–17 years) with at least moderately symptomatic ADHD and an inadequate response to previous MPH therapy.
- Patients were randomized (1:1) to an optimized daily dose of LDX (30, 50 or 70 mg) or ATX (patients <70 kg, 0.5–1.2 mg/kg with total daily dose not to exceed 1.4 mg/kg; patients ≥70 kg, 40, 80 or 100 mg).
- The primary efficacy outcome was time(days) to first clinical response. Clinical response was defined as a Clinical Global Impressions-Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved).

Vyvanse provides a faster and more robust treatment response than atomoxetine (ATX) in patients with **a clinically inadequate response to MPH**. efficacy outcomes following treatment with Vyvanse vs. ATX showed that:

PROPORTION OF PATIENTS WITH A CLINICAL RESPONSE TO VYVANSE OR ATX TREATMENT (DEFINED AS A CGI-I SCORE OF 1 OR 2) AT EACH WEEKLY VISIT



Adapted from Dittmann RW et al. 2013.
***p<0.001 **p<0.01
CGI-I:
Clinical Global Impression-Improvement.

By week 9, 81.7% of patients receiving Vyvanse had responded to treatment compared with 63.6% of those receiving ATX (p=0.001)

References:
1. Dittmann et al. CNS Drugs 2013;27:1081–92

VYVANSE:

CHILDREN (AGED 6 TO 12) & ADOLESCENTS (AGED 13 TO 17) CONSISTENT IMPROVEMENT IN ADHD SYMPTOMS UP TO 1 YEAR

STUDY DESIGN[1]

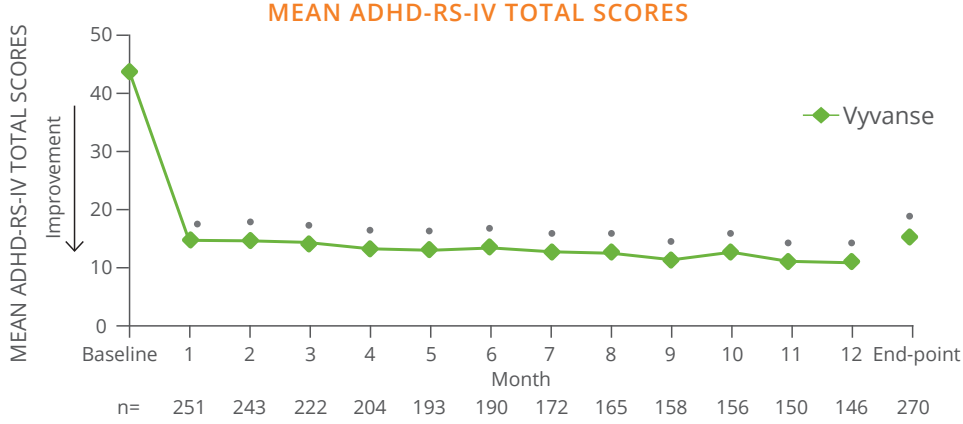
CHILDREN (AGED 6 TO 12)

- In an open-label, multicentre, single-arm, US study designed to assess the long term safety, tolerability and efficacy of Vyvanse in 272 6–12 year olds with ADHD. Subjects were titrated to Vyvanse 30, 50 or 70mg/day over four weeks and placed on maintenance treatment for 11 months
- Primary outcome: mean change from baseline ADHD-RS-IV total score to endpoint

ADOLESCENTS[2]

(AGED 13 TO 17)

- Open-label multicenter study enrolled eligible participants after their participation in a randomized, double blind, placebo-controlled 4 week trial in 269 adolescents aged 13 to 17 years with ADHD. The study objective was to evaluate the safety and effectiveness of Vyvanse over 52 weeks
- The primary measure of effectiveness was changes from baseline to end point in ADHD-RS-IV total score



*p<0.0001 vs. baseline: ITT population (n=270): results at endpoint are last-observation-carried-forwaeds results for ITT population

Vyvanse demonstrated a long-term safety profile similar to that of other long-acting psychostimulants and was effective, as indicated by improvements in ADHD symptoms in adolescents with ADHD.

References:
1. Findling RL et al. J CNS Spectr 13 (7), 2008.
2. Findling RL et al. Journal Of Child and Adolescent **Psychopharmacology 23 (1), 2013**

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VYVANSE:
WELL TOLERATED WITH A PREDICTABLE ADVERSE EVENT PROFILE[1]

- Most TEAEs were mild or moderate in intensity[1]
- Similar to other stimulants[1]
- The most common treatment emergent adverse events in children and adolescents are: decreased appetite, insomnia, upper abdominal pain, irritability, vomiting and weight decrease[1]
- Cardiovascular system:

  Changes in systolic or diastolic blood pressure, pulse rate, ECG parameters, Heart Rate – all small and not clinically meaningful[1]

References:
1. Vyvanse Prescribing Information approved by MoH, 2014.

VYVANSE:
EASY ADMINISTRATION

Recommended Starting Dose

30 mg

50 mg

Maximum Recommended Dose

70 mg

Capsules shown at actual size.

RECOMMENDED DOSING[1]

Take whole capsule once daily in the morning with or without food

VYVANSE CAPSULES MAY BE TAKEN WHOLE OR OPENED AND MIXED IN WATER, ORANGE JUICE OR YOGURT[1]

Open the capsule and mix contents in water, orange juice or yogurt until completely dispersed

- Stir to break apart any compacted powder
- Consume immediately (do not store)
- Take full contents of capsule (do not divide)

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VYVANSE SUMMARY
FOR PATIENTS WITH ADHD

- The prodrug Vyvanse is metabolized by red blood cells to release active d-amphetamine[1] in a controlled and predictable manner
- Low inter and intra subject variability[2]
- Vyvanse has been shown to provide significant and sustained improvements in the symptoms of ADHD[3]
- Vyvanse is well tolerated with a predictable adverse event profile[1]
- Long duration of efficacy - in children up to 13 hours post dose[4]
- Vyvanse capsules may be taken whole or opened and mixed in water, orange juice or yogurt[1]
  - Can be a good solution for patients who have difficulties have difficulties swallowing medications

References:
1. Vyvanse Prescribing Information approved by MoH, 2014.
2. Ermer JC et al. J Clin Pharmacol 2010; 50: 1001–1010.
3. Coghill D et al. European Neuropsychopharmacology(2013) 23, 1208–1218.
4. Wigal SB, et al. Child Adolesc Psychiatry Ment Health. 2009;3(1):17.

HIGHLIGHTS OF PHYSICIAN PRESCRIBING INFORMATION

INDICATIONS AND USAGE:
Vyvanse is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients ages 6 years and above

DOSAGE AND ADMINISTRATION:
- Recommended starting dose: 30 mg once daily in the morning in patients ages 6 and above
- Increase in increments of 20 mg at weekly intervals if needed Maximum dose: 70 mg per day
- Severe renal impairment: Maximum dose should not exceed 50 mg/day
- End stage renal disease (ESRD): Maximum recommended dose of 30 mg/day
- Prior to treatment, assess for presence of cardiac disease

DOSAGE FORMS AND STRENGTHS:
Capsules: 30 mg, 50 mg, 70 mg

CONTRAINDICATIONS:
- Known hypersensitivity to amphetamine products or other ingredients in Vyvanse
- Use with monoamine oxidase (MAO) inhibitor, or within 14 days of the last MAO inhibitor dose

WARNINGS AND PRECAUTIONS:
- Serious Cardiovascular Reactions: Sudden death in children and adolescents with serious heart problems, as well as sudden death, stroke, and myocardial infarction in adults reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease
- Blood Pressure and Heart Rate Increases: Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic
- Psychiatric Adverse Reactions: May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use
- Suppression of Growth: Monitor height and weight in pediatric patients during treatment
- Peripheral Vasculopathy, including Raynaud's phenomenon: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants

DRUG INTERACTIONS:
Acidifying and Alkalinizing Agents: Agents that alter urinary pH can alter blood levels of amphetamine. Acidifying agents decrease amphetamine blood levels, while alkalinizing agents increase amphetamine blood levels. Adjust Vyvanse dosage accordingly

USE IN SPECIFIC POPULATIONS:
- Pregnancy: Based on animal data, may cause fetal harm
- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to the mother

SAFETY INFORMATION:
Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) in children, adolescents, and/or adults were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.

CNS stimulants (amphetamines and methylphenidate-containing products) have a high potential for abuse and dependence.
Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

Side effects should be also reported to both:
Medison Pharma: pv@medison.co.il
Shire: globalpharmacovigilance@shire.com
www.health.gov.il ניתן גם לדווח בטופס המקוון באתר של משרד הבריאות

For further information (including side effects) please read the PI as approved by the Israel MOH (www.health.gov.il)

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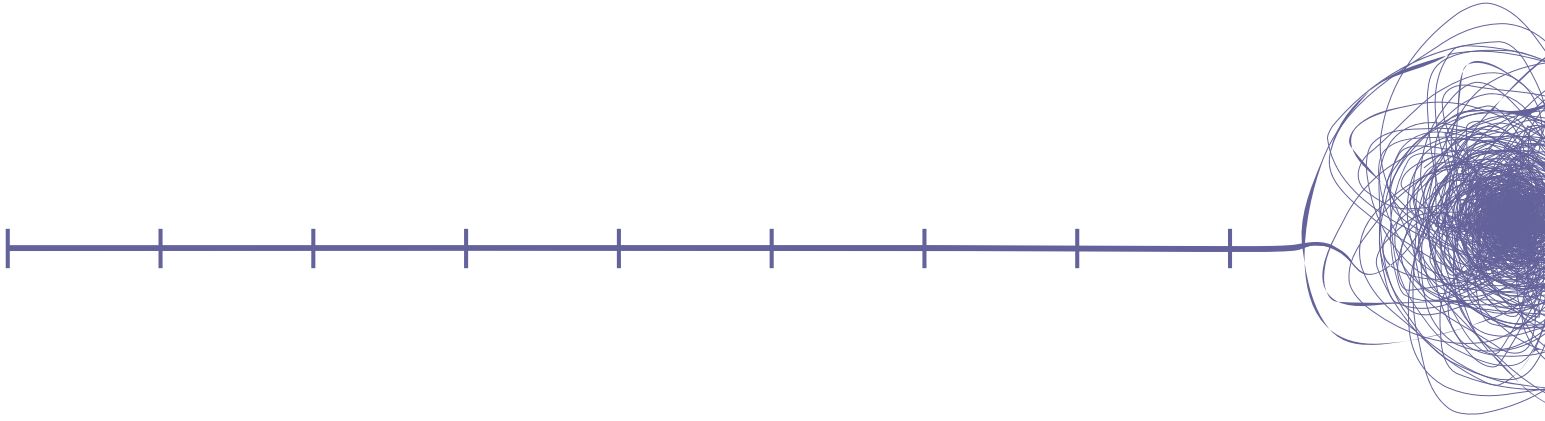

ADHD-01-01-0316 Date of preparation: March 2016 IL/C-APROM/VVV/16/0003

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Shire