הודעה על החמרה (מידע בטיחות) בעלון לרופא,
(מעודכן 05.2013)

תאריך: **01/01/2017**

שם תכשיר באנגלית ומספר הרישום: **Vyvanse 30mg,50mg,70mg 1531933994,1532034001,1532134000**

שם בעל הרישום: **מדיסון פארמה בע"מ**

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
Induction of a Manic Episode in Patients with Bipolar Disorder CNS stimulants may induce a mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, and depression).	*Induction of a Manic Episode in Patients with Bipolar Disorder* CNS stimulants may induce a mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen patients for risk factors for developing a manic episode.	5.4 Psychiatric Adverse Reactions
The following adverse reactions are discussed in greater detail in other sections of the labeling • Known hypersensitivity to amphetamine products or other ingredients of VYVANSE [see Contraindications (4)] • Hypertensive Crisis When Used Concomitantly with Monoamine Oxidase Inhibitors [see Contraindications (4) and Drug Interactions (7.1)] • Drug Dependence [see Boxed Warning, Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.2, 9.3)]	The following adverse reactions are discussed in greater detail in other sections of the labeling	6 ADVERSE REACTIONS

• Serious Cardiovascular Reactions *[see Warnings and Precautions (5.2)]* • Blood Pressure and Heart Rate Increases *[see Warnings and Precautions (5.3)]* • Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]* • Suppression of Growth *[see Warnings and Precautions (5.5)]* • Peripheral Vasculopathy, including Raynaud's phenomenon *[see Warnings and Precautions (5.6)]*	• Serious Cardiovascular Reactions *[see Warnings and Precautions (5.2)]* • Blood Pressure and Heart Rate Increases *[see Warnings and Precautions (5.3)]* • Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]* • Suppression of Growth *[see Warnings and Precautions (5.5)]* • Peripheral Vasculopathy, including Raynaud's phenomenon *[see Warnings and Precautions (5.6)]*	
The following adverse reactions have been identified during post approval use of Vyvanse. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events are as follows: palpitations, cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, dysgeusia, tics, bruxism, depression, dermatillomania, aggression, Stevens-Johnson Syndrome, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, and constipation.	The following adverse reactions have been identified during post approval use of Vyvanse. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events are as follows: palpitations, cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, tics, bruxism, depression, dermatillomania, aggression, Stevens-Johnson Syndrome, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, and constipation.	6.2 Postmarketing Experience
Table 4: ~~Effect of Other~~ Drugs ~~on Vyvanse~~ having clinically important interactions with amphetamins ~~Concomitant Drug Name or Drug Class~~ ***MAO Inhibitors (MAOI)***	**Table 4: Effect of Other Drugs on Vyvanse** Concomitant Drug Name or Drug Class / Clinical Rationale / Clinical Recommendation	7 DRUG INTERACTIONS

~~Acidifying and Alkalinizing Agents~~ Clinical Impact	~~Ascorbic acid and other agents that acidify urine increase urinary excretion and decrease the half-life of amphetamine. Sodium bicarbonate and other agents that alkalinize urine decrease urinary excretion and extend the half-life of amphetamine.~~ MAOI antidepressants slow amphetamine metabolism, increasing amphetamines effect on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Intervention	Do not administer VYVANSE during or within 14 days following the administration of MAOI [see *Contraindications (4)*].
Examples	selegiline, isocarboxazid, phenelzine, tranylcypromine
Alkalinizing Agents	
Clinical Impact	Urinary alkalinizing agents can increase blood levels and potentiate the action of amphetamine.
Intervention	Co-administration of VYVANSE and urinary alkalinizing agents should be avoided.
Examples	Urinary alkalinizing agents (e.g. acetazolamide, some thiazides).
Acidifying Agents	
Clinical Impact	Urinary acidifying agents can lower blood levels and efficacy of amphetamines.
Intervention	Increase dose based on clinical response.
Examples	Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts).
Tricyclic Antidepressants	
Clinical Impact	May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.
Intervention	Monitor frequently and adjust or use alternative therapy based on clinical response.
Examples	desipramine, protriptyline

~~**Table 5: Effect of Vyvanse on Other Drugs**~~

Ac idifying and Alkalinizing Agents	Ascorbic acid and other agents that acidify urine increase urinary excretion and decrease the half-life of amphetamine. Sodium bicarbonate and other agents that alkalinize urine decrease urinary excretion and extend the half-life of amphetamine.	Adjust the dose accordingly [see Dosage and Administration (2.4)]

Table 5: Effect of Vyvanse on Other Drugs

Concomitant Drug ame or Drug lass	Clinical Rationale	Clinical Recommendation
Monoamine Oxidase Inhibitors (MAOIs)	Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.	Do not administer Vyvanse concomitantly or within 14 days after discontinuing MAOI treatment [see Contraindications (4)]

~~Concomitant Drug Name or Drug Class~~	~~Clinical Rationale~~	~~Clinical Recommendation~~		
~~Monoamine Oxidase Inhibitors (MAOIs)~~	~~Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.~~	~~Do not administer Vyvanse concomitantly or within 14 days after discontinuing MAOI treatment [see Contraindications (4)]~~		
Risk Summary ~~There are no adequate~~ **The limited available data from published literature and ~~well-controlled studies with Vyvanse~~ postmarketing reports on use of VYVANSE in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines [see Clinical Considerations]. In animal reproduction studies, lisdexamfetamine dimesylate (a prodrug of d-amphetamine) had no effects on embryo-fetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis. Pre- and**			Pregnancy Category C **Risk Summary** There are no adequate **and** well-controlled studies with Vyvanse **in pregnant women**. **Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines**. **Long-term neurochemical and behavioral effects have been reported in animal developmental studies using clinically relevant doses of amphetamine** (d- or d,l-). Animal reproduction studies performed with lisdexamfetamine dimesylate in rats and rabbits showed no effects on embryofetal morphological development and survival. Vyvanse should be used during pregnancy	8.1 Pregnancy

postnatal studies were not conducted with lisdexamfetamine dimesylate. However, amphetamine (d- to l- ratio of 3:1) administration to pregnant rats during gestation and lactation caused a decrease in pup survival and a decrease in pup body weight that correlated with a delay in developmental landmarks at clinically relevant doses of amphetamine. In addition, adverse effects on reproductive performance were observed in pups whose mothers were treated with amphetamine. Long-term neurochemical and behavioral effects have also been reported in animal developmental studies using clinically relevant doses of amphetamine ~~(d- or d,l-)~~. ~~Animal reproduction studies performed with lisdexamfetamine dimesylate in rats and rabbits showed no effects on embryofetal morphological development and survival. Vyvanse should be used during pregnancy only if the potential benefit justifies~~ [see Data]. **The estimated background risk of major birth defects and miscarriage for the ~~potential risk to~~ indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the ~~fetus~~. U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.** **Clinical Considerations** **Fetal/Neonatal Adverse Reactions** **Amphetamines, such as VYVANSE, cause vasoconstriction and thereby may decrease placental perfusion. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. Infants born to amphetamine-dependent mothers have an increased risk of premature delivery and low birth weight.**	only if the potential benefit justifies **the** potential risk to **the** fetus. **Clinical Considerations** **Amphetamines, such as** Vyvanse**, cause vasoconstriction and thereby may decrease placental perfusion. Infants born to amphetamine-dependent mothers have an increased risk of premature delivery and low birth weight.**	

Monitor infants born to mothers taking amphetamines for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness.	**Monitor infants born to mothers taking amphetamines for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness.**	
~~**Human Data**~~ ~~Available data in women using amphetamines during pregnancy do not show a clear increased risk of major congenital malformations. Two case control studies of over a thousand patients in total exposed to amphetamines at different gestational ages did not show an increase in congenital abnormalities~~. ***Animal Data*** **Lisdexamfetamine dimesylate had no apparent effects on embryo-fetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 40 and 120 mg/kg/day, respectively. These doses are approximately 4 and 27 times, respectively, the maximum recommended human dose (MRHD) of 70 mg/day given to adolescents, on a mg/m2 body surface area basis.** **A study was conducted with amphetamine (d- to l-enantiomer ratio of 3:1) in which pregnant rats received daily oral doses of 2, 6, and 10 mg/kg from gestation day 6 to lactation day 20. These doses are approximately 0.8, 2, and 4 times the MRHD of amphetamine (d- to l- ratio of 3:1) for adolescents of 20 mg/day, on a mg/m2 basis. All doses caused hyperactivity and decreased weight gain in the dams. A**	Human **Data** Available data in women using amphetamines during pregnancy do not show a clear increased risk of major congenital malformations. Two case control studies of over a thousand patients in total exposed to amphetamines at different gestational ages did not show an increase in congenital abnormalities. ***Animal Data*** **Lisdexamfetamine dimesylate had no apparent effects on** embryofetal **morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 40 and 120 mg/kg/day, respectively. These doses are approximately 4 and 27 times, respectively, the maximum recommended human dose of 70 mg/day given to adolescents, on a mg/m2**	

decrease in pup survival was seen at all doses. A decrease in pup body weight was seen at 6 and 10 mg/kg which correlated with delays in developmental landmarks, such as preputial separation and vaginal opening. Increased pup locomotor activity was seen at 10 mg/kg on day 22 postpartum but not at 5 weeks postweaning. When pups were tested for reproductive performance at maturation, gestational weight gain, number of implantations, and number of delivered pups were decreased in the group whose mothers had been given 10 mg/kg. **A number of studies from the literature in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d,l-) at doses similar to those used clinically can result in long- term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.**	**body surface area basis.** **A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d,l-) at doses similar to those used clinically can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.**	
~~.3 Nursing Mothers~~ ~~Amphetamines are excreted into~~ 8.2 Lactation Risk Summary Lisdexamfetamine is a pro-drug of dextroamphetamine. Based on limited case reports in published literature, amphetamine (d- or d, l-) is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no	8.3 Nursing Mothers Amphetamines are excreted into human milk. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.	~~Amphetamines are excreted into~~ 8.2 Lactation

reports of adverse effects on the breastfed infant. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. It is possible that large dosages of dextroamphetamine might interfere with milk production, especially in women whose lactation is not well established. Because of the potential for serious adverse reactions in nursing infants, ~~a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother~~ including serious cardiovascular reactions, blood pressure and heart rate increase, suppression of growth, and peripheral vasculopathy, advise patients that breastfeeding is not recommended during treatment with VYVANSE.		
12.1 Mechanism of Action Lisdexamfetamine is a prodrug of dextroamphetamine. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The exact mode of therapeutic action in ADHD is not known. **12.2 Pharmacodynamics** Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.	12.1 Mechanism of Action Lisdexamfetamine is a prodrug of dextroamphetamine. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.	12 CLINICAL PHARMACOLOGY

הודעה על החמרה (מידע בטיחות) בעלון לצרכן
(מעודכן 05.2013)

<u>תאריך:</u> 22.12.2016

<u>שם תכשיר באנגלית ומספר הרישום:</u> Vyvanse 30mg,50mg,70mg 1531933994,1532034001,1532134000

<u>שם בעל הרישום:</u> מדיסון פארמה בע"מ

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**

1. לפני שימוש בתרופה	**אם אתה לוקח , או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.** במיוחד יש ליידע את הרופא או הרוקח אם אתה לוקח: • תכשירים נגד דיכאון כולל ממשפחת מעכבי מונו אמינו אוקסידאז (MAOI) • ויטמין סי (חומצה אסקורבית) • סודה לשתייה (ביקרבונאט) **הריון והנקה** השפעה של התרופה על העובר אינה ידועה.	**אם אתה לוקח , או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.** במיוחד יש ליידע את הרופא או הרוקח אם אתה לוקח: • תכשירים נגד דיכאון כולל ממשפחת מעכבי מונו אמינו אוקסידאז (MAOI)- לדוגמא: סלג'לין,איזוקרבוקזיד ,פאנלזין,טרנילסיפרומין • ויטמין סי (חומצה אסקורבית) • סודה לשתייה (ביקרבונאט) • חומרים המעלים את בסיסיות השתן כגון אצטאזולאמיד,טיאזידים • חומרים המעלים את חומציות השתן כגון אמוניום כלוריד , נתרן חומצה פוספט, מלחי מתנאמין • תרופות נגד דיכאון טריציקליות כגון- דסיפראמין , פרוטריפטלין **הריון והנקה** ~~השפעה של התרופה על העובר אינה ידועה.~~ לא מומלץ להניק בזמן הטיפול בויואנס .
4. תופעות לוואי	תופעות לוואי נוספות בשכיחות לא ידועה: • קוצר נשימה או נפיחות ברגליים (סימנים של מחלת שריר ל • הרחבת אישוני העיניים ,ראייה כפולה ,ראיה מטושטשת א קושי בלהתמקד בעצמים. • פגיעה בכבד ממקור אלרגי עם אפשרות לצהבת בעיניים ו/	תופעות לוואי נוספות בשכיחות לא ידועה: • קוצר נשימה או נפיחות ברגליים (סימנים של מחלת שריר לב) • הרחבת אישוני העיניים ,ראייה כפולה ,ראיה מטושטשת או קושי בלהתמקד בעצמים. • פגיעה בכבד ממקור אלרגי עם אפשרות לצהבת בעיניים ו/או העור • תגובה אלרגית חמורה המאופיינת בירידה חדה בלחץ דם , קושי בנשימה ,סרפדת

	העור • תגובה אלרגית חמורה המאופיינת בירידה חדה בלחץ דם קושי בנשימה ,סרפדת /גירוד • תנועות לא רצוניות בלתי מבוקרות • טיקים(נשמט מהעלון) • חריקת שיניים • תחושת דיכאון, תוקפנות • גרד עור כפייתי • נפיחות של העור או פריחה חמורה בעור כשלפוחיות חמורו העור והרירויות (תסמונת סטיבן ג׳ונסון) • נפיחות של העור • חרלת (אורטיקריה) • פרכוסים • שינוי בחשק המיני • זקפה תכופה או מתמשכת • עצירות • זרימת דם לקויה שגורמת לאובדן תחושה באצבעות הידיים	/גירוד • תנועות לא רצוניות בלתי מבוקרות • תחושת טעם רע בפה(מלוח ,מתכתי,מעופש,מקולקל) • טיקים • חריקת שיניים • תחושת דיכאון, תוקפנות • גרד עור כפייתי • נפיחות של העור או פריחה חמורה בעור כשלפוחיות חמורות של העור והרירויות (תסמונת סטיבן ג׳ונסון) • נפיחות של העור • חרלת (אורטיקריה) • פרכוסים • שינוי בחשק המיני • זקפה תכופה או מתמשכת • עצירות • זרימת דם לקויה שגורמת לאובדן תחושה באצבעות הידיים והרגליים וגורמת לעור להיות חיוור (תסמונת ריינו)

	והרגליים וגורמת לעור להיות חיוור (תסמונת ריינו)	