AUSTRALIAN PRODUCT INFORMATION

VYVANSE® (Lisdexamfetamine dimesilate)

VYVANSE has a potential for abuse, misuse, dependence, or diversion for non-therapeutic uses. Physicians should assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy. VYVANSE should be prescribed cautiously to patients with a history of substance abuse or dependence. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

1 NAME OF THE MEDICINE

Lisdexamfetamine dimesilate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VYVANSE capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg or 70 mg of lisdexamfetamine dimesilate as the active ingredient.

VYVANSE (lisdexamfetamine dimesilate) was developed as a capsule for once-a-day oral administration. The chemical designation for lisdexamfetamine dimesilate is (2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate.

Lisdexamfetamine dimesilate is a white to off-white powder that is highly soluble in water. Lisdexamfetamine dimesilate has a 2-octanol/water partition coefficient (logP) of -1.76; pKa1 of 10.5 / pKa2 of 7.7; and pH of 4.1 when dissolved in water.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Capsules

Appearance
VYVANSE 20 mg capsule: ivory opaque body and ivory opaque cap, printed ‘S489’ and ‘20 mg’ in black ink.

VYVANSE 30 mg capsule: white opaque body and pink opaque cap, printed ‘S489’ and ‘30 mg’ in black ink.

VYVANSE 40 mg capsule: white opaque body and blue/green opaque cap, printed ‘S489’ and ‘40 mg’ in black ink.

VYVANSE50 mg capsule: white opaque body and blue opaque cap, printed ‘S489’ and ‘50 mg’ in black ink.

VYVANSE 60 mg capsule: aqua blue opaque body and aqua blue opaque cap, printed ‘S489’ and ‘60 mg’ in black ink.

VYVANSE 70 mg capsule: blue opaque body and pink opaque cap, printed 'S489' and '70 mg' in black ink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Attention Deficit Hyperactivity Disorder (ADHD)

VYVANSE is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Treatment should be commenced by a specialist.

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before 12 years of age.

Need for comprehensive treatment programme:
VYVANSE is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational and social) for patients with this syndrome. Stimulants are not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Long term use:
The physician who elects to use VYVANSE for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Binge Eating Disorder (BED)

VYVANSE is indicated for the treatment of moderate to severe BED in adults when non-pharmacological treatment is unsuccessful or unavailable. Treatment should be commenced and managed by a psychiatrist.

Need for comprehensive treatment programme:
VYVANSE is indicated as part of a total treatment program for BED that optimally includes other measures (nutritional, psychological, and medical) for patients with this disorder. When remedial measures including psychotherapy are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Limitation of Use:
VYVANSE is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of VYVANSE for the treatment of obesity have not been established.

Prescribers should consider that serious cardiovascular events have been reported with this class of sympathomimetic drugs. The BED clinical trials were not designed to assess cardiovascular safety. While there is an accumulation of safety data with VYVANSE use in

the ADHD population, this is of limited relevance regarding cardiovascular risk in the BED population. Given the higher cardiovascular risk associated with obesity, the BED population may be at a higher risk. See Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Cardiovascular Disease and 4.2 DOSE AND METHOD OF ADMINISTRATION.

Long term use:

For BED the initial treatment period is 12 weeks. Patients should then be observed to assess whether further treatment with VYVANSE is required. Periodic re-evaluation of the usefulness of VYVANSE for the individual patient should be undertaken. See Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials.

4.2 DOSE AND METHOD OF ADMINISTRATION

Patients should be reviewed at least annually to assess if there is an ongoing requirement for treatment with VYVANSE. Blood pressure and cardiovascular status should also be regularly reviewed.

VYVANSE should be administered orally at the lowest possible dosage and should then be slowly adjusted to the lowest effective dose for each individual. VYVANSE should be taken in the morning with or without food; avoid afternoon doses because of the potential for insomnia.

VYVANSE capsules may be taken whole, or the capsule may be opened and the entire contents emptied and mixed with a soft food such as yogurt or in a glass of water or orange juice. If the contents of the capsule include any compacted powder, a spoon may be used to break apart the powder in the soft food or liquid. The contents should be mixed until completely dispersed. The patient should consume the entire mixture of soft food or liquid immediately; it should not be stored. The active ingredient dissolves completely once dispersed; however, a film containing the inactive ingredients may remain in the glass or container once the mixture is consumed. The patient should not take anything less than one capsule per day and a single capsule should not be divided.

The maximum recommended dose is 70 mg/day; doses greater than 70 mg/day of VYVANSE have not been studied. The effectiveness of VYVANSE has not been studied in adults over 55 years of age. Due to reduced clearance in patients with severe renal insufficiency (GFR 15 to < 30 mL/min/1.73m^2) the maximum dose should not exceed 50 mg/day. Further dosage reduction should be considered in patients undergoing dialysis. See Section 5.2 PHARMACOKINETIC PROPERTIES, Special Populations and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Lisdexamfetamine and dexamphetamine are not dialysable.

Treatment of ADHD

In patients who are either starting treatment for the first time or switching from another medication, 30 mg once daily in the morning is the recommended starting dose. If the decision is made to increase the dose beyond 30 mg/day, daily dosage may be adjusted in increments of 20 mg in intervals no more frequently than weekly. VYVANSE has not been studied in children under 6 years of age.

Treatment of BED

VYVANSE should be commenced and managed by a psychiatrist as part of a comprehensive treatment programme for BED.

The recommended starting titration dose is 30 mg/day to be adjusted in increments of 20 mg at approximately weekly intervals to achieve the recommended target dose of 50 or 70 mg/day. Dose titration should be guided by clinical outcome to an optimal dose, with a maximum dose of 70 mg/day.

VYVANSE should be prescribed for the shortest duration that is clinically indicated. The initial treatment period is 12 weeks. Patients should then be observed to assess whether further treatment with VYVANSE is required. Periodic re-evaluation of the usefulness of VYVANSE for the individual patient should be undertaken.

4.3 CONTRAINDICATIONS

VYVANSE is contraindicated in patients with:

- Advanced arteriosclerosis
- Symptomatic cardiovascular disease including cardiac arrhythmia, ischaemic heart disease
- Moderate to severe hypertension
- Hyperthyroidism
- Known hypersensitivity or idiosyncratic reaction to sympathomimetic amines or any of the excipients
- Glaucoma
- Agitated states such as severe anxiety, tension and agitation
- During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result)
- Phaeochromatocytoma
- Tics, Tourette's syndrome
- Patients who currently exhibit severe depression, anorexia nervosa, psychotic symptoms or suicidal tendency
- Patients with known drug dependence or alcohol abuse

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Drug abuse and dependence

Note: Because of the liability for abuse, drugs of the amphetamine type are subject to special restrictions on their availability. Prescriptions of this substance may require validation by State or Territory Health Departments or Commissions.

Amphetamines have a high potential for drug abuse. Care should be exercised in the selection of patients for amphetamine therapy and prescription size should be limited to that required to achieve the therapeutic goal. Patients should be cautioned against increasing the recommended dosage. Should psychological dependence occur, gradual withdrawal of the medication is recommended. Abrupt cessation following prolonged high dosage results in extreme fatigue and mental depression; changes have also been noted on the sleep EEG.

Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

Pre-treatment assessment

Before starting treatment with VYVANSE, it is important to consider the patient's personal and family cardiac and psychiatric history. In patients with identified or potential cardiovascular or psychiatric risk factors, further investigation or specialist review may be considered.

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g. electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Cardiovascular disease

Serious cardiovascular events have been reported with the use of sympathomimetic drugs, including VYVANSE, in the ADHD population (see below). Given the higher cardiovascular risk associated with obesity, the BED population may be at a higher risk. Prescribers should consider this potential risk when treating BED. See Section 4.1 THERAPEUTIC INDICATIONS and Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Limited cardiovascular safety information is provided by the BED clinical trials, given the exclusion of higher risk patients (e.g., those with diabetes, moderate to severe hypertension and cardiovascular disease, and older than 55 years of age) combined with limited patient numbers and limited treatment duration.

Sudden death and pre-existing structural cardiac abnormalities or other serious heart problems

Children and Adolescents:
Sudden death has been reported in children and adolescents taking CNS stimulants at usual doses, including those with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults:
Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities,

coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and other cardiovascular conditions

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Psychiatric disorders

Pre-existing psychosis

Administration of stimulants may exacerbate symptoms of behaviour disturbance and thought disorder in patients with pre-existing psychotic disorder.

Bipolar illness

Particular care should be taken in using stimulants to treat ADHD patients with comorbid bipolar disorder because of concern for possible induction of mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of new psychotic or manic symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate.

Aggression

Aggressive behaviour or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD, including VYVANSE. Stimulants may cause aggressive behaviour or hostility. Patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behaviour or hostility.

Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizure, in patients with prior EEG abnormalities in absence of seizures, and very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

Tics

Stimulants have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

Long-term suppression of growth (height and weight)

VYVANSE was associated with dose-related reductions in weight in children, adolescents and adults in short-term studies. Although a causal relationship has not been established, suppression of growth (i.e. weight and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

Peripheral vasculopathy, including Raynaud's Phenomenon

Stimulants, including Vyvanse, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, have been observed in postmarketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Prescribing and dispensing

The least amount of VYVANSE feasible should be prescribed or dispensed at one time in order to minimise the possibility of overdosage. Consideration should be given when using VYVANSE in patients who use other sympathomimetic drugs.

For BED the initial treatment period is 12 weeks. Patients should then be observed to assess whether further treatment with VYVANSE is required. Periodic re-evaluation of the usefulness of VYVANSE for the individual patient should be undertaken.

Paediatric use

ADHD

VYVANSE should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

BED

Safety and effectiveness have not been established in children and adolescents under the age of 18 years. Clinical studies on the use of VYVANSE in this age group with BED have not been conducted.

Adult patients aged over 55 years

Safety and efficacy has not been established in adult patients over the age of 55 years.

Use in hepatic impairment

No studies have been conducted in patients with hepatic impairment.

Use in renal impairment

Due to reduced clearance in patients with severe renal insufficiency (GFR 15 to <30 mL/min/1.73 m2) the maximum dose should not exceed 50 mg/day. Further dosage reduction should be considered in patients undergoing dialysis. See Section 5 PHARMACOLOGY, Special Populations.

Lisdexamfetamine and dexamphetamine are not dialysable.

Effects on laboratory tests

Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamine may interfere with urinary steroid determinations.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

***In vitro* and *in vivo* enzyme inhibition and induction**

Lisdexamfetamine dimesilate was not an *in vitro* inhibitor of the major human CYP450 isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) in human hepatic microsomal suspensions, nor was it an *in vitro* inducer of CYP1A2, CYP2B6 or CYP3A4/5 in cultured fresh human hepatocytes. Lisdexamfetamine dimesilate was not an *in vitro* substrate for P-gp in MDCKII cells nor an *in vitro* inhibitor of P-gp in Caco-2 cells and is therefore unlikely to be involved in clinical interactions with drugs transported by the P-gp pump.

In an *in vivo* human study, the co-administration of a single dose of lisdexamfetamine dimesilate did not result in any clinically meaningful effect on the pharmacokinetics of single doses of drugs metabolised by CYP1A2, CYP2D6, CYP2C19, or CYP3A.

Agents whose blood levels may be impacted by VYVANSE

Extended release guanfacine: In a drug interaction study, administration of an extended release guanfacine in combination with VYVANSE induced a 19% increase in guanfacine maximum plasma concentrations, whereas, exposure (area under the curve; AUC) was increased by 7%. These small changes are not expected to be clinically meaningful. In this

study, no effect on dexamphetamine exposure was observed following coadministration of extended release guanfacine and VYVANSE.

Extended release venlafaxine: In a drug interaction study, administration of 225 mg extended release venlafaxine, a CYP2D6 substrate, in combination with 70 mg VYVANSE induced a 9% decrease in the Cmax and 17% decrease in the AUC for the primary active metabolite o-desmethylvenlafaxine and a 10% increase in Cmax and 13% increase in AUC for venlafaxine. VYVANSE (dexamphetamine) may be a weak inhibitor of CYP2D6. Lisdexamfetamine has no effect on the AUC and Cmax of the composite of venlafaxine and o-desmethylvenlafaxine.These small changes are not expected to be clinically meaningful. In this study, no effect on dexamphetamine exposure was observed following co-administration of extended release venlafaxine and VYVANSE.

Agents and conditions that alter urinary pH and impact the urinary excretion and half-life of amphetamine

Ascorbic acid and other agents or conditions that acidify urine increase urinary excretion and decrease half-life of amphetamine. Sodium bicarbonate and other agents or conditions that alkalinise urine decrease urinary excretion and extend the half-life of amphetamine.

Monoamine oxidase inhibitors

Do not administer VYVANSE concomitantly with monoamine oxidase inhibitors or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Severe outcomes including death may occur. See Section 4.3 CONTRAINDICATIONS.

Serotonergic drugs

Serotonin syndrome can occur in association with the use of amphetamines such as VYVANSE, when given in conjunction with serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). It has also been reported in association with overdose of amphetamines, including VYVANSE. See Section 4.9 OVERDOSAGE.

Agents whose effects may be reduced by amphetamines

Antihypertensives: Amphetamines may decrease the effectiveness of antihypertensive medications.

Agents whose effects may be potentiated by amphetamines

Amphetamines potentiate the analgesic effect of narcotic analgesics.

Agents that may reduce the effects of amphetamines

Chlorpromazine: Chlorpromazine blocks dopamine and noradrenaline receptors, thus inhibiting the central stimulant effects of amphetamines.

Haloperidol: Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.

Lithium Carbonate: The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A fertility study of lisdexamfetamine dimesilate has not been conducted. Amphetamine (d- to l-enantiomer ratio of 3:1) did not adversely affect fertility or early embryonic development in the rat at oral doses of up to 20 mg total amphetamine base/kg/day. This dose resulted in a plasma amphetamine AUC which was 4 (males) and 6 (females) fold the AUC expected in adults at the maximum recommended dose of 70 mg.

Use in pregnancy

Australian Pregnancy Categorisation (Category B3)

The effects of VYVANSE on labour and delivery in humans are unknown.
There are no adequate and well-controlled studies with VYVANSE in pregnant women.
VYVANSE should be used during pregnancy only if the potential benefit justifies the potential risk to foetus.

Infants born to mothers taking amphetamines should be monitored for symptoms of withdrawal such as feeding difficulties, irritability, agitation and excessive drowsiness.
Lisdexamfetamine dimesilate had no apparent effects on embryofoetal 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 resulted in respective plasma dexamphetamine AUC values which were 5 and 2 fold the AUC expected in adults at the maximum recommended dose of 70 mg, and respective plasma lisdexamfetamine AUC values which were 12 and 40 fold the AUC expected in adults at the maximum recommended dose.

A study of lisdexamfetamine dimesilate has not been conducted in rats treated throughout gestation and lactation. Amphetamine sulphate (d- to l- enantiomer ratio of 3:1), when given orally to rats from early gestation through to weaning at doses of 2, 6 and 10 mg total amphetamine base/kg/day, reduced the number of liveborn pups and pup viability during lactation. Body weight gain of offspring was reduced during lactation and after weaning, development was delayed, and increases in locomotor activity were observed. The reproductive performance of the offspring was also reduced. Some effects were observed at the 2 mg/kg/day dose, which was associated with a plasma amphetamine AUC about half that expected in adults at the maximum recommended dose of 70 mg.

Use in lactation

Amphetamines are excreted in human milk. Mothers taking VYVANSE should be advised to refrain from breast feeding.

Oral administration of amphetamine sulfate to rats from early gestation through to weaning was associated with adverse effects on offspring, see Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in pregnancy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

VYVANSE can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision. These are uncommon but could have a moderate influence on the ability to drive and use machines. If affected, patients should avoid potentially hazardous activities such as driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse drug reactions observed with VYVANSE treatment mainly reflect side effects commonly associated with amphetamine use. Tables 1 - 3 present common adverse drug reactions (ADRs) reported in parallel-group, controlled clinical trials of children, adolescents and adults meeting DSM criteria for ADHD who received VYVANSE. Table 4 presents common ADRs reported in long-term, open-label clinical trials in children, adolescents and adults meeting DSM criteria for ADHD who received VYVANSE. Table 5 presents common ADRs reported in two parallel-group, placebo-controlled dose-optimisation clinical trials of adults meeting DSM criteria for BED who received VYVANSE. Table 6 presents common ADRs reported in long-term, open-label clinical trials in adults meeting DSM criteria for BED who received VYVANSE.

Adverse Reactions Associated with Discontinuation of Treatment in ADHD Clinical Trials:
In the controlled trial in patients aged 6 to 12 years, 8% (18/218) of VYVANSE-treated patients discontinued due to adverse reactions compared to 0% (0/72) of placebo-treated patients. The most frequently reported adverse reactions 1% or more and twice rate of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, decreased appetite and rash [2 instances for each adverse reaction, i.e., 2/218 (1%)]. Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) included abdominal pain upper, dry mouth, weight decreased, dizziness, somnolence, logorrhea, chest pain, anger and hypertension.

In the controlled trial in patients aged 13 to 17 years, 3% (7/233) of VYVANSE-treated patients discontinued due to adverse reactions compared to 1% (1/77) of placebo-treated patients. The most frequently reported adverse reactions (1% or more and twice rate of placebo) were decreased appetite (2/233; 1%), and insomnia (2/233; 1%). Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) included irritability, dermatillomania, mood swings, and dyspnea.

In the controlled adult trial, 6% (21/358) of VYVANSE-treated patients discontinued due to adverse reactions compared to 2% (1/62) of placebo-treated patients. The most frequently reported adverse reactions (1% or more and twice rate of placebo) were insomnia (8/358; 2%), tachycardia (3/358; 1%), irritability (2/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnoea (3/358; 1%). Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) included palpitations, diarrhea, nausea, decreased appetite, dizziness, agitation, depression, paranoia and restlessness.

Adverse Reactions Associated with Discontinuation of Treatment in BED Clinical Trials:
In controlled trials of patients aged 18 to 55 years, 5.1% (19/373) of VYVANSE treated patients discontinued due to adverse reactions compared to 2.4% (9/372) of placebo-treated patients. No single adverse reaction led to discontinuation in 1% or more of VYVANSE-

treated patients. The most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in adults were dry mouth, insomnia, decreased appetite, increased heart rate, constipation, feeling jittery, and anxiety. Less commonly reported adverse reactions (less than 1% or less than twice rate of placebo) included increased heart rate, headache, abdominal pain upper, dyspnea, rash, insomnia, irritability, feeling jittery and anxiety.

Table 1: Adverse Drug Reactions Occurring in ³ 5% of Children meeting DSM criteria for ADHD who Received VYVANSE in Short-term, Parallel-group, Controlled Studies

	NRP104.301 (forced dose; 4 weeks)		SPD489-325 (dose optimisation; 7 weeks)		
System Organ Class Preferred Term	VYVANSE N=218 (n [%])	Placebo N=72 (n [%])	VYVANSE N=77 (n [%])	Placebo N=79 (n [%])	OROS MPH N=80 (n [%])
Gastrointestinal disorders					
Abdominal pain upper	25 (11.5)	4 (5.6)	6 (7.8)	5 (6.3)	6 (7.5)
Diarrhoea	1 (0.5)	2 (2.8)	4 (5.2)	1 (1.3)	2 (2.5)
Nausea	13 (6.0)	2 (2.8)	8 (10.4)	2 (2.5)	6 (7.5)
Vomiting	19 (8.7)	3 (4.2)	3 (3.9)	1 (1.3)	2 (2.5)
General disorders and administration site conditions					
Irritability	21 (9.6)	0	3 (3.9)	0	3 (3.8)
Pyrexia	5 (2.3)	1 (1.4)	3 (3.9)	0	4 (5.0)
Investigations					
Weight decreased	21 (9.6)	2 (2.8)	10 (13.0)	0	4 (5.0)
Metabolism and nutrition disorders					
Anorexia	16 (7.3)	1 (1.4)	8 (10.4)	2 (2.5)	3 (3.8)
Decreased appetite	72 (33.0)	2 (2.8)	19 (24.7)	3 (3.8)	14 (17.5)
Nervous system disorders					
Dizziness	11 (5.0)	0	1 (1.3)	1 (1.3)	1 (1.3)
Headache	26 (11.9)	7 (9.7)	9 (11.7)	12 (15.2)	13 (16.3)
Psychiatric disorders					
Aggression	3 (1.4)	0	4 (5.2)	1 (1.3)	3 (3.8)
Initial insomnia	8 (3.7)	0	2 (2.6)	1 (1.3)	4 (5.0)
Insomnia	42 (19.3)	2 (2.8)	12 (15.6)	0	6 (7.5)

Note: Subjects are only counted once within each treatment group and by system organ class and preferred term. Percentages are based on the number of subjects in the Safety Population for each treatment group.

Table 2: Adverse Drug Reactions Occurring in ³ 5% of Adolescents meeting DSM criteria for ADHD who Received VYVANSE or Active Treatment in Short-term, Parallel-group, Controlled Studies

	SPD489-305 (forced dose; 4 weeks)		SPD489-325 (dose optimisation; 7 weeks)		
System Organ Class Preferred Term	VYVANSE N=233 (n [%])	Placebo N=77 (n [%])	VYVANSE N=34 (n [%])	Placebo N=31 (n [%])	OROS MPH N=31 (n [%])
Gastrointestinal disorders					
Abdominal pain upper	2 (0.9)	3 (3.9)	2 (5.9)	1 (3.2)	3 (9.7)
Dry mouth	11 (4.7)	1 (1.3)	2 (5.9)	0	1 (3.2)
Nausea	9 (3.9)	2 (2.6)	4 (11.8)	1 (3.2)	2 (6.5)
Vomiting	3 (1.3)	4 (5.2)	1 (2.9)	0	2 (6.5)
General disorders and administration site conditions					
Fatigue	10 (4.3)	2 (2.6)	2 (5.9)	1 (3.2)	0
Irritability	17 (7.3)	3 (3.9)	1 (2.9)	0	1 (3.2)
Investigations					
Weight decreased	24 (10.3)	0	5 (14.7)	0	1 (3.2)
Metabolism and nutrition disorders					
Anorexia	4 (1.7)	0	4 (11.8)	0	3 (9.7)

Decreased appetite	80 (34.3)	2 (2.6)	9 (26.5)	0	3 (9.7)
Nervous system disorders					
Dizziness	10 (4.3)	3 (3.9)	3 (8.8)	0	1 (3.2)
Headache	34 (14.6)	10 (13.0)	7 (20.6)	10 (32.3)	9 (29.0)
Psychiatric disorders					
Initial insomnia	6 (2.6)	0	1 (2.9)	0	3 (9.7)
Insomnia	26 (11.2)	3 (3.9)	4 (11.8)	0	3 (9.7)
Note: Subjects are only counted once within each treatment group and by system organ class and preferred term. Percentages are based on the number of subjects in the Safety Population for the treatment group.					

Table 3: Adverse Drug Reactions Occurring in ≥5% of Adults meeting DSM criteria for ADHD who Received VYVANSE in Short-term, Parallel-group, Controlled Studies

	VYVANSE	Placebo
System Organ Class	N=493	N=202
Preferred Term	(n [%])	(n [%])
Gastrointestinal disorders		
Decreased appetite	122 (24.7)	6 (3.0)
Dry mouth	113 (22.9)	8 (4.0)
Diarrhoea	29 (5.9)	2 (1.0)
Nausea	26 (5.3)	5 (2.5)
Nervous system disorders		
Headache	100 (20.3)	13 (6.4)
General disorders and administration site conditions		
Irritability	31 (6.3)	7 (3.5)
Fatigue	25 (5.1)	7 (3.5)
Feeling jittery	25 (5.1)	0
Investigations		
Weight decreased	19 (3.9)	0
Psychiatric disorders		
Insomnia	79 (16.0)	12 (5.9)
Initial insomnia	26 (5.3)	6 (3.0)
Anxiety	25 (5.1)	0
Note: Subjects were counted once within each preferred term and treatment group. Percentages are based on the number of subjects in the Safety Population for each treatment group. Adverse events were coded using Medical Dictionary for Regulatory Activities Version 11.1.		

Table 4: Adverse Drug Reactions Occurring in > 5% of Children, Adolescents or Adults meeting DSM criteria for ADHD who Received VYVANSE in Long-term, Open-label Studies

	NRP104.302 (children) (52 weeks open-label VYVANSE)	**SPD489-306 (adolescents)** (52 weeks open-label VYVANSE)	**NRP104.304 (adults)** (52 weeks open-label VYVANSE)
System Organ Class	N=270	N=265	N=349
Preferred Term	(n [%])	(n [%])	(n [%])
Gastrointestinal disorders			
Abdominal pain upper	28 (10.4)	8 (3.0)	5 (1.4)
Dry mouth	0	14 (5.3)	58 (16.6)
Vomiting	23 (8.5)	7 (2.6)	3 (0.9)
General disorders and administration site conditions			
Irritability	26 (9.6)	33 (12.5)	39 (11.2)
Investigations			
Weight decreased	44 (16.3)	43 (16.2)	21 (6.0)
Metabolism and nutrition disorders			
Decreased appetite	84 (31.1)	56 (21.1)	50 (14.3)
Nervous system disorders			
Dizziness	0	14 (5.3)	15 (4.3)
Headache	48 (17.8)	55 (20.8)	60 (17.2)
Psychiatric disorders			
Affect lability	17 (6.3)	0	2 (0.6)

Anxiety	3 (1.1)	3 (1.1)	29 (8.3)
Insomnia	48 (17.8)	32 (12.1)	68 (19.5)
Note: Subjects are only counted once within each study and by system organ class and preferred term. Percentages are based on the number of subjects in each study.			

Table 5: Adverse Drug Reactions Occurring in ≥ 2% of Adults meeting DSM criteria for BED who Received VYVANSE in two Short-term, Parallel-group, Controlled Studies

	Pooled data from SPD489-343 and SPD489-344 (dose optimisation; 12 weeks)	
System Organ Class Preferred Term	VYVANSE N=373 (n [%])	Placebo N=372 (n [%])
Gastrointestinal disorders		
Dry mouth	136 (36)	27 (7)
Constipation	21 (6)	5 (1)
Diarrhoea	16 (4)	7 (2)
Vomiting	9 (2)	2 (1)
Upper abdominal pain	7 (2)	1 (0)
General disorders and administration site conditions		
Feeling jittery	21 (6)	2 (1)
Investigations		
Heart rate increased	26 (7)	5 (1)
Weight decreased	14 (4)	0 (0)
Metabolism and nutritional disorders		
Decreased appetite	28 (8)	9 (2)
Nervous system disorders		
Dysgeusia	6 (2)	3 (1)
Psychiatric disorders		
Insomnia	74 (20)	28 (8)
Anxiety	20 (5)	3 (1)
Restlessness	6 (2)	0 (0)
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	15 (4)	1 (0)
Note: Subjects are only counted once within each treatment group and by system organ class and preferred term. Percentages are based on the number of subjects in the Safety Population for the treatment group.		

Table 6: Adverse Drug Reactions Occurring in ≥ 2% of Adults meeting DSM criteria for BED who Received VYVANSE in Long-term, Open-label Study

	SPD489-345
System Organ Class Preferred Term	(53 weeks, open-label VYVANSE) N=599 (n [%])
Cardiac Disorders	
Tachycardia	14 (2.3)
Gastrointestinal disorders	
Dry mouth	183 (30.6)
Nausea	43 (7.2)
Constipation	42 (7.0)
Diarrhoea	26 (4.3)
Vomiting	15 (2.5)
General disorders and administration site conditions	
Irritability	42 (7.0)
Fatigue	37 (6.2)
Feeling jittery	32 (5.3)
Investigations	
Blood pressure increased	26 (4.3)
Weight decreased	26 (4.3)
Heart rate increased	15 (2.5)

Metabolism and nutritional disorders	
Decreased appetite	44 (7.3)
Nervous system disorders	
Headache	83 (13.9)
Dizziness	21 (3.5)
Somnolence	14 (2.3)
Psychiatric disorders	
Insomnia	78 (13.0)
Bruxism	37 (6.2)
Anxiety	32 (5.3)
Initial insomnia	26 (4.3)
Middle insomnia	12 (2.0)
Skin and Subcutaneous Tissue Disorders	
Hyperhidrosis	19 (3.2)
Note: Subjects are only counted once within each study and by system organ class and preferred term. Percentages are based on the number of subjects in each study.	

The following definitions apply to the frequency terminology used:

Incidence Categories:

Very common	(≥10%)
Common	(≥1% and <10%)
Uncommon	(≥0.1% and <1%)
Rare	(≥0.01% and <0.1%)
Very rare	(<0.01%)
Incidence not known	(cannot be estimated from the available data)

Table 7: Additional Adverse Reactions Reported with VYVANSE in clinical trials and postmarketing
Italic text denotes ADRs identified postmarketing

System/Organ Class	Adverse Drug Reaction	ADHD			BED
		Adults	Adolescents	Children	Adults
Immune System Disorders	Anaphylactic reaction	*Incidence not known*	*Incidence not known*	*Incidence not known*	*Incidence not known*
	Hypersensitivity	Uncommon	Uncommon	Uncommon	Uncommon
Psychiatric Disorders	Agitation	Common	Uncommon	Uncommon	Uncommon
	Logorrhoea	Uncommon	Uncommon	Uncommon	Uncommon
	Libido decreased	Common	*Incidence not known*	Not applicable	Uncommon
	Depression	Uncommon	Common	Uncommon	Uncommon
	Tic	Uncommon	Uncommon	Common	Uncommon
	Affect lability	Common	Uncommon	Common	Common
	Dysphoria	Uncommon	Uncommon	Uncommon	Uncommon
	Euphoria	Uncommon	Uncommon	*Incidence not known*	Uncommon
	Psychomotor hyperactivity	Common	Uncommon	Uncommon	Uncommon
	Bruxism	Common	Uncommon	Uncommon	Common
	Dermatillomania	Uncommon	Uncommon	Uncommon	Uncommon
	Psychotic episodes	*Incidence not known*	*Incidence not known*	*Incidence not known*	*Incidence not known*
	Mania	Uncommon	Uncommon	Uncommon	Uncommon
	Hallucination	*Incidence not known*	Uncommon	Uncommon	*Incidence not known*
	Aggression	Incidence not known	Uncommon	Common	Incidence not known
Nervous System Disorders	Dizziness	Common	Common	Common	Common
	Restlessness	Common	Common	Uncommon	Common
	Tremor	Common	Common	Uncommon	Common
	Somnolence	Uncommon	Common	Common	Uncommon
	Seizure	*Incidence not known*	*Incidence not known*	*Incidence not known*	*Incidence not known*
	Dyskinesia	Uncommon	Uncommon	Uncommon	Uncommon
	Dysgeusia	*Uncommon*	*Uncommon*	*Uncommon*	*Common*
Eye Disorders	Vision blurred	Uncommon	*Incidence not known*	Uncommon	Uncommon
	Mydriasis	*Incidence not known*	Uncommon	Uncommon	*Incidence not known*
Cardiac Disorders	Tachycardia	Common	Common	Common	Common
	Palpitation	Common	Common	Uncommon	Common
	Cardiomyopathy	*Incidence not known*	Uncommon	*Incidence not known*	*Incidence not known*
Vascular Disorders	Raynaud's phenomenon	*Incidence not known*	*Incidence not known*	Uncommon	Uncommon
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Common	Common	Uncommon	Uncommon

Gastrointestinal Disorders	Diarrhoea	Common	Common	Common	Common
	Constipation	Common	Uncommon	Common	Common
	Vomiting	Uncommon	Common	Common	Common
Hepatobilary Disorders	Eosinophilic Hepatitis	*Incidence not known*	*Incidence not known*	*Incidence not known*	*Incidence not known*
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	Common	Uncommon	Uncommon	Common
	Urticaria	Uncommon	Uncommon	Uncommon	Uncommon
	Rash	Uncommon	Uncommon	Common	Common
	Angioedema	*Incidence not known*	*Incidence not known*	*Incidence not known*	*Incidence not known*
	Stevens-Johnson Syndrome	*Incidence not known*	*Incidence not known*	*Incidence not known*	*Incidence not known*
General Disorders and Administration Site Conditions	Chest Pain	*Common*	*Uncommon*	*Uncommon*	*Uncommon*
	Pyrexia	Uncommon	Common	Common	Uncommon
Investigations	Blood pressure increased	Common	Uncommon	Uncommon	Common
	Weight decreased	Common	Very Common	Very Common	Common
Reproductive System and Breast Disorders	Erectile dysfunction	Common	Uncommon	Not applicable	Common

Suppression of growth in paediatric patients with ADHD

Weight

Weight change compared to placebo has been evaluated in 4-week trials for children (age 6-12) and adolescents (age 13-17). Higher doses were associated with greater weight loss. In children, mean weight loss from baseline to endpoint was -0.39, -0.84, and -1.12kg, respectively, for patients assigned to receive 30 mg, 50 mg, and 70 mg of VYVANSE, compared to a 0.46kg weight gain for patients receiving placebo. In adolescents, mean weight change from baseline to endpoint was -1.24, -1.94, and -2.16kg, respectively, for patients assigned to receive 30 mg, 50 mg, and 70 mg of VYVANSE, compared to a 0.9kg weight gain for patients receiving placebo.

In children and adolescents who received VYVANSE over 12 months, careful monitoring of weight suggested that consistent medication (i.e., treatment for 7 days per week throughout the year) resulted in a slowing of growth as measured by body weight. In children, the average weight percentiles at baseline (n=271) and 12 months (n=146), were 60.9 and 47.2, respectively. The age- and sex-normalised mean change from baseline in percentile over 1 year was -13.4. In adolescents, the average weight percentiles at baseline (n=265) and 12 months (n=156), were 66.0 and 61.5, respectively. The age- and sex-normalised mean change from baseline in percentile over 1 year was -6.5. See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

In children and adolescents (aged 6-17) who received VYVANSE over two years, careful monitoring of weight suggested that consistent medication (i.e., treatment for 7 days per week throughout the two years) resulted in a slowing of growth as measured by body weight. In children and adolescents, the average weight percentiles and standard deviations (SD) at baseline (N=314) and 24 months (week 104, N=189), were 65.4 (SD 27.11) and 48.2 (SD

29.94), respectively. The age- and sex-normalized mean change from baseline in percentile over 2 years was -16.9 (SD 17.33).

Long term growth

Long term controlled height and weight data with use of VYVANSE are not available. In a long-term study, careful follow-up of weight and height in children ages 7 to 10 years who were randomised to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and nonmedication treated children over 36 months (to the ages of 10 to 13 years) (total of all subgroups n=370), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

Weight Changes in Adults with BED

In the two phase 3 controlled adult trials after treatment with 50 and 70mg of VYVANSE, mean weight loss after 12 weeks was 5.8 kilograms for patients receiving VYVANSE (baseline mean BMI 33.8 kg/m2, baseline mean weight of 94.5 kilograms), compared to a mean weight change of 0.0 kilograms for patients receiving placebo (baseline mean BMI 33.2 kg/m2, baseline mean weight of 92.9 kilograms); no subject on active treatment shifted to a BMI category of underweight (less than 18.5kg/m2). Weight data from long term controlled studies (greater than 12 weeks) with VYVANSE are not available.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre telephone: 131126 (Australia).

Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, aggression, hallucinations, panic states, hyperpyrexia, rhabdomyolysis and other features of serotonin syndrome. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhoea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes administration of activated charcoal and sedation. If acute severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved.

Lisdexamfetamine and dexamphetamine are not dialysable. Acidification of the urine increases amphetamine excretion but is believed to increase risk of acute renal failure if myoglobinuria is present.

The prolonged release of VYVANSE in the body should be considered when treating patients with overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

General

Lisdexamfetamine is a pharmacologically inactive prodrug of dexamphetamine, which is a central nervous system stimulant.

Mechanism of action

After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and hydrolysed primarily in whole blood to dexamphetamine, which is responsible for the drug's activity. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action of amphetamine in Attention Deficit Hyperactivity Disorder (ADHD) is not fully established, however it is thought to be due to its ability to block the reuptake of noradrenaline 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 noradrenaline and dopamine *in vitro*.

Clinical trials

The effects of VYVANSE in the treatment of ADHD have been demonstrated in two controlled trials in children aged 6 to 12 years, one controlled study in adolescents aged 13 to 17 years, one controlled study in children and adolescents (6 to 17 years), two controlled trials in adults, one maintenance trial in children and adolescents and one maintenance trial in adults.

In clinical studies conducted in children and adults, the effects of VYVANSE were ongoing at 13 hours after dosing in children and at 14 hours in adults when the product was taken once daily in the morning (data presented below).

In dose optimisation studies, the mean daily dose of VYVANSE tended to be slightly lower in studies in children (range 44.3-50.5 mg) than in adolescents (range 53.5-58.8 mg) or adults (range 52.3-56.8 mg). This observation is consistent with the lower weights of children.

Children aged from 6 to 12 years with ADHD

A double-blind, randomised, placebo-controlled, parallel-group study was conducted in children aged 6 to 12 (N=290) who met American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomised to fixed dose treatment groups receiving final doses of 30, 50, or 70 mg of VYVANSE or placebo once daily in the morning for four weeks. All subjects receiving VYVANSE were initiated on 30 mg for the first week of treatment. Subjects assigned to the 50 and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. Significant improvements in ADHD symptoms, based upon investigator ratings on the ADHD Rating Scale (ADHD-RS), were observed at

endpoint for all VYVANSE doses compared to patients who received placebo. Mean effects at all doses were fairly similar, although the highest dose (70 mg/day) was numerically superior to both lower doses (30 and 50 mg/day). The effects were maintained throughout the day based on parent ratings (Conners' Parent Rating Scale) in the morning (approximately 10 am), afternoon (approximately 2 pm), and early evening (approximately 6 pm). ADHD-RS results for Study NRP104.301 are shown in the following table:

Table 8: ADHD-RS Total Score at Endpoint (Children; Study NRP104.301; Full Analysis Set)

	Baseline		Change from Baseline				≥50% Response[a]		
Treatment	n	Mean (SD)	n	LS Mean (SE) Change	LS Means Diff.	95% CI	p-value[b]	n	Percent	p-value[c]
Placebo	72	42.4 (7.13)	72	-6.2 (1.56)				72	12.5	
VYVANSE 30mg	69	43.2 (6.68)	69	-21.8 (1.60)	-15.58	(-20.78, -10.38)	<0.0001	71	52.1	<0.001
VYVANSE 50mg	71	43.3 (6.74)	71	-23.4 (1.56)	-17.21	(-22.33, -12.08)	<0.0001	74	60.8	<0.001
VYVANSE 70mg	73	45.1 (6.82)	73	-26.7 (1.54)	-20.49	(-25.63, -15.36)	<0.0001	73	71.2	<0.001

[a] Defined as a ³ 50% decrease from baseline in ADHD-RS Total Score at endpoint
[b] p-value is adjusted based on Dunnett's multiple comparison procedure for comparing the active doses to placebo.
[c] p-value is based on Cochran-Mantel-Haenszel test comparing each active dose to placebo controlling for pooled site.
Note: Endpoint is the last post-randomisation treatment week for which a valid ADHD-RS-IV Total Score is obtained. Response is defined as a percentage reduction from baseline in the ADHD-RS-IV Total Score of ³ 50%
Full Analysis Set=full analysis set (all subjects who took at least 1 dose of investigational product and who had a valid baseline and at least 1 post-baseline ADHD-RS total score); SE=standard error.

A second double-blind, placebo-controlled, randomised, crossover design, analog classroom study was conducted in children aged 6 to 12 (N=129) who met DSM criteria for ADHD (either the combined type or the hyperactive-impulsive type). Following a 4-week open-label dose titration with VYVANSE (30, 50, 70 mg), patients were randomly assigned to continue VYVANSE or placebo once daily in the morning for 1 week each treatment. A significant difference in patient behaviour, based upon the average of investigator ratings on the SKAMP-Deportment scores across all 7 assessments conducted at 1.5, 2.5, 5.0, 7.5, 10.0, 12.0, and 13.0 hours post-dose, were observed between patients who received VYVANSE compared to patients who received placebo. Significant differences at all assessments from 1.5 hours through 13 hours post-dose were observed between patients who received VYVANSE compared to patients who received placebo.

Adolescents aged from 13 to 17 years with ADHD

A double-blind, randomised, placebo-controlled, parallel-group study was conducted in adolescents aged 13 to 17 (N=314) who met DSM criteria for ADHD. In this four-week study, patients were randomised in a 1:1:1:1 ratio to a daily morning dose of VYVANSE (30, 50 or 70 mg/day) or placebo for a double-blind stepwise forced dose titration (3 weeks) followed by a 1-week Dose Maintenance Period. All subjects receiving VYVANSE were initiated on 30 mg for the first week of treatment. Subjects assigned to the 50 and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. Significant improvements in ADHD symptoms, based upon investigator ratings on the ADHD Rating Scale (ADHD-RS), were observed at endpoint for all VYVANSE doses compared to placebo. ADHD-RS results for Study SPD489-305 are shown in the following table:

Table 9: ADHD-RS Total Score at Endpoint (Adolescents; Study SPD489-305; Full Analysis Set)

	Baseline		Change from Baseline				≥50% Response [a]		
Treatment	n	Mean (SD)	n	LS Mean (SE) Change	LS Means Diff.	95% CI	p-value[b]	n	Percent	p-value[c]
Placebo	77	38.5 (7.11)	76	-12.8 (1.25)				77	33.8	
VYVANSE 30mg	78	38.3 (6.71)	76	-18.3 (1.25)	-5.5	(-9.7, -1.3)	0.0056	78	50.0	0.041
VYVANSE 50mg	76	37.3 (6.33)	72	-21.1 (1.28)	-8.3	(-12.5, -4.1)	<0.0001	77	59.7	0.001
VYVANSE 70mg	78	37.0 (7.30)	75	-20.7 (1.25)	-7.9	(-12.1, -3.8)	<0.0001	78	56.4	0.005

[a] Defined as a ³ 50% decrease from baseline in ADHD-RS Total Score at endpoint
[b] p-value is adjusted based on Dunnett's multiple comparison procedure for comparing the active doses to placebo.
[c] p-value is based on Cochran-Mantel-Haenszel test comparing each active dose to placebo controlling for pooled site
Note: Endpoint is the last post-randomisation treatment week for which a valid ADHD-RS-IV Total Score is obtained. Response is defined as a percentage reduction from baseline in the ADHD-RS-IV Total Score of ³ 50%
Full Analysis Set=full analysis set (all subjects who took at least 1 dose of investigational product and who had a valid baseline and at least 1 post-baseline ADHD-RS total score); SE=standard error.

VYVANSE was studied in two double-blind, parallel-group, active-controlled (OROS-methylphenidate [MPH]) studies conducted in adolescents aged 13-17 years with ADHD. Both studies also included a placebo reference arm. The primary objective of these studies was to evaluate the efficacy of VYVANSE compared with OROS-MPH as assessed by the ADHD-RS-IV total score.

The 8-week dose-optimisation study (SPD489-405) had a 5-week dose-optimisation period and a 3-week dose-maintenance period. During the dose-optimisation period, subjects were titrated once weekly based on TEAEs and clinical response to an optimal dose of 30, 50, or 70 mg/day (for VYVANSE subjects) or 18, 36, 54, or 72 mg/day (for OROS-MPH subjects), which was maintained throughout a 3-week dose-maintenance period. The mean doses at endpoint were 57.9 mg and 55.8 mg for VYVANSE and OROS-MPH, respectively. In this study, neither VYVANSE nor OROS-MPH was found to be statistically superior to the other product at Week 8. The between group difference in the LS mean change from baseline to week 8 was -2.1 (95% CI of -4.3, 0.2) (p=0.0717). The 6-week fixed-dose study (SPD489-406) had a 4-week forced-dose titration period and a 2-week dose-maintenance period. At the highest doses of VYVANSE (70 mg/day) and OROS-MPH (72 mg/day), VYVANSE treatment was found to be superior to OROS-MPH as measured by the primary efficacy analysis (change from baseline at Week 6 on the ADHD-RS Total score). The between group difference in the LS mean change from baseline to week 6 was -3.4 (95% CI of--5.4, -1.3) (p=0.0013).

Children and Adolescents aged from 6 to 17 years with ADHD

A double-blind, randomised, placebo- and active-controlled parallel-group, dose-optimisation study was conducted in children and adolescents aged 6 to 17 years (N=336) who met DSM criteria for ADHD. In this eight-week study, patients were randomised to a daily morning dose of VYVANSE (30, 50 or 70mg/day), a long-acting methylphenidate formulation (OROS-MPH) (18mg, 36 mg or 54 mg/day) or placebo (1:1:1). The study consisted of 3 periods, as follows: a Screening and Washout Period (up to 42 days), a 7-week Double-blind

Evaluation Period (consisting of a 4-week Dose-Optimisation Period followed by a 3-week Dose-Maintenance Period), and a 1-week Washout and Follow-up Period. During the 4-week Dose Optimisation Period, subjects were titrated until an optimal dose, based on TEAEs and clinical judgment, was reached.

VYVANSE showed significantly greater efficacy than placebo. The placebo-adjusted mean reduction from baseline in the ADHD-RS-IV total score was 18.6 ($p<0.001$). With regard to functional outcome, 78.0% of subjects on VYVANSE showed Improvement ("very much improved" or "much improved") on the Clinical Global Impression-Improvement (CGI-I) rating scale. VYVANSE also showed significant improvement in child achievement in academic performance, as measured by the Health Related Quality of Life instrument CHIP-CE:PRF Achievement Domain, VYVANSE demonstrated a significant improvement compared to placebo from baseline (VYVANSE: 9.4 vs. Placebo -1.1) with a mean difference between the two treatment groups of 10.5 ($p<0.001$). Outcome results for Study SPD489-325 are shown in the following table:

Table 10: Results for Study SPD489-325 at Endpoint (Children and Adolescents; Full Analysis Set)

	VYVANSE	Placebo	OROS-MPH
Change in ADHD-RS IV Total Score			
Least Square Mean	-24.3	-5.7	-18.7
Effect size (versus Placebo)	1.804	N/A	1.263
P-value (versus Placebo)	<0.001	N/A	<0.001
Percent with ≥50% Response[a]	65.4	13.2	49.5
P-value (versus Placebo)	<0.001		<0.001
Analysis of CGI-I			
Patients Showing Improvement[b]	78% (78/100)	14% (15/104)	61% (63/104)
Difference in improvement from placebo (percentage point improvement)	64	N/A	46
P-value (versus Placebo)	<0.001	N/A	<0.001
Change in CHIP-CE: PRF Achievement Domain			
Least Square Mean	9.4	-1.1	6.4
Effect size (versus Placebo)	1.28	N/A	0.912
P-value (versus Placebo)	<0.001	N/A	<0.001

[a] Defined as a ³ 50% decrease from baseline in ADHD-RS Total Score at endpoint
[b] Improvement ("very much improved" or "much improved")
Note: Endpoint is defined as the last on-treatment post-Baseline visit of the dose optimisation or dose maintenance Period (Visits 1-7) with a valid value

The long-acting methylphenidate formulation (OROS-MPH) was included as a reference arm to validate the results of the trial.

Maintenance of Efficacy Study:
A double-blind, placebo-controlled, randomised withdrawal study was conducted in children and adolescents aged 6 to 17 years (N=276) who met the diagnosis of ADHD (DSM criteria). A total of 276 patients were enrolled into the study, 236 patients participated in the preceding study SPD489-325 and 40 subjects directly enrolled. In order to ensure that the appropriate population was included in the randomised withdrawal period to evaluate the long-term maintenance of efficacy, subjects were treated with open-label VYVANSE for an extended period (at least 26 weeks) prior to being assessed for entry into the randomised withdrawal period. Eligible patients had to demonstrate treatment response as defined by CGI-S <3 and total score on the ADHD-RS ≤22. ADHD-RS Total score is a measure of core symptoms of ADHD. Of patients that maintained open label treatment response, 157 were randomised to ongoing treatment with the same dose of VYVANSE (N=78) or switched to placebo (N=79)

during the double-blind phase. Patients were observed for relapse (treatment failure) during the 6 week double blind phase. Maintenance of efficacy was demonstrated based on the significantly lower proportion of treatment failure among VYVANSE subjects (15.8%) compared to placebo (67.5%) at endpoint of the randomised withdrawal period ($p<0.001$). The endpoint measurement was defined as the last post-randomisation treatment week at which a valid ADHD-RS total score and CGI-S were observed. Treatment failure was defined as a ≥50% increase (worsening) in the ADHD-RS total score and a ≥2-point increase in the CGI-S score compared to scores at entry into the double-blind randomised withdrawal phase. For the majority of subjects (70.3%) who were treatment failures ADHD symptoms worsened at or before the week 2 visit following randomisation.

Adults with ADHD

A double-blind, randomised, placebo-controlled, parallel-group study was conducted in adults (N=420) who met DSM criteria for ADHD. In this four-week study, patients were randomised to fixed dose treatment groups receiving final doses of 30, 50, or 70 mg of VYVANSE or placebo. All subjects receiving VYVANSE were initiated on 30 mg for the first week of treatment. Subjects assigned to the 50 and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. Significant improvements in ADHD symptoms, based upon investigator ratings on the ADHD Rating Scale (ADHD-RS), were observed at endpoint for all VYVANSE doses compared to placebo. ADHD-RS results for Study NRP104.303 are shown in the following table:

Table 11: ADHD-RS Total Score at Endpoint (Adults; Study NRP104.303; Full Analysis Set)

	Baseline		Change from Baseline				≥50% Response[a]		
Treatment	n	Mean (SD)	n	LS Mean (SE) Change	LS Means Diff.	95% CI	p-value[b]	n	Percent	p-value[c]
Placebo	62	39.4 (6.42)	62	-8.2 (1.43)				62	12.9	
VYVANSE 30mg	115	40.5 (6.21)	115	-16.2 (1.06)	-8.04	(-12.14, -3.95)	<0.0001	119	36.1	0.002
VYVANSE 50mg	117	40.8 (73.0)	117	-17.4 (1.05)	-9.16	(-13.25, -5.08)	<0.0001	117	40.2	<0.001
VYVANSE 70mg	120	41.0 (6.02)	120	-18.6 (1.03)	-10.41	(-14.49, -6.33)	<0.0001	122	44.3	<0.001

[a] Defined as a ³ 50% decrease from baseline in ADHD-RS Total Score at endpoint
[b] p-value is adjusted based on Dunnett's multiple comparison procedure for comparing the active doses to placebo.
[c] p-value is based on Cochran-Mantel-Haenszel test comparing each active dose to placebo controlling for pooled site
Note: Endpoint is the last post-randomisation treatment week for which a valid ADHD-RS-IV Total Score is obtained.
Note: Response is defined as a percentage reduction from baseline in the ADHD-RS-IV Total Score of ³ 50%
Full Analysis Set=full analysis set (all subjects who took at least 1 dose of investigational product and who had a valid baseline and at least 1 post-baseline ADHD-RS total score); SE=standard error.

The second study was a multi-centre, randomised, double-blind, placebo-controlled, crossover design, modified analog classroom study of VYVANSE to simulate a workplace environment in 142 adults who met DSM criteria for ADHD. There was a 4-week open-label, dose optimisation phase with VYVANSE (30, 50, or 70 mg/day in the morning). Subjects were then randomised to one of two treatment sequences: 1) VYVANSE (optimised dose) followed by placebo, each for one week, or 2) placebo followed by VYVANSE, each for one week. Efficacy assessments occurred at the end of each week, using the Permanent Product Measure of Performance (PERMP). The PERMP is a skill-adjusted mathematics test that

measures attention in ADHD. VYVANSE treatment, compared to placebo, resulted in a statistically significant improvement in attention across all post-dose time points, as measured by average PERMP total scores over the course of one assessment day, as well as at each time point measured. The PERMP assessments were administered at pre-dose (-0.5 hours) and at 2, 4, 8, 10, 12, and 14 hours post-dose. In this study most subjects (> 80%) required a dose greater than 30 mg. The majority of subjects (~50%) had a final dose of 50 mg.

Maintenance of Efficacy Study:
A double-blind, placebo-controlled, randomised withdrawal design study was conducted in adults aged 18 to 55 (N=123) who met DSM criteria for ADHD. At study entry, subjects must have had documentation of treatment with VYVANSE for a minimum of 6 months and had to demonstrate treatment response as defined by CGI-S ≤3 and Total Score on the ADHD-RS with adult prompts <22. ADHD-RS with adult prompts Total Score is a measure of core symptoms of ADHD. Subjects that maintained treatment response at week 3 of open label treatment phase (N=116) were eligible to enter the 6 week double-blind randomised withdrawal phase, and received their entry dose of VYVANSE (N=56) or placebo (N=60). Maintenance of efficacy for subjects treated with VYVANSE was demonstrated by the significantly lower proportion of treatment failure (<9%) compared to subjects receiving placebo (75%) in the double-blind randomised withdrawal phase ($p<0.0001$). Treatment failure was defined as a ≥50% increase in the ADHD-RS with adult prompts Total Score and ≥2-point increase in the CGI-S score compared to scores at entry into the double-blind randomised withdrawal phase. For subjects receiving VYVANSE, the median and mean duration in the double-blind randomised withdrawal phase was 42.0 and 39.1 days, respectively. For subjects receiving placebo, the median and mean duration in the double-blind randomised withdrawal phase was 13.0 and 18.2 days, respectively. The difference in duration between the two treatment groups was because the majority of treatment failures occurred in the first 14 days after subjects were switched from open-label SPD489 treatment to placebo.

Adults with Binge Eating Disorder (BED)

The efficacy of VYVANSE in the treatment of BED was demonstrated in two 12 week randomised, double-blind, multicentre, parallel-group, placebo-controlled, dose-optimisation studies in adults aged 18-55 years with moderate to severe BED (SPD489-343: N=374 and SPD489-344: N=350). A diagnosis of BED was confirmed using DSM criteria for BED. Severity of BED was determined based on having at least 3 binge days per week for 2 weeks prior to the Baseline Visit and on having a CGI-S score of ≥ 4 at the Baseline Visit. For both studies, a binge day was defined as a day with at least 1 binge episode, as determined from the subject's daily binge diary and confirmed by the clinician.

Both 12-week studies consisted of a 4-week Dose-optimisation Period and an 8-week Dose-maintenance Period. During dose-optimisation, subjects assigned to VYVANSE began treatment at the titration dose of 30mg/day and, after 1 week of treatment, were subsequently up-titrated to 50mg/day. Additional increases to 70mg/day were made as tolerated and clinically indicated. Following the Dose-optimisation Period, subjects continued on their optimised dose for the duration of the Dose-maintenance Period.
The primary efficacy endpoint for the two studies was defined as the change from baseline at Weeks 11/12 in the number of binge days per week. Baseline was defined as the weekly average of the number of binge days per week for the 14 days prior to the Baseline Visit. Subjects from both studies on VYVANSE had a statistically significantly ($p<0.001$) greater reduction from baseline in mean number of binge days per week at Weeks 11/12. In addition,

subjects on VYVANSE showed greater improvement as compared to placebo across key secondary outcomes with higher proportion of subjects rated improved on the CGI-I rating scale, higher proportion of subjects with 4-week binge cessation, and greater reduction in the Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) total score in both studies.

Table 12: Summary of Primary Efficacy Results in BED

Study Number	**Treatment Group**	**Primary Efficacy Measure: Binge Days per Week at Week 12**		
		Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference[a] (95% CI)**
Study SPD489-343	VYVANSE (50 or 70 mg/day)*	4.79 (1.27)	-3.87 (0.12)	-1.35 (-1.70, -1.01)
	Placebo	4.60 (1.21)	-2.51 (0.13)	--
Study SPD489-344	VYVANSE (50 or 70 mg/day)*	4.66 (1.27)	-3.92 (0.14)	-1.66 (-2.04, -1.28)
	Placebo	4.82 (1.42)	-2.26 (0.14)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

Maintenance of Efficacy Study:
A double-blind, placebo controlled, randomised withdrawal design study was conducted to evaluate maintenance of efficacy based on time to relapse between VYVANSE and placebo in adults aged 18 to 55 (N=267) with moderate to severe BED. In this longer-term study patients who had responded to VYVANSE in the preceding 12-week open-label treatment phase were randomised to continuation of VYVANSE or placebo for up to 26 weeks of observation for relapse. Response in the open-label phase was defined as 1 or fewer binge days each week for four consecutive weeks prior to the last visit at the end of the 12-week open-label phase and a CGI-S score of 2 or less at the same visit. Relapse during the double-blind phase was defined as having 2 or more binge days each week for two consecutive weeks (14 days) prior to any visit and having an increase in CGI-S score of 2 or more points compared to the randomised-withdrawal baseline. Maintenance of efficacy for patients who had an initial response during the open-label period and then continued on VYVANSE during the 26-week double-blind randomised-withdrawal phase was demonstrated with VYVANSE being superior over placebo as measured by time to relapse. Additionally, the group continuing on VYVANSE had a lower proportion of relapse (5/136, 3.7%) as compared to the placebo group (42/131, 32.1%)

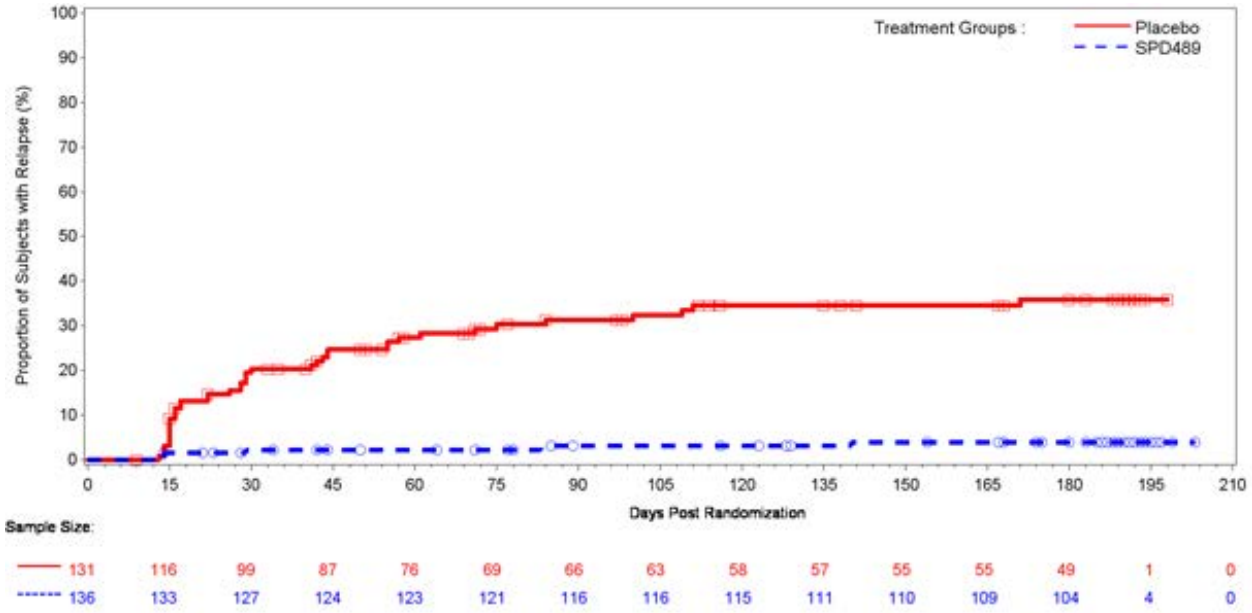


Figure 1: Kaplan-Meier Survival Plot of Time to Relapse (Full Analysis Set) – Study SPD489-346

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetic studies of dexamphetamine after oral administration of lisdexamfetamine dimesilate have been conducted in healthy adult and paediatric (6–12 years) patients with ADHD.

Absorption

After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract, thought to be mediated by the high capacity PEPT1 transporter.

In 18 paediatric patients (6–12 years) with ADHD, the Tmax of dexamphetamine was approximately 3.5 h following single-dose oral administration of lisdexamfetamine dimesilate either 30 mg, 50 mg, or 70 mg after an 8-hour overnight fast. The Tmax of lisdexamfetamine dimesilate was approximately 1 h. Linear pharmacokinetics of dexamphetamine after single-dose oral administration of lisdexamfetamine dimesilate was established over the dose range of 30 mg to 70 mg in children aged 6 to 12 years and over the dose range of 50 mg to 250 mg in adults. Dexamphetamine pharmacokinetic parameters following administration of lisdexamfetamine in adults exhibited low inter-subject (<25%) and intra-subject (<8%) variability. Safety and efficacy have not been studied above the maximum recommended dose of 70 mg.

Food (a high fat meal or soft food such as yogurt) or orange juice does not affect the observed AUC and C_{max} of dexamphetamine in healthy adults after single-dose oral administration of 70 mg of VYVANSE capsules. Food prolongs Tmax by approximately 1 hour (from 3.8 h at fasted state to 4.7 h after a high fat meal or to 4.2 h after soft food such as yogurt).

After an 8-hour fast, the AUC for dexamphetamine following oral administration of lisdexamfetamine dimesilate in solution and as intact capsules were equivalent. Weight/Dose normalised AUC and Cmax for dexamphetamine were 22% and 12% lower, respectively, in adult females than in males on day 7 following a 70 mg/day dose of lisdexamfetamine for 7 days. Weight/Dose normalised AUC and Cmax values were the same in girls and boys following single doses of 30-70 mg.

Distribution

There is no accumulation of dexamphetamine AUC at steady state in healthy adults and no accumulation of lisdexamfetamine dimesilate after once-daily dosing for 7 consecutive days.

Metabolism

Lisdexamfetamine is converted to dexamphetamine and L-lysine, not by cytochrome P450 enzymes metabolism, but by metabolism in blood primarily due to the hydrolytic activity of red blood cells. Red blood cells have a high capacity for metabolism of lisdexamfetamine as *in vitro* data demonstrated substantial hydrolysis occurs even at low haematocrit levels. Amphetamine is reported to be oxidised at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain α or β carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively. Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidised to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine.

Excretion

Following the oral administration of a 70 mg dose of radiolabelled lisdexamfetamine dimesilate to 6 healthy subjects, approximately 96% of the oral dose radioactivity was recovered in the urine and only 0.3% recovered in the faeces over a period of 120 hours. Of the radioactivity recovered in the urine, 42% of the dose was related to amphetamine, 25% to hippuric acid, and 2% to intact lisdexamfetamine. Plasma concentrations of unconverted lisdexamfetamine are low and transient, generally becoming non-quantifiable by 8 hours after administration. The plasma elimination half-life of lisdexamfetamine typically averaged less than 1 hour in studies of lisdexamfetamine dimesilate in volunteers.

Special populations

Age

The pharmacokinetics of dexamphetamine, as evaluated by clearance, is similar in paediatric (aged 6 to 12) and adolescent (aged 13 to 17) ADHD patients, and healthy adult volunteers after correcting for body weight. Following administration of lisdexamfetamine dimesilate in a study of 47 subjects aged 55 years of age or older, amphetamine clearance was approximately 0.7 L/h/kg for subjects 55-74 years of age and 0.55 L/h/kg for subjects ≥75 years of age. This is slightly reduced compared to younger adults (approximately 1 L/h/kg for subjects 18-45 years of age).

Sex

Following administration of lisdexamfetamine dimesilate, systemic exposure to dexamphetamine is similar for men and women given the same mg/kg dose.

Race

Formal pharmacokinetic studies for race have not been conducted.

Renal Disease

In a pharmacokinetic study of lisdexamfetamine in subjects with normal and impaired renal function dexamphetamine clearance was reduced from 0.7 L/h/kg in normal subjects to 0.4L/hr/kg in subjects with severe renal impairment (GFR 15 to <30 mL/min/1.73m2). See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

In subjects with ESRD requiring dialysis mean dexamphetamine clearance was reduced to 0.3 L/h/kg both pre- and post-dialysis. Dialysis did not significantly affect the clearance of dexamphetamine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Lisdexamfetamine dimesilate was negative (not clastogenic) in the mouse micronucleus test *in vivo* and was negative in the bacterial reverse mutation test and the L5178Y/TK+/- mouse lymphoma assay *in vitro.*

Carcinogenicity

Carcinogenicity studies of lisdexamfetamine dimesilate have not been performed.
No evidence of carcinogenicity was found in studies in which d-, l-amphetamine sulphate (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

VYVANSE capsules contain the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The capsule shells contain gelatin, titanium dioxide (all strengths), erythrosine (30mg and 70 mg), brilliant blue FCF (40 mg, 50 mg, 60mg and 70 mg), iron oxide yellow (20 mg and 40 mg), iron oxide black (40 mg) and TekPrint SW-9008 (all strengths). Refer to Section 2 – QUALITATIVE AND QUANTITATIVE COMPOSITION.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

For interactions, please refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

20mg, 40mg, 60mg: 36 months from date of manufacture.
30mg, 50mg, 70mg: 30 months from date of manufacture.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

VYVANSE should be stored below 25º C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type

VYVANSE capsules are packed in high density polyethylene (HDPE) bottles with polypropylene child resistant (PP CR) cap, inside a cardboard carton.

Pack size

30 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

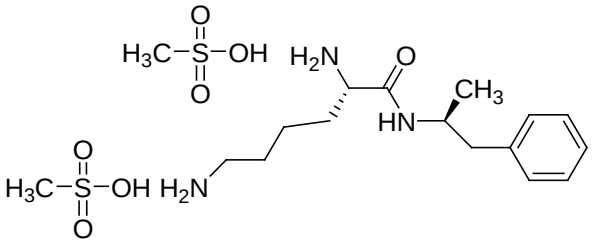
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Formula

$C_{17}H_{33}N_3O_7S_2$

Chemical structure



CAS numbers

Lisdexamfetamine: 608137-32-2
Lisdexamfetamine dimesilate: 608137-33-3

Molecular weight

455.59

7 MEDICINE SCHEDULE (POISONS STANDARD)

Controlled Drug (S8)

8 SPONSOR

Shire Australia Pty Limited
Level 39
225 George Street
Sydney, NSW 2000
Australia
Telephone: 1800 012 612
www.shireaustralia.com.au

9 DATE OF FIRST APPROVAL

VYVANSE 30 mg, 50 mg, 70 mg capsules:	22 July 2013
VYVANSE 40 mg, 60 mg:	17 November 2017
VYVANSE 20 mg:	22 November 2017

10 DATE OF REVISION

24 January 2018

Summary table of changes

Section Changed	Summary of new information

4.1, 4.2	Addition of details for use in Binge Eating Disorder
4.4	Addition of safety information under cardiovascular disease, prescribing and dispensing, use in children
4.8, 5.1	Update to ADHD section and addition section for Binge Eating Disorder