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APPROVED PROFESSIONAL INFORMATION

AMFETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMFETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO MEDICINE DEPENDENCE. MISUSE OF AMFETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

SCHEDULING STATUS

S6

1 NAME OF THE MEDICINE

VYSERA 30 mg (Lisdexamfetamine dimesilate) Capsules

VYSERA 50 mg (Lisdexamfetamine dimesilate) Capsules,

VYSERA 70 mg (Lisdexamfetamine dimesilate) Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VYSERA capsules contain 30 mg, 50 mg, or 70 mg of lisdexamfetamine dimesilate as the active ingredient

Sugar Free

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Capsules (hard)

Appearance

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

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

VYSERA 70 mg capsules: blue opaque body and pink opaque cap, printed ‘S489’ and ‘70 mg’ in black ink.

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4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention Deficit Hyperactivity Disorder (ADHD)

VYSERA is indicated for the treatment of Attention Deficit Hyperactivity Disorder. Diagnosed according to the most recent DSM diagnostic criteria for ADHD in patients ≥ 13 years of age up to 55 years of age when treatment with methylphenidate and atomoxetine has failed. Treatment with VYSERA should be part of a comprehensive treatment program for ADHD.

Long term use:

The need for continuation of treatment with VYSERA should be re-assessed every 6 months.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a medical practitioner experienced in treatment of patients with ADHD. Patients should be reviewed at least every 6 months to assess if there is an on-going need for treatment with VYSERA. Blood pressure and cardiovascular status should also be regularly reviewed.

Dosage should be individualised according to the therapeutic needs and response of the patient. Careful dose titration is necessary at the start of treatment with VYSERA.

VYSERA should be administered orally at the lowest possible dosage and should then be slowly adjusted to the lowest effective dose for each individual.

VYSERA should be taken in the morning with or without food; avoid afternoon doses because of the potential for insomnia.

VYSERA 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 VYSERA have not been studied. The effectiveness of VYSERA has not been established in adults over 55 years of age. Due to reduced clearance in patients with severe renal insufficiency (GFR 15

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to <30 mL/min/1,73 m^2) the maximum daily dose should not exceed 50 mg. 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 dexamfetamine are not dialysable.

VYSERA should not be used in children under the age of 13 years as the available formulations are not appropriate for up or down titration to find an optimal dose in children aged 6-12 years. Safety and efficacy in children under the age of 6 years have not been established

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 at weekly intervals. VYSERA should be administered orally at the lowest possible dosage.

VYSERA has not been studied in children under 6 years of age and up or down titration in children 6 to 12 years of age to optimise the dose needed cannot be achieved with the current available formulations.

4.3 Contraindications

VYSERA is contraindicated in patients with:

- Known hypersensitivity to sympathomimetic amines or any of the excipients listed in Section 6.1.
- Advanced arteriosclerosis
- Symptomatic cardiovascular disease including cardiac dysrhythmias, ischaemic heart disease and other structural and/or functional cardiac disorders. Moderate to severe hypertension
- Hyperthyroidism or thyrotoxicosis
- Glaucoma
- Agitated states
- Concomitant use of monoamine oxidase inhibitors (MAOIs) or within 14 days after MAOIs treatment including MAOIs such as linezolid or intravenous methylene blue (risk of

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hypertensive crisis).

- Phaeochromatocytoma
- Tics, Tourette's syndrome
- Patients with severe depression, anorexia nervosa, psychotic symptoms or suicidal tendency
- Patients with known drug dependence or alcohol abuse
- Pregnancy and lactation (see Section 4.6 Pregnancy, Lactation and Fertility)

4.4 Special Warnings and Precautions For Use

VYSERA has a potential for abuse, misuse, dependence, or diversion for non-therapeutic uses. Medical practitioners should assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy. VYSERA 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.

Stimulants including VYSERA have a potential for abuse, misuse, or diversion that medical practitioners should consider when prescribing VYSERA. The risk of misuse may be greater in adults (especially young adults) than in paediatric use. Stimulants should be prescribed cautiously to patients with a history of substance abuse or dependence.

Patients should be cautioned against increasing the recommended dosage. Should psychological and/or physical 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 electro-encephalogram (EEG).

Manifestations of chronic intoxication with amfetamines 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 VYSERA, it is important to consider the patient's personal and

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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 dysrhythmias) and physical examination 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 medicines, including VYSERA, in the ADHD population.

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 medicine.

Adults:
Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant medicines 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 medicines.

Hypertension and other cardiovascular conditions
Stimulant medications cause a modest increase in average mean blood pressure (about 2-4

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mm Hg) and mean heart rate (about 3-6 bpm), and individuals may have larger increases. 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 dysrhythmias.

Lisdexamfetamine has shown to prolong the QTc interval in some patients. It should be used with caution in patients with prolongation of the QTc interval, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances.

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 post-marketing experience of some medications indicated for the treatment of ADHD, including VYSERA. 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.

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Seizures

Stimulants may lower the convulsive threshold in patients with prior history of seizure, in patients with prior EEG abnormalities without previous seizures, and in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, VYSERA should be discontinued.

Visual disturbance

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

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 the use of stimulant medications. (see Section 4.3 Contraindications)

Long-term suppression of growth (height and weight)

VYSERA 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 VYSERA, 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 post-marketing 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 the medicine. 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

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

Paediatric use

ADHD

VYSERA should not be used in children under the age of 13 years. Current available formulation do not allow optimisation of the dose requirements (best benefit risk balance) for children 6 -12 years. Safety and efficacy of VYSERA in children under the age of 6 years have not been established.

Adult patients aged over 55 years

VYSERA safety and efficacy have 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 impairment (GFR 15 to <30 mL/min/1,73 m^2) the maximum VYSERA daily dose should not exceed 50 mg. Further dosage reduction should be considered in patients undergoing dialysis. See Section 5 PHARMACOLOGICAL PROPERTIES, Special populations.

Lisdexamfetamine and dexamfetamine are not dialysable.

Effects on laboratory tests

Amfetamines, such as VYSERA can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amfetamine may interfere with urinary steroid determinations.

Use with other sympathomimetic drugs

VYSERA should be used with caution in patients who use other sympathomimetic drugs (see section 4.5).

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially

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'sodium-free'.

4.5 Interaction with Other Medicines and Other Forms of Interaction

***In vitro* enzyme inhibition**

VYSERA 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. VYSERA 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.

Medicines whose blood levels may be impacted by VYSERA

Extended release guanfacine:

In a drug interaction study, administration of an extended release guanfacine in combination with VYSERA 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 dexamfetamine exposure was observed following co-administration of extended release guanfacine and VYSERA.

Extended release venlafaxine:

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

Medicines and conditions that alter urinary pH and impact the urinary excretion and half-life of amfetamine

Ascorbic acid and other medicines or conditions that acidify urine increase urinary excretion and decrease the half-life of amfetamine.

Sodium bicarbonate and other medicines or conditions that alkalinise urine decrease urinary excretion and extend the half-life of amfetamine.

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Monoamine oxidase inhibitors

Do not administer VYSERA concomitantly with MAOIs or within 14 days after discontinuing MAOIs treatment. Concomitant use of MAOIs and CNS stimulants, such as VYSERA, can cause hypertensive crisis. Severe outcomes including death may occur (See Section 4.3 Contraindications).

Serotonergic medicines

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

Medicines whose effects may be reduced by amfetamines

Anti-hypertensives: Amfetamines may decrease the effectiveness of antihypertensive medications.

Medicines whose effects may be potentiated by amfetamines

Amfetamines, such as VYSERA potentiate the analgesic effect of narcotic analgesics.

Medicines that may reduce the effects of amfetamines

Chlorpromazine:

Chlorpromazine blocks dopamine and norepinephrine (noradrenaline) receptors, thus inhibiting the central stimulant effects of amfetamines.

Haloperidol:

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

Lithium Carbonate:

The anorectic and stimulatory effects of amfetamines may be inhibited by lithium carbonate.

Use with alcohol

There are limited data on the possible interaction with alcohol.

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4.6 Pregnancy, Lactation and Fertility

Pregnancy

VYSERA should not be used in pregnancy as harm to the foetus cannot be excluded. Dexamfetamine, the active metabolite of lisdexamfetamine, crosses the placenta. Amfetamines such as VYSERA cause vasoconstriction and may decrease placental perfusion which may affect the developing foetus. It also stimulates uterine contractions increasing the risk of premature delivery and low birth weight babies. There is some evidence, although inconclusive, that amfetamine use in early pregnancy, may be associated with an increased risk of pre-eclampsia.

Women of childbearing age being treated with VYSERA should be advised not to become pregnant.

Effects on infants

Infants born to mothers taking amfetamines should be monitored for symptoms of withdrawal such as feeding difficulties, irritability, agitation and excessive drowsiness.

Effects on embryo-foetal development

In animal reproduction studies, VYSERA had no apparent effects on embryo foetal 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 dexamfetamine 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 VYSERA has not been conducted in rats treated throughout gestation and lactation. Amfetamine 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 amfetamine base/kg/day, reduced the number of live born 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 amfetamine AUC about half that expected in adults at the maximum recommended dose of 70 mg.

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Lactation

Women on treatment with VYSERA should not breastfeed their infants.

Amfetamines are excreted in human milk. There is a risk of severe adverse reactions in the infant including cardiovascular reactions, blood pressure and heart rate increases, suppression of growth and peripheral vasculopathy. Long term neurodevelopmental effects on infants from amfetamine exposure are unknown**.**

Fertility

The effect of VYSERA on human fertility has not been investigated. The effects of VYSERA on fertility and early embryonic development have not been investigated in animal reproductive studies. Amfetamine has shown no harmful effects on fertility in a rat study. Amfetamine (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 amfetamine base/kg/day. This dose resulted in a plasma amfetamine AUC which was 4 (males) and 6 (females) fold the AUC expected in adults at the maximum recommended dose of 70 mg.

4.7 Effects on Ability to Drive and Use Machines

VYSERA may affect the ability of patients to drive or use machinery. Patients should not drive or use machinery until they know how treatment with VYSERA affects them. VYSERA can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision.

4.8 Undesirable Effects

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 VYSERA.

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 VYSERA.

Adverse Reactions Associated with Discontinuation of Treatment in ADHD Clinical Trials:

In patients aged 6 to 12 years, 8 % of VYSERA -treated patients discontinued due to adverse reactions compared to 0 % of placebo-treated patients. The most frequently reported adverse reactions were ECG criteria for left ventricular hypertrophy, tics, vomiting, psychomotor hyperactivity, insomnia, decreased appetite and rash. Less frequently reported adverse reactions included upper abdominal pain, dry mouth, decreased weight, dizziness, somnolence,

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logorrhoea, chest pain, anger and hypertension.

In patients aged 13 to 17 years, 3 % of VYSERA -treated patients discontinued due to adverse reactions compared to 1% of placebo-treated patients. The most frequently reported adverse reactions were decreased appetite (1 %), and insomnia (1 %). Less frequently reported adverse reactions included irritability, dermatillomania, mood swings, and dyspnoea.

In the controlled adult trial, 6 % of VYSERA -treated patients discontinued due to adverse reactions compared to 2 % of placebo-treated patients. The most frequently reported adverse reactions were insomnia (2 %), tachycardia (1 %), irritability (1 %), hypertension (1 %), headache (1 %), anxiety (1 %), and dyspnoea (1 %). Less frequently reported adverse reactions included palpitations, diarrhoea, nausea, decreased appetite, dizziness, agitation, depression, paranoia and restlessness.

Table 1: Adverse Drug Reactions Occurring in ≥2 % of Children meeting DSM criteria for ADHD who Received VYSERA in Short-term, Parallel-group, Controlled Studies

	NRP104.301 (forced dose; 4 weeks)		**SPD489-325 (dose optimisation; 7 weeks)**	
System Organ Class Preferred Term	VYSERA N=218 (n [%])	Placebo N=72 (n [%])	VYSERA N=77 (n [%])	Placebo N=79 (n [%])
Gastrointestinal disorders				
Abdominal discomfort/pain	2 (0,9)	2 (2,8)	6 (7,8)	4 (5,1)
Abdominal pain upper	25 (11,5)	4 (5,6)	6 (7,8)	5 (6,3)
Diarrhoea	1 (0,5)	2 (2,8)	4 (5,2)	1 (1,3)
Dry mouth	10 (4,6)	0 (0,0)		
Nause	13 (6,0)	2 (2,8)	8 (10,4)	2 (2,5)
Toothache			0	2 (2,5)
Vomiting	19 (8,7)	3 (4,2)	3 (3,9)	1 (1,3)
General disorders and administration site conditions				
Fatigue			3 (3,9)	2 (2,5)
Irritability	21 (9,6)	0	3 (3,9)	0
Pyrexia	5 (2,3)	1 (1,4)	3 (3.9)	0
Investigations				
ECG QT prolongation			2 (2.6)	1 (1,3)
Weight decreased	19 (8,7)	2 (2,8)	10 (13,0)	0
Infections and Infestations				
Nasopharyngitis			4 (5,2)	5 (6,3)
Rhinitis			2 (2,60)	2 (2,5)
Upper respiratory tract infections			1 (1,3)	2 (2,5)

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Metabolism and nutrition disorders				
Anorexia	16 (7,3)	1 (1,4)	8 (10,4)	2 (2,5)
Decreased appetite	88 (40,4)	3 (4,2)	19 (24,7)	3 (3,8)
Nervous system disorders				
Dizziness	11 (5,0)	0	1 (1,3)	1 (1,3)
Headache	26 (11,9)	7 (9,7)	9 (11,7)	12 (15,2)
Somnolence	5 (2,3)	1 (1,4)		
Psychiatric disorders				
Affect lability	9 (4,1)	0		
Aggression	3 (1,4)	0	4 (5,2)	1 (1,3)
Initial insomnia	8 (3,7)	0	2 (2,6)	1 (1,3)
Insomnia	42 (19,3)	2 (2,8)	12 (15,6)	0
Sleep disorders			4 (5,2)	1 (1,3)
Restlessness			1 (1,3)	2 (2,5)
Tic	5 (2,3)	0	2 (2,5)	2 (2,5)
Respiratory, Thoracic, Mediastinal disorders				
Cough	3 (1,4)	4 (5,6)	3 (3,9)	0
Nasal congestion	3 (1,4)	4 (5,6)		
Oropharyngeal pain	7 (3,2)	2 (2,8)		
Skin and subcutaneous disorders				
Erythema			1 (1,3)	2 (2,5)
Rash	6 (2,8)	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 each treatment group				

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

	SPD489-305 (forced dose; 4 weeks)		**SPD489-325 (dose optimisation; 7 weeks)**	
	VYSERA	Placebo	VYSERA	Placebo
System Organ Class Preferred Term	N=233 (n [%])	N=77 (n [%])	N=34 (n [%])	N=31 (n [%])
Gastrointestinal disorders				
Abdominal discomfort/pain	4 (1,7)	3 (3,9)	0	2 (6,5)
Abdominal pain upper	2 (0,9)	3 (3,9)	2 (5,9)	1 (3,2)
Dry mouth	10 (4,3)	1 (1.3)	2 (5,9)	0
Diarrhoea	6 (2,6)	2 (2,6)	1 (2,9)	
Nausea	9 (3,9)	2 (2,6)	4 (11.8)	1 (3,2)
Toothache			1 (2,9)	0
Vomiting	3 (1,3)	4 (5,2)	1 (2,9)	0
General disorders and administration site conditions				

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Chills			1 (2,9)	0
Peripheral coldness			1 (2,9)	0
Thirst			1 (2,9)	1 (3,2)
Fatigue	10 (4,3)	2 (2,6)	2 (5,9)	1 (3,2)
Irritability	16 (6,9)	3 (3,9)	1 (2,9)	0
Infections and Infestations				
Gastroenteritis			3.(8,8)	0
Nasopharyngitis	7 (3,0)	1 (1,3)	4 (11,8)	3 (9,7)
Sinusitis	1 (0,4)	3 (3,9)	0	2 (6,5)
Upper respiratory tract infection	10 (4,3)	6 (7,8)	2(5,9)	0
Investigations				
Blood Pressure Increase			0	1 (3,2)
ECG QT Prolongation			1 (2,9)	0
Weight decreased	22 (9,4)	0	5 (14,7)	0
Metabolism and nutrition disorders				
Anorexia	4 (1,7)	0	4 (11,8)	0
Decreased appetite	83 (35,6)	2 (2,6)	9 (26,5)	0
Polydipsia			1 (2,9)	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal chest pain			1 (2,9)	1 (3,2)
Neck pain			1 (2,9)	1 (3,2)
Cardiac disorders				
Angina			1 (2,9)	0
Tachycardia			1 (2,9)	1 (3,2)
Palpitations	5 (2,1)	1 (1,3)	1 (2,9)	1 (3,2)
Nervous system disorders				
Dizziness	10 (4,3)	3 (3,9)	3 (8,8)	0
Headache	34 (14,6)	10 (13,0)	7 (20,6)	10 (32,3)
Migraine			2 (5,9)	0
Somnolence	1 (0,4)	2 (2,6)		
Poor quality sleep			1 (2,9)	0
Tremor			1 (2,9)	1 (3,2)
Psychiatric disorders				
Initial insomnia	6 (2,6)	0	1 (2,9)	0
Insomnia	26 (11,2)	3 (3,9)	4 (11,8)	0
Euphoric mood			1 (2,9)	0
Sleep disorder			2 (5,9)	0
Respiratory, Thoracic and mediastinal disorders				
Allergic Bronchitis			1 (2,9)	0
Dyspnoea			1 (2,9)	1 (3,2)
Skin and subcutaneous skin disorders				

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Pruritus	1 (2,9)	
Vascular disorders		
Flushing	1 (2,9)	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 3: Adverse Drug Reactions Occurring in ≥2 % of Adults meeting DSM criteria for ADHD who Received VYSERA in Short-term, Parallel-group, Controlled Studies

System Organ Class Preferred Term	VYSERA N=493 (n [%])	Placebo N=202 (n [%])
Gastrointestinal disorders		
Upper abdominal pain	11 (2,2)	2 (1,0)
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		
Dizziness	13 (2,6)	4 (2,0)
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
Infections and Infestations		
Nasopharyngitis	12 (2,4)	5 (2,5)
Upper respiratory tract infections	29 (5,9)	4 (2,0)
Investigations		
Blood pressure increase	11 (2,2)	1 (0,5)
Weight decreased	19 (3,9)	0
Metabolism and nutritional disorders		
Decreased appetite	143 (29,0)	6 (3,0)
Respiratory Thoracic and mediastinal disorders		
Dyspnoea	12 (2,4)	0
Psychiatric disorders		
Insomnia	79 (16,0)	12 (5,9)
Agitation	12 (2,4)	1 (0,5)
Initial insomnia	26 (5,3)	6 (3,0)
Middle insomnia	13 (2,6)	0 (0,5)
Anxiety	25 (5,1)	0
Skin and subcutaneous tissue disorders		

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Hyperhidrosis	14 (2,8)	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 ≥ 2 % of Children, Adolescents or Adults meeting DSM criteria for ADHD who Received VYSERA in Long-term, Open-label Studies

System Organ Class Preferred Term	**NRP104.302 (children)** (52 weeks open-label VYSERA) N=270 (n [%])	**SPD489-306 (adolescents)** (52 weeks open-label VYSERA) N=265 (n [%])	**NRP104.304 (adults)** (52 weeks open-label VYSERA) N=349 (n [%])
Gastrointestinal disorders			
Abdominal discomfort	7 (2,6)	5 (1,9)	
Abdominal pain upper	29 (10,7)	8 (3,0)	
Constipation			10 (2,9)
Diarrhoea	9 (3,3)	6 (2,3)	11 (3,2)
Dyspepsia			8 (2,3)
Dry mouth	5 (1,9)	15 (5,7)	58 (16,6)
Nausea			16 (4,6)
Toothache	6 (2,2)	9 (3,4)	
Vomiting	23 (8,5)	7 (2,6)	
General disorders and administration site conditions			
Fatigue	7 (2,6)	6 (2,3)	15 (4,3)
Feeling Jittery			11 (3,2)
Pyrexia	13 (4,8)	10 (3,8)	
Irritability	27 (10,0)	33 (12.5)	39 (11,2)
Infections and Infestations			
Bronchitis	2 (0,7)	9 (3,4)	
Ear Infection	7 (2,6)	2 (0,8)	
Gastroenteritis	5 (1,9)	9 (3,4)	14 (4,0)
Gastroenteritis viral	11(4,1)	6 (2,3)	13 (3,7)
Influenza	16 (5,9)	18 (6,8)	16 (3,6)
Nasopharyngitis	25 (9,3)	19 (7,2)	26 (7,4)
Pharyngitis Streptococcal	8 (3,0)	6 (2,3)	
Sinusitis			23 (6,6)
Upper respiratory tract infection	29 (10,7)	58 (21,9)	76 (21,8)
Investigations			
Blood pressure increase			8 (2,3)
Heart rate increased	1 (0,4)	6 (2,3)	10 (2,9)

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Weight decreased	48 (17,8)	45(17,0)	21 (6,0)
Metabolism and nutrition disorders			
Anorexia			12 (3,4)
Decreased appetite	92 (34,1)	61 (23,0)	50 (14,3)
Musculoskeletal and connective tissue disorders			68 (22,6)
Nervous system disorders			
Dizziness	4 (1,5)	14 (5,3)	15 (4,3)
Headache	48 (17,8)	55 (20,8)	60 (17,2)
Psychiatric disorders			
Affect lability	17 (6,3)	5 (1,9)	
Anxiety	3 (1,1)	3 (1,1)	29 (8,3)
Insomnia	48 (17,8)	32 (12,1)	68 (19,5)
Initial insomnia	8 (3,0)	6 (2,3)	17 (4,9)
Mood Swings	9 (3,3)	5 (1,9)	
Tearfulness	10 (3,7)	0	
Respiratory, Thoracic and Mediastinal disorders			
Cough	19 (7,0)	9 (3,4)	17 (4,9)
Oropharyngeal pain	9 (3,3)	8 (3,0)	15 (4,3)
Sinus congestion			12 (3,4)
Skin and subcutaneous tissue disorders			40 (11,5)
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.			

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)

Additional Adverse Reactions reported with VYSERA in Clinical Trials

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Table 5: Additional Adverse Reactions reported with VYSERA in Clinical Trials

System/Organ Class	Adverse Drug Reaction	ADHD		
		Adults	Adolescents	Children
Immune System Disorders	*Anaphylactic reaction	Frequency not known	Frequency not known	Frequency not known
	Hypersensitivity	Uncommon	Uncommon	Uncommon
Psychiatric Disorders	*Insomnia	Very common	Very common	Very common
	Agitation	Common	Uncommon	Uncommon
	Anxiety	Common	Common	Uncommon
	Logorrhoea	Uncommon	Uncommon	Uncommon
	Libido decreased	Common	Not reported	Not applicable
	Depression	Uncommon	Common	Uncommon
	Tic	Uncommon	Uncommon	Common
	Affect lability	Common	Uncommon	Common
	Dysphoria	Uncommon	Uncommon	Uncommon
	Euphoria	Uncommon	Uncommon	Frequency not known
	Psychomotor hyperactivity	Common	Uncommon	Uncommon
	Bruxism	Common	Uncommon	Uncommon
	Dermatillomania	Uncommon	Uncommon	Uncommon
	*Psychotic episodes	Frequency not known	Frequency not known	Frequency not known
	Mania	Uncommon	Uncommon	Uncommon
	Hallucination	Frequency not known	Uncommon	Uncommon
	Aggression	Frequency not known	Uncommon	Common

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Nervous System Disorders	Headache	Very common	Very common	Very common
	Dizziness	Common	Common	Common
	Restlessness	Common	Common	Uncommon
	Tremor	Common	Common	Uncommon
	Somnolence	Uncommon	Common	Common
	*Seizure	Frequency not known	Frequency not known	Frequency not known
	Dyskinesia	Uncommon	Uncommon	Uncommon
	*Dysgeusia	Uncommon	Uncommon	Uncommon
	Syncope	Uncommon	Uncommon	Uncommon
Eye Disorders	*Vision blurred	Uncommon	Frequency not known	Uncommon
	*Mydriasis	Frequency not known	Uncommon	Uncommon
Cardiac Disorders	Tachycardia	Common	Common	Common
	Palpitation	Common	Common	Uncommon
	*QTc prolongation	Frequency not known	Frequency not known	Frequency not known
	*Cardiomyopathy	Frequency not known	Uncommon	Frequency not known
Vascular Disorders	*Raynaud's phenomenon	Frequency not known	Frequency not known	Uncommon
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Common	Common	Uncommon
Gastrointestinal Disorders	Dry mouth	Very common	Common	Common
	Diarrhoea	Common	Common	Common
	Constipation	Common	Uncommon	Common
	Upper abdominal pain	Common	Common	Very common
	Nausea	Common	Common	Common
	Vomiting	Uncommon	Common	Common
	Hyperhidrosis	Common	Uncommon	Uncommon
	Urticaria	Uncommon	Uncommon	Uncommon

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Skin and Subcutaneous Tissue Disorders	Rash	Uncommon	Uncommon	Common
	*Angioedema	Frequency not known	Frequency not known	Frequency not known
	*Stevens-Johnson Syndrome	Frequency not known	Frequency not known	Frequency not known
General Disorders and Administration Site Conditions	*Chest Pain	Common	Uncommon	Uncommon
	Irritability	Common	Common	Common
	Fatigue	Common	Common	Common
	Feeling jittery	Common	Common	Uncommon
	Pyrexia	Uncommon	Common	Common
Investigations	Blood pressure increased	Common	Uncommon	Uncommon
	Weight decreased	Common	Very Common	Very Common
Reproductive System and Breast Disorders	Erectile dysfunction	Common	Uncommon	Not applicable
Hepatobiliary	*Eosinophilic Hepatitis	Frequency not known	Frequency not known	Frequency not known

*The following Adverse Drug reactions have been identified during post marketing surveillance

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 -1,12 kg, for patients assigned to receive 30 mg, 50 mg, and 70 mg of VYSERA respectively, compared to a 0,46 kg weight gain for patients receiving placebo. In adolescents, mean weight change from baseline to endpoint was -1,24, -1,94, and -2,16 kg, , for patients assigned to receive 30 mg, 50 mg, and 70 mg of VYSERA respectively, compared to a 0,9 kg weight gain for patients receiving placebo.

In children and adolescents who received VYSERA 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

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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 VYSERA 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 VYSERA 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 non-medication 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 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of VYSERA is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Manifestations of acute overdosage with amfetamines 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

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dysrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhoea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

There is no specific antidote to amfetamine overdose. Management of acute amfetamine intoxication is largely symptomatic and supportive which includes administration of activated charcoal (during the first hour of intoxication if the patient is conscious), administration of a cathartic and sedation.

Lisdexamfetamine and dexamfetamine are not dialysable.

In case of amfetamine overdose, consult a poison control centre for guidance or treat as clinically indicated. The prolonged release of VYSERA in the body should be considered when treating patients with overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Class: A 1.6 Other central nervous system stimulants
Pharmacotherapeutic Group
Centrally Acting Sympathomimetics, ATC Code: N06BA12

General

Lisdexamfetamine is a pharmacologically inactive pro-drug of dexamfetamine, 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 dexamfetamine, which is responsible for the medicine activity. Amfetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action of amfetamine 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 norepinephrine (noradrenaline) and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent active ingredient, lisdexamfetamine, does not bind to the sites responsible for the reuptake of noradrenaline and dopamine *in vitro.*

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Clinical trials

The efficacy of lisdexamfetamine dimesylate in the treatment of ADHD has been demonstrated in four controlled trials in adults, three controlled studies in adolescents aged 13-17 years, three controlled trials in children and adolescents (6 to 17 years) and three controlled studies in children aged 6 to 12 years. The patients in all these studies met DSM criteria for ADHD.

In clinical studies conducted in children and adults, the effects of VYSERA were on-going 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 (range) daily dose of VYSERA tended to be slightly lower in studies in children 47,4 mg (range [44,3-50,5 mg]) than in adolescents 56,15 mg (range [53,5-58,8 mg]) or adults 54,55 mg (range [52,3-56,8 mg]). Dose optimisation to achieve the best benefit harm balance in children 6 – 12 years of age cannot be done with the available formulations of VYSERA.

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 VYSERA (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 VYSERA 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 VYSERA doses compared to placebo. ADHD-RS results for Study SPD489-305 are shown in the following table:

ADHD-RS Total Score at Endpoint (Adolescents; Study SPD489-305; Full Analysis Set)			
	Baseline	**Change from Baseline**	**≥50 % Response [a]**

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Treatment	Mean (SD)	n	LS Mean (SE) Change	LS Means Diff.	95% CI	p-value[b]	n	Percent	-value[c]
Placebo	77 38,5 (7,11)	76	-12,8 (1,25)				77	33,8	
VYSERA 30mg	78 38,3 (6,71)	76	-18,3 (1,25)	-5,5	(-9,7; -1,3)	0,0056	78	50,0	0,041
VYSERA 50mg	76 37,3 (6,33)	72	-21,1 (1,28)	-8,3	(-12,5; -4,1)	<0,0001	77	59,7	0,001
VYSERA 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 ≥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 ≥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.

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. Subjects were treated with open-label VYSERA 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. Of patients that maintained open label treatment response, 157 were randomised to on-going treatment with the same dose of VYSERA (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 VYSERA 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

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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 VYSERA or placebo. All subjects receiving VYSERA 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 VYSERA doses compared to placebo. ADHD-RS results for Study NRP104.303 are shown in the following table:

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	
VYSERA 30mg	115	40,5 (6,21)	115	-16,2 (1,06)	-8,04	(-12,14; -3,95)	<0,0001	119	36,1	0,002
VYSERA 50mg	117	40,8 (73,0)	117	-17,4 (1,05)	-9,16	(-13,25; -5,08)	<0,0001	117	40,2	<0,001
VYSERA 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 ≥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 ≥50 %

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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 VYSERA 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 VYSERA (30, 50, or 70 mg/day in the morning). Subjects were then randomised to one of two treatment sequences: 1) VYSERA (optimised dose) followed by placebo, each for one week, or 2) placebo followed by VYSERA, 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. VYSERA 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 VYSERA 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 VYSERA (N=56) or placebo (N=60). Maintenance of efficacy for subjects treated with VYSERA 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 VYSERA, 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

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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.

Abuse liability studies

In a human abuse liability study, when equivalent oral doses of 100 mg lisdexamfetamine dimesylate and 40 mg immediate-release dexamfetamine sulphate were administered to individuals with a history of drug abuse, lisdexamfetamine dimesylate 100 mg produced subjective responses on a scale of “Drug Liking Effects” (primary endpoint) that were significantly less than dexamfetamine immediate-release 40 mg. However, oral administration of 150 mg lisdexamfetamine dimesylate produced increases in positive subjective responses on this scale that were comparable to the positive subjective responses produced by 40 mg of oral immediate-release dexamfetamine and 200 mg of diethylpropion.

Intravenous administration of 50 mg lisdexamfetamine dimesylate to individuals with a history of drug abuse produced positive subjective responses on scales measuring “Drug Liking”, “Euphoria”, “Amfetamine Effects”, and "Benzedrine Effects" that were greater than placebo but less than those produced by an equivalent dose (20 mg) of intravenous dexamfetamine.

5.2 Pharmacokinetic properties

Absorption

After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract, thought to be mediated by the high capacity peptide transporter-1 (PEPT-1).

In 18 paediatric patients (6–12 years) with ADHD, the Tmax of dexamfetamine 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 dexamfetamine 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. Dexamfetamine 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 AUC and Cmax of dexamfetamine in healthy adults after single-dose oral administration of 70 mg of

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VYSERA capsules. Food delays 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 dexamfetamine, following oral administration of lisdexamfetamine dimesilate in solution, and as intact capsules were equivalent.

Weight/Dose normalised AUC and Cmax for dexamfetamine 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 dexamfetamine 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 dexamfetamine 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.

Amfetamine is reported to be oxidised at the 4 position of the benzene ring to form 4-hydroxyamfetamine, or on the side chain α or β carbons to form alpha-hydroxy-amfetamine or norepinephrine (noradrenaline), respectively. Norepinephrine (noradrenaline) and 4-hydroxy-amfetamine are both active and each is subsequently oxidised to form 4-hydroxy-norepinephrine (noradrenaline). Alpha-hydroxy-amfetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amfetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amfetamine.

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 amfetamine, 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.

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Special populations

Age

The pharmacokinetics of dexamfetamine, 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, amfetamine 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 dexamfetamine 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 dexamfetamine clearance was reduced from 0,7 L/h/kg in normal subjects to 0,4 L/h/kg in subjects with severe renal impairment (GFR 15 to <30 mL/min/1,73m^2). See Section 4.4 Special Warnings and Precautions For Use.

In subjects with ESRD requiring dialysis mean dexamfetamine clearance was reduced to 0,3 L/h/kg both pre- and post-dialysis. Dialysis did not significantly affect the clearance of dexamfetamine.

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.

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No evidence of carcinogenicity was found in studies in which d-, l-amfetamine 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

VYSERA capsules contain the following inactive ingredients:
croscarmellose sodium, magnesium stearate and microcrystalline cellulose.
The capsule shells contain gelatin, titanium dioxide (E171) (all strengths), erythrosine (E127) (30 mg and 70 mg), brilliant blue FCF (E133) (50 mg and 70 mg), and TekPrint SW-9008 (all strengths).

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 Interaction with Other Medicines and Other Forms of Interaction.

6.3 Shelf life

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

6.4 Special precautions for storage

Store at or below 25 ºC.

6.5 Nature and contents of container

Container type
VYSERA capsules are packed in high density polyethylene (HDPE) bottles with polypropylene child resistant (PP CR) cap with a foil inner seal, inside a cardboard carton.

Pack size
30 capsules

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6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Web based educational tools for Prescribers

Should you require educational tools please contact

medinfoemea@takeda.com

7 HOLDER OF CERTIFICATE OF REGISTRATION

Takeda (Pty) Ltd

Building A, Monte Circle

64 Montecasino Boulevard

Fourways 2191,

Gauteng, South Africa

8 REGISTRATION NUMBER(S)

VYSERA 30 mg: 60/1.6/0799

VYSERA 50 mg: 60/1.6/0800

VYSERA 70 mg: 60/1.6/0801

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 September 2025

10 DATE OF REVISION OF THE TEXT

09 September 2025