Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tyvense 50 mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg lisdexamfetamine dimesylate, equivalent to 14.8 mg of dexamfetamine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

White opaque body and blue opaque cap, printed ‘S489’ and ‘50 mg’ in black ink.

Each capsule measures approximately 16 mm long and 6 mm wide.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tyvense is indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in children aged 6 years and over when response to previous methylphenidate treatment is considered clinically inadequate.

Tyvense is also indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in adults with pre-existing symptoms of ADHD in childhood.

Treatment must be under the supervision of a specialist in childhood and/or adolescent behavioural disorders (for paediatric patients) or a specialist in behavioural disorders (for adult patients). Diagnosis should be based on a complete history and evaluation of the patient according to current DSM criteria or ICD guidelines. Diagnosis cannot be made solely on the presence of one or more symptoms.

In adults, the presence of pre-existing symptoms of ADHD in childhood is required and should be confirmed retrospectively (according to the patient's medical record or, if not available, through appropriate and structured instruments or interviews). Based on clinical judgment, patients should have ADHD of at least moderate severity as indicated by at least moderate functional impairment in two or more settings (for example, social, academic, and/or occupational functioning), affecting several aspects of an individual's life.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

Tyvense is not indicated in all patients with ADHD and the decision to use the medicinal product must take into consideration the profile of the patient, including a thorough assessment of the severity and chronicity of the patient's symptoms, the potential for abuse, misuse or diversion and clinical response to any previous pharmacotherapies for the treatment of ADHD.

A comprehensive treatment programme typically includes psychological, educational, behavioural, occupational and social measures as well as pharmacotherapy, as appropriate, and is aimed at stabilising the patient with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired (for paediatric patients).

Appropriate educational placement is essential (for paediatric patients), and psychosocial intervention is generally necessary. The use of Tyvense should always be used in this way according to the licensed indication.

4.2 Posology and method of administration

Treatment must be initiated under the supervision of an appropriate specialist in behavioural disorders.

Pre-treatment evaluation

Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death, and accurate recording of pre-treatment weight. For paediatric patients, height and weight should be recorded on a growth chart (see section 4.3 and section 4.4).

Consistent with other stimulants, the potential for abuse, misuse or diversion of Tyvense should be considered prior to prescribing (see section 4.4).

Ongoing monitoring

Growth (paediatric patients), psychiatric, and cardiovascular status should be continually monitored (see also section 4.4).

- Blood pressure and pulse should be recorded at each adjustment of dose and at least every six months. For paediatric patients this should be recorded on a centile chart.

- For paediatric patients: height, weight, and appetite should be recorded at least six-monthly with maintenance of a growth chart.
- Weight should be recorded in adults regularly.
- Development of *de novo* or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then at least every six months and at every visit.
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Patients should be monitored for the risk of diversion, misuse, and abuse of Tyvense.

Posology

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 Tyvense.

The starting dose is 30 mg taken once daily in the morning. When in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 20 mg once daily in the morning.

The dose may be increased by 10 or 20 mg increments, at approximately weekly intervals. Tyvense should be administered orally at the lowest effective dosage.

The maximum recommended dose is 70 mg/day; higher doses have not been studied.

Treatment must be stopped if the symptoms do not improve after appropriate dosage adjustment over a 1-month period. If paradoxical aggravation of symptoms or other intolerable adverse events occur, the dosage should be reduced or discontinued.

Method of administration

Tyvense may be taken with or without food.

Tyvense may be swallowed whole, or the capsule 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 include any compacted powder, a spoon may be used to break apart the powder in the soft food or liquid. The contents should be stirred 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.

In the event of a missed dose, Tyvense dosing can resume the next day. Afternoon doses should be avoided because of the potential for insomnia.

Long-term use

Pharmacological treatment of ADHD may be needed for extended periods. The physician who elects to use Tyvense for extended periods (over 12 months) should re-evaluate the usefulness of Tyvense at least yearly, and consider trial periods off medication to assess the patient's functioning without pharmacotherapy, preferably during times off from school or work.

Elderly population
Data is limited in elderly patients; therefore, a thorough pre-treatment evaluation and ongoing monitoring of blood pressure and cardiovascular status is required (see sections 4.3 and 4.4).
Dexamfetamine clearance is reduced in the elderly, therefore dose adjustment may be required (see section 5.2).

Patients with renal impairment

Due to reduced clearance in patients with severe renal insufficiency (GFR 15 to < 30 mL/min/1.73 m^2 or CrCl < 30 mL/min) the maximum dose should not exceed 50 mg/day. Further dosage reduction should be considered in patients undergoing dialysis. Lisdexamfetamine and dexamfetamine are not dialysable.

Patients with hepatic impairment

No studies have been conducted in patients with hepatic impairment.
Children under 6 years

Tyvense should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

4.3 Contraindications

Hypersensitivity to sympathomimetic amines or any of the excipients listed in section 6.1.
Concomitant use of monoamine oxidase inhibitors (MAOI) or within 14 days after MAOI treatment (hypertensive crisis may result; see section 4.5).
Hyperthyroidism or thyrotoxicosis.
Agitated states.
Symptomatic cardiovascular disease.
Advanced arteriosclerosis.
Moderate to severe hypertension.
Glaucoma.

4.4 Special warnings and precautions for use

Abuse and dependence

Stimulants including lisdexamfetamine dimesylate have a potential for abuse, misuse, dependence, or diversion for non-therapeutic uses that physicians should consider when prescribing this product. 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.

Abuse of amfetamines can lead to tolerance, and psychological dependence with varying degrees of abnormal behaviour. Symptoms of amfetamine abuse may include dermatoses, insomnia, irritability, hyperactivity, emotional lability and psychosis. Withdrawal symptoms such as fatigue and depression have been reported.

Caregivers and/or patients should be advised on the proper storage and disposal of unused medicinal product to prevent diversion (e.g., through friends and relatives).

Cardiovascular adverse events

Sudden death in patients with 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, 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.

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

The use of lisdexamfetamine dimesylate is contraindicated in patients with symptomatic cardiovascular disease and also in those patients with moderate to severe hypertension (see section 4.3). As the prevalence of hypertension increases with increasing age, a continued monitoring of blood pressure and cardiovascular status is required during treatment (see section 4.2).

Cardiomyopathy

Cardiomyopathy has been reported with chronic amfetamine use. It has also been reported with lisdexamfetamine dimesylate .

Assessing cardiovascular status in patients being treated with stimulant medications

All patients 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 or 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.

Psychiatric adverse events

Pre-existing psychosis

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

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 lisdexamfetamine dimesylate . 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.

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 effect on growth (height and weight)

In children and adolescents aged 6 to 17 years

Stimulants have been associated with a slowing of weight gain and a reduction in attained height. Growth should be monitored during treatment with stimulants, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted. Height, weight, and appetite should be recorded at least 6-monthly.

In a controlled study of patients aged 6 to 17 years the mean (SD) changes in body weight after seven weeks were -2.35 (2.084) kg for lisdexamfetamine dimesylate , +0.87 (1.102) kg for placebo, and -1.36 (1.552) kg for methylphenidate hydrochloride.

In adults

Stimulants have been associated with weight loss. Weight should be monitored during treatment with stimulants, and patients who are losing weight may need to have their treatment interrupted.

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 new onset or worsening seizures, the drug should be discontinued.

Visual disturbance

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

Prescribing and dispensing

The least amount of lisdexamfetamine dimesylate feasible should be prescribed or dispensed in order to minimise the risk of possible overdose by the patient.

Use with other sympathomimetic drugs

Lisdexamfetamine dimesylate 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 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro enzyme inhibition

Lisdexamfetamine dimesylate 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 dimesylate 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. An *in vivo* human study of lisdexamfetamine dimesylate did not result in any clinically meaningful effect on the pharmacokinetics of drugs metabolised by CYP1A2, CYP2D6, CYP2C19, or CYP3A.

Agents whose blood levels may be impacted by lisdexamfetamine dimesylate

Extended release guanfacine: In a drug interaction study, administration of an extended release guanfacine in combination with lisdexamfetamine dimesylate induced a 19% increase in guanfacine maximum plasma concentrations (C_{max}), 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 lisdexamfetamine dimesylate.

Extended release venlafaxine: In a drug interaction study, administration of 225 mg extended release venlafaxine, a CYP2D6 substrate, in combination with 70 mg lisdexamfetamine dimesylate induced a 9% decrease in the C_{max} and 17% decrease in the AUC for the primary active metabolite o-desmethylvenlafaxine and a 10% increase in C_{max} and 13% increase in AUC for venlafaxine. Dexamfetamine may be a weak inhibitor of CYP2D6. Lisdexamfetamine has no effect on the AUC and C_{max} of the composite of venlafaxine and o-desmethylvenlafaxine. 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 lisdexamfetamine dimesylate.

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

Ascorbic acid and other agents and conditions(thiazide diuretics, diets high in animal protein, diabetes, respiratory acidosis) that acidify urine increase urinary excretion and decrease the half-life of amfetamine. Sodium bicarbonate and other agents and conditions (diets high in fruits and vegetables, urinary tract infections and vomiting) that alkalinise urine decrease urinary excretion and extend the half-life of amfetamine.

Monoamine oxidase inhibitors
Amfetamine should not be administered during or within 14 days following the administration of monoamine oxidase inhibitors (MAOI) because it can increase the release of norepinephrine and other monoamines. This can cause severe headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal outcomes (see section 4.3).

Serotonergic drugs

Serotonin syndrome has rarely occurred in association with the use of amfetamines such as lisdexamfetamine dimesylate, 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 amfetamines, including lisdexamfetamine dimesylate (see section 4.9).

Agents whose effects may be reduced by amfetamines

Antihypertensives: Amfetamines may decrease the effectiveness of guanethidine or otherantihypertensive medications.

Agents whose effects may be potentiated by amfetamines

Amfetamines potentiate the analgesic effect of narcotic analgesics.

Agents that may reduce the effects of amfetamines

Chlorpromazine: Chlorpromazine blocks dopamine and norepinephrine 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.

Drug/laboratory test interactions

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Dexamfetamine, the active metabolite of lisdexamfetamine, crosses the placenta. Data from a cohort study of in total approximately 5 570 pregnancies exposed to amfetamine in the first trimester do not suggest an increased risk of congenital malformation. Data from another cohort study in approximately 3 100 pregnancies exposed to amfetamine during the first 20 weeks of pregnancy, suggest an increased risk of preeclampsia, and preterm birth. Newborns exposed to amfetamine during pregnancy may experience withdrawal symptoms.

In animal reproduction studies, lisdexamfetamine dimesylate had no effect on embryofoetal development or survival when administered orally to pregnant rats and rabbits (see section 5.3). Administration of lisdexamfetamine dimesylate to juvenile rats was associated with reductions in growth measurements at clinically relevant exposures.

The physician should discuss lisdexamfetamine dimesylate treatment with female patients of child-bearing potential.Lisdexamfetamine dimesylate should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

Amfetamines are excreted in human milk. Lisdexamfetamine dimesylate should not be used during breast-feeding.

Fertility

The effects of lisdexamfetamine dimesylate 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 (see section 5.3). The effects of lisdexamfetamine dimesylate on human fertility has not been investigated.

4.7 Effects on ability to drive and use machines

Lisdexamfetamine dimesylate can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation and blurred vision. These could have a moderate influence on the ability to drive and use machines. Patients should be warned of these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions observed with lisdexamfetamine dimesylate treatment mainly reflect side effects commonly associated with stimulant use. Very common adverse reactions include decreased appetite, insomnia, dry mouth, headache, upper abdominal pain, and weight decreased.

Tabulated summary of adverse reactions

The following table presents all adverse reactions based on clinical trials and spontaneous reporting.

The following definitions apply to the frequency terminology used hereafter:
Very common (≥ 1/10)

Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Frequency not known (cannot be estimated from the available data).

An asterisk (*) indicates that additional information on the respective adverse reaction is provided below the table.

System/Organ Class	Adverse Reaction	Children (6 to 12 years)	Adolescents (13 to 17 years)	Adults
Immune System Disorders	Anaphylactic reaction	Frequency not known	Frequency not known	Frequency not known
	Hypersensitivity	Uncommon	Uncommon	Uncommon
Metabolism and Nutrition Disorders	Decreased appetite	Very common	Very common	Very common
Psychiatric Disorders	*Insomnia	Very common	Very common	Very common
	Agitation	Uncommon	Uncommon	Common
	Anxiety	Uncommon	Common	Common
	Logorrhea	Uncommon	Uncommon	Uncommon
	Libido decreased	Not applicable	Not reported	Common
	Depression	Uncommon	Common	Uncommon
	Tic	Common	Uncommon	Uncommon
	Affect lability	Common	Uncommon	Common
	Dysphoria	Uncommon	Uncommon	Uncommon
	Euphoria	Frequency not known	Uncommon	Uncommon
	Psychomotor hyperactivity	Uncommon	Uncommon	Common
	Bruxism	Uncommon	Uncommon	Common
	Dermatillomania	Uncommon	Uncommon	Uncommon
	Psychotic episodes	Frequency not known	Frequency not known	Frequency not known
	Mania	Uncommon	Uncommon	Uncommon
	Hallucination	Uncommon	Uncommon	Frequency not known
	Aggression	Common	Uncommon	Frequency not known
	Tourette's Disorder aggravated	Frequency not known	Frequency not known	Frequency not known
Nervous System Disorders	Headache	Very common	Very common	Very common
	Dizziness	Common	Common	Common
	Restlessness	Uncommon	Common	Common
	Tremor	Uncommon	Common	Common
	Somnolence	Common	Common	Uncommon
	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	Uncommon	Uncommon	Frequency not known
Cardiac Disorders	Tachycardia	Common	Common	Common
	Palpitation	Uncommon	Common	Common
	QTc prolongation	Frequency not known	Frequency not known	Frequency not known
	Cardiomyopathy	Frequency not known	Uncommon	Frequency not known
Vascular disorders	Raynaud's phenomenon	Uncommon	Frequency not known	Frequency not known
	Epistaxis	Uncommon	Uncommon	Uncommon

Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Uncommon	Common	Common
Gastrointestinal Disorders	Dry mouth	Common	Common	Very common
	Diarrhoea	Common	Common	Common
	Constipation	Common	Uncommon	Common
	Upper abdominal pain	Very common	Common	Common
	Nausea	Common	Common	Common
	Vomiting	Common	Common	Uncommon
Hepatobiliary Disorders	*Eosinophilic Hepatitis	Frequency not known	Frequency not known	Frequency not known
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	Uncommon	Uncommon	Common
	Urticaria	Uncommon	Uncommon	Uncommon
	Rash	Common	Uncommon	Uncommon
	*Angioedema	Frequency not known	Frequency not known	Frequency not known
	*Stevens-Johnson Syndrome	Frequency not known	Frequency not known	Frequency not known
Reproductive System and Breast Disorders	Erectile dysfunction	Not applicable	Uncommon	Common
General Disorders and Administration Site Conditions	Chest Pain	Uncommon	Uncommon	Common
	Irritability	Common	Common	Common
	Fatigue	Common	Common	Common
	Feeling jittery	Uncommon	Common	Common
	Pyrexia	Common	Common	Uncommon
Investigations	Blood pressure increased	Uncommon	Uncommon	Common
	*Weight decreased	Very Common	Very Common	Common

Description of selected adverse reactions

Insomnia

Includes insomnia, initial insomnia, middle insomnia, and terminal insomnia.

Weight decreased

In a 4-week controlled trial of lisdexamfetamine dimesylate in children aged 6 to 12 years, mean weight loss from baseline to endpoint was 0.4, 0.9, and 1.1 kg, for patients assigned to receive 30 mg, 50 mg, and 70 mg of lisdexamfetamine dimesylate respectively, compared to a 0.5 kg weight gain for patients receiving placebo. Higher doses were associated with greater weight loss with 4 weeks of treatment. Careful follow-up for weight in children aged 6 to 12 years who received lisdexamfetamine dimesylate over 12 months suggests that continuous treatment (i.e., treatment for 7 days per week throughout the year) slows growth rate measured by body weight as demonstrated by an age- and sex-normalised mean change from baseline in percentile of -13.4 over 1 year. The average percentiles at baseline (n=271) and 12 months (n=146) were 60.9 and 47.2, respectively.

In a 4-week controlled trial of lisdexamfetamine dimesylate in adolescents aged 13 to 17 years, mean weight loss from baseline to endpoint was 1.2, 1.9, and 2.3 kg for patients assigned to receive 30 mg, 50 mg, and 70 mg of lisdexamfetamine dimesylate respectively, compared to a 0.9 kg weight gain for patients receiving placebo. Careful follow-up for weight in adolescents aged 13 to 17 years who received lisdexamfetamine dimesylate over 12 months suggests that continuous treatment (i.e., treatment for 7 days per week throughout the year) slows growth rate measured by body weight as demonstrated by an age- and sex-normalised mean change from baseline in percentile of -6.5 over 1 year. The average percentiles at baseline (n=265) and 12 months (n=156) were 66.0 and 61.5, respectively.

In children and adolescents (aged 6-17) who received lisdexamfetamine dimesylate over two years, careful monitoring of weight suggested that consistent medication (ie, 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).

In a controlled clinical trial of lisdexamfetamine dimesylate in children ages 4 to 5 years who received 5 – 30 mg of lisdexamfetamine dimesylate, there were no clinically meaningful changes in weight from baseline after 6 weeks of follow-up. Careful follow-up for weight in children aged 4 to 5 years who received lisdexamfetamine dimesylate over 12 months in an open-label extension study suggests that continuous treatment (i.e., treatment for 7 days per week throughout the year) slows growth rate measured by body weight as demonstrated by an age- and sex-normalised mean change from baseline in percentile of -17.92 (SD=13.767) over 1 year. The average percentiles at baseline (n=113) and 12 months (n=69) were 66.51 (SD=25.173) and 47.45 (SD=26.144), respectively.

Eosinophilic hepatitis

No cases were reported in the clinical studies.

Angioedema

No cases were reported in the clinical studies.

Stevens-Johnson syndrome

No cases were reported in the clinical studies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via

Ireland:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

The prolonged release of dexamfetamine after administration of lisdexamfetamine dimesylate should be considered when treating patients with overdose.

Manifestations of acute overdosage with amfetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, aggression, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. 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.

There is no specific antidote to amfetamine overdose. Management of acute amfetamine intoxication is largely symptomatic and may include administration of activated charcoal, 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 duration of action of amfetamine should be considered when treating patients with overdose

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Centrally Acting Sympathomimetics, ATC code: N06 BA12.

Mechanism of action

Lisdexamfetamine dimesylate is a pharmacologically inactive prodrug. After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and hydrolysed primarily by red blood cells to dexamfetamine, which is responsible for the drug's activity.

Amfetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action of amfetamine in ADHD is not fully established, however it is thought to be due to its ability to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The prodrug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.

Clinical efficacy and safety

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

In clinical studies conducted in children and adults, the effects of lisdexamfetamine dimesylate 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.

Paediatric population

Three hundred and thirty-six patients aged 6-17 years were evaluated in the pivotal Phase 3 European Study SPD489-325. In this seven-week randomised double-blind, dose-optimised, placebo- and active-controlled study, lisdexamfetamine dimesylate showed significantly greater efficacy than placebo.

The ADHD Rating Scale is a measure of the core symptoms of ADHD. The placebo-adjusted mean reduction from baseline in patients treated with lisdexamfetamine dimesylate on the ADHD-RS-IV Total Score was 18.6 ($p < 0.001$). At every on-treatment visit and at Endpoint the percentages of subjects who met pre-defined response criteria (a ≥ 30% reduction from Baseline in ADHD-RS-IV Total Score and a CGI-I value of 1 or 2) was significantly higher ($p < 0.001$) for lisdexamfetamine dimesylate when compared to placebo. The endpoint of this study is defined in Table 1. The results were also significantly higher for lisdexamfetamine dimesylate when compared to placebo when the individual components of the response criteria were evaluated. In addition, mean scores for ADHD symptoms following treatment discontinuation did not exceed baseline scores prior to treatment, indicating there was no rebound effect.

In addition to a reduction in symptoms, clinical studies have demonstrated that lisdexamfetamine dimesylate significantly improves functional outcomes. Specifically, in Study SPD489-325, 75.0% of subjects on lisdexamfetamine dimesylate showed Improvement (defined as "very much improved" or "much improved") on the Clinical Global Impression-Improvement (CGI-I) rating scale compared to 14.2% on placebo ($p < 0.001$).

Lisdexamfetamine dimesylate showed significant improvement in child achievement in academic performance, as measured by the Health Related Quality of life instrument, Parent Report Form of the Child Health and Illness Profile-Child Edition (CHIP-CE:PRF) Achievement Domain. Lisdexamfetamine dimesylate demonstrated a significant improvement from baseline compared to placebo (lisdexamfetamine dimesylate : 9.4 **versus** Placebo -1.1) with a mean difference between the two treatment groups of 10.5 ($p < 0.001$).

Table 1: Outcome Results for Study SPD489-325 at Endpoint1 (Full Analysis Set)

	Lisdexamfetamine dimesylate	Placebo	Methylphenidate hydrochloride
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
ADHD-RS-IV Responders			
Patients Showing a response[2]	83.7% (87/104)	22.6% (24/106)	68.2% (73/107)
Difference in response from placebo	61.0	N/A	45.6
P-value (versus Placebo)	< 0.001	N/A	< 0.001
CGI-I Responders			
Patients Showing Improvement[3]	75.0% (78/104)	14.2% (15/106)	58.9 % (63/107)
Difference in improvement from placebo	60.8	N/A	44.7

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)	1.280	N/A	0.912
P-value (versus Placebo)	< 0.001	N/A	< 0.001

[1] Endpoint = the last on-treatment post-Baseline visit of the dose optimisation or dose maintenance Period (Visits 1-7) with a valid value
[2] Response is defined as percentage reduction from Baseline in the ADHD-RS-IV Total Score of ≥ 30%
[3]Improvement ("very much improved" or "much improved")

Similar results for ADHD-RS and CGI-I have been shown in two placebo controlled studies, one in children (n=297) and the other in adolescents (n=314), both conducted in the United States.

A double-blind, randomised, active-controlled, dose-optimisation study was conducted in children and adolescents aged 6 to 17 years (n=267) who met DSM-IV criteria for ADHD. In this nine-week study, patients were randomised (1:1) to a daily morning dose of lisdexamfetamine dimesylate (30, 50 or 70 mg/day), or atomoxetine (dosed as appropriate for the subject's weight up to 100 mg). During a 4-week Dose Optimisation Period, patients were titrated until an optimal dose, based on treatment emergent adverse events (TEAEs) and clinical judgement, was reached. Patients treated with lisdexamfetamine dimesylate had a shorter time to first response compared to patients treated with atomoxetine (median 13.0 vs 21.0 days, respectively; p=0.003), where response was defined as having a CGI-I score of 1 (very much improved) or 2 (much improved) at any of the double-blind treatment visits. Across all of the double blind treatment visits, the proportion of responders in the lisdexamfetamine dimesylate group was consistently higher than the proportion of responders in the atomoxetine group. The difference ranged from 16-24 percentage points. At the study endpoint the least square mean changes from baseline in ADHD-RS-IV Total Score for lisdexamfetamine dimesylate and atomoxetine were -26.1 and -19.7, respectively, with a between-group difference of -6.4.

Two double-blind, parallel-group, active-controlled (OROS-MPH [Concerta]) studies have been conducted in adolescents aged 13 to 17 years with ADHD. Both studies also included a placebo reference arm. 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 SPD489 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 SPD489 and OROS-MPH, respectively. In this study, neither SPD489 nor OROS-MPH was found to be statistically superior to the other product at Week 8. 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 SPD489 (70 mg) and OROS-MPH (72 mg), SPD489 treatment was found to be superior to OROS-MPH as measured by both the primary efficacy analysis (change from baseline at Week 6 on the ADHD-RS Total score) and the key secondary efficacy analysis (at last study visit on the CGI-I) (see Table 2).

Table 2: Change from Baseline on ADHD-RS-IV Total Score and Endpoint on CGI-I (Full Analysis Set)

SPD489-405	**Primary at Week 8 ADHD-RS-IV**		**Placebo**	**SPD489**	**OROS-MPH**
	Baseline Total Score	N Mean (SE)	89 38.2 (0.73)	179 36.6 (0.48)	184 37.8 (0.45)
	Change from baseline at Week 8	N LS Mean (SE) [a]	67 -13.4 (1.19)	139 -25.6 (0.82)	152 -23.5 (0.80)
	Lisdexamfetamine vs OROS-MPH difference	LS Mean (SE) [a] (95% CI) [a] Effect size [b] p-value	NA	-2.1 (1.15) -4.3, 0.2 0.2 0.0717	NA
	Active vs Placebo difference	LS Mean (SE) [a] (95% CI) [a] Effect size [b] p-value	NA	-12.2 (1.45) -15.1, -9.4 1.16 < 0.0001	-10.1 (1.43) -13.0, -7.3 0.97 < 0.0001
	Key Secondary Endpoint CGI-I				
	Subjects analysed (n)		89	178	184
	Improved (%) [c] Not improved (%) [d]		31 (34.8) 58 (65.2)	148 (83.1) 30 (16.9)	149 (81.0) 35 (19.0)

	Lisdexamfetamine vs OROS-MPH [e] Active treatment vs Placebo [e]		NA NA	0.6165 < 0.0001	NA < 0.0001
SPD489-406	**Primary at Week 6 ADHD-RS-IV**		**Placebo**	**SPD489**	**OROS-MPH**
	Baseline Total Score	N Mean (SE)	106 36.1 (0.58)	210 37.3 (0.44)	216 37.0 (0.44)
	Change from baseline at Week 6	N LS Mean (SE) [a]	93 -17.0 (1.03)	175 -25.4 (0.74)	181 -22.1 (0.73)
	Lisdexamfetamine vs OROS-MPH difference	LS Mean (SE) [a] (95% CI) [a] Effect size [b] p-value	NA	-3.4 (1.04) -5.4, -1.3 0.33 0.0013	NA
	Active vs Placebo difference	LS Mean (SE) [a] (95% CI) [a] Effect size [b] p-value	NA	-8.5 (1.27) -11.0, -6.0 0.82 < 0.0001	-5.1 (1.27) -7.6, -2.6 0.50 < 0.0001
	Key Secondary Endpoint CGI-I				
	Subjects analysed (n)		106	210	216
	Improved (%) [c] Not improved (%) [d]		53 (50.0) 53 (50.0)	171 (81.4) 39 (18.6)	154 (71.3) 62 (28.7)
	Lisdexamfetamine vs OROS-MPH [e] Active treatment vs Placebo [e]		NA NA	0.0188 < 0.0001	NA 0.0002

[a] From a mixed effects model for repeated measures (MMRM) that includes treatment group, nominal visit, interaction of the treatment group with the visit as factors, baseline ADHD-RS-IV total score as a covariate, and an adjustment for the interaction of the baseline ADHD-RS-IV total score with the visit. The model is based on a REML method of estimation and utilizes an unstructured covariance type.
[b] The effect size is the difference in LS mean divided by the estimated standard deviation from the unstructured covariance matrix.
[c] The 'Improved' category includes responses of 'Very much improved' and 'Much improved'.
[d] The 'Not improved' category includes responses of 'Minimally improved', 'No change', 'Minimally worse', 'Much worse' and 'Very much worse'.
[e] From a CMH test stratified by baseline CGI-S.
Note: N = number of subjects in each treatment group, n = number of subjects analysed.

A 2-year open label safety study conducted in children and adolescents (ages 6 to 17) with ADHD enrolled 314 patients. Of these, 191 patients completed the study.

In addition, maintenance of effect was demonstrated in a double-blind, placebo-controlled, randomised withdrawal study conducted in children and adolescents ages 6 to 17 (n=157) who met the diagnosis of ADHD (DSM-IV criteria). Patients were optimised to open-label lisdexamfetamine dimesylate for an extended period (at least 26 weeks) prior to entry into the 6-week randomised withdrawal period. Eligible patients were randomised to continue receiving their optimised dose of lisdexamfetamine dimesylate or to switch to placebo. Patients were observed for relapse (treatment failure) during the 6-week double-blind phase. 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. Treatment failure was significantly lower ($p < 0.001$) for the lisdexamfetamine dimesylate subjects (15.8%) compared to placebo (67.5%). For the majority of subjects (70.3%) who were treatment failures regardless of treatment, ADHD symptoms worsened at or before the Week 2 visit following randomisation.

A fixed-dose safety and efficacy study was conducted in preschool children aged 4 to 5 years with ADHD. Subjects were randomised in a 5:5:5:5:6 ratio to lisdexamfetamine dimesylate (5, 10, 20, 30 mg dose strength) or placebo (see also section 5.2). The duration of the double-blind evaluation period was 6 weeks. In this study, the most commonly reported TEAEs for subjects receiving Tyvense were decreased appetite (13.7% of subjects), irritability (9.6% of subjects), and affect lability and cough (4.8% subjects each). In a 52-week open-label study, the most common TEAE was decreased appetite (15.9%) (see section 4.8).

Adult population

The efficacy of lisdexamfetamine dimesylate in the treatment of adults who met DSM-IV-TR criteria for ADHD has been demonstrated in four controlled trials in which 846 patients were enrolled.

Adult Study 1 was a double-blind, randomised, placebo-controlled, parallel-group study conducted in adults (n=420). In this 4-week study, patients were randomised to fixed dose treatment groups receiving final doses of 30, 50, or 70 mg of lisdexamfetamine dimesylate or placebo. All subjects receiving lisdexamfetamine dimesylate 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 with adult prompts total score (ADHD-RS), were observed at endpoint for all lisdexamfetamine dimesylate doses compared to placebo (see Table 1). Treatment with lisdexamfetamine dimesylate significantly reduced the degree of functional impairment as measured by improvement on the Clinical Global Impression-Improvement (CGI-I) rating scale compared to placebo.

Table 3: Change from Baseline to Endpoint in ADHD-RS with Adult Prompts Total Score at Endpoint[1] (Full Analysis Set)

		Placebo	**30 mg**	**50 mg**	**70 mg**
Baseline Total Score	N	62	115	117	120
	Mean (SD)	39.4 (6.42)	40.5 (6.21)	40.8 (7.30)	41.0 (6.02)
Change from baseline at Endpoint	N	62	115	117	120
	LS Mean (SE)	-8.2 (1.43)	-16.2 (1.06)	-17.4 (1.05)	-18.6 (1.03)
Placebo-adjusted difference	LS Mean (95% CI) p-value	NA	-8.04 (-12.14, -3.95) < 0.0001	-9.16 (-13.25, -5.08) < 0.0001	-10.41 (-14.49, -6.33) < 0.0001

[1] Endpoint is the last post-randomisation treatment week for which a valid ADHD-RS-IV Total Score is obtained.
Note: Dunnett's test was used for the construction of Cis and p-values; p-values are the adjusted p-values and should be compared to a critical alpha of 0.05.
LS=least squares; SD= standard deviation; SE=standard error.

Adult Study 2 was a 10-week, double-blind, placebo-controlled study conducted to evaluate change in executive function behaviours, key quality of life outcomes, and ADHD symptoms in adults with ADHD and a clinically significant impairment in executive function. The study enrolled adults aged 18 to 55 years (n=161) who met DSM-IV criteria for ADHD as assessed by a total score of ≥ 65 on the Behaviour Rating Inventory of Executive Function – Adult Version (BRIEF-A) Global Executive Composite (GEC) T-score by subject-report and a score of ≥ 28 using the Adult ADHD-RS with prompts at the Baseline visit. At Week 10 the mean subject-reported BRIEF-A GEC T-score was 68.3 for the placebo group and 57.2 for the SPD489 group, representing LS mean changes from baseline of -11.1 and -22.3, respectively. The effect size was 0.74 in favour of the SPD489 group. The difference in LS mean change from baseline to Week 10 (-11.2) was significantly better in the lisdexamfetamine dimesylate group compared with placebo ($p < 0.0001$). Secondary efficacy measures of Adult ADHD Impact Module (AIM-A), ADHD-RS with adult prompts, CGI-I and the ADHD Index T-score of the Conners' Adult ADHD Rating Scale – Observer: Short Version (CAARS-O:S) were all significantly better in the lisdexamfetamine dimesylate group compared with placebo.

Adult Study 3 was a multi-centre, randomised, double-blind, placebo-controlled, crossover study. This study of lisdexamfetamine dimesylate was designed to simulate a workplace environment and enrolled 142 adults. Following a 4-week open-label, dose optimisation phase with lisdexamfetamine dimesylate (30, 50, or 70 mg/day in the morning), subjects were randomised to one of two treatment sequences: 1) lisdexamfetamine dimesylate (optimised dose) followed by placebo, each for one week, or 2) placebo followed by lisdexamfetamine dimesylate 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 maths test that measures attention in ADHD. Lisdexamfetamine dimesylate 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.

Adult Study 4 examined maintenance of efficacy. This study was a double-blind, placebo-controlled, randomised withdrawal design study was conducted in adults aged 18 to 55 (n=123) who met DSM-IV criteria for ADHD. At study entry, subjects must have had documentation of treatment with lisdexamfetamine dimesylate 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 double-blind randomised withdrawal phase, and received their entry dose of lisdexamfetamine dimesylate (n=56) or placebo (n=60). Maintenance of efficacy for subjects treated with lisdexamfetamine dimesylate was demonstrated by the significantly lower proportion of treatment failure (< 9%) compared to subjects receiving placebo (75%) in the double-blind randomised withdrawal phase. Treatment failure was defined as a ≥ 50% increase (worsening) 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.

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 werecomparable 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 dimesylate is rapidly absorbed from the gastrointestinal tract of healthy adults and children (6 to 12 years) with ADHD, thought to be mediated by the high capacity PEPT1 transporter.

Food does not affect the observed AUC and C_{max} of dexamfetamine in healthy adults after single-dose oral administration of 70 mg of lisdexamfetamine dimesylate but prolongs T_{max} by approximately 1 hour (from 3.8 hours at fasted state to 4.7 hours after a high fat meal). After an 8-hour fast, the AUCs for dexamfetamine following oral administration of lisdexamfetamine dimesylate in solution and as intact capsules were equivalent.

Distribution

In 18 children (6 to 12 years) with ADHD, the T_{max} of dexamfetamine was approximately 3.5 hours following single-dose oral administration of lisdexamfetamine dimesylate either 30 mg, 50 mg, or 70 mg administered after an 8-hour overnight fast. The T_{max} of lisdexamfetamine dimesylate was approximately 1 hour. Linear pharmacokinetics of dexamfetamine after single-dose oral administration of lisdexamfetamine dimesylate was established over the dose range of 30 mg to 70 mg in children aged 6 to 12 years.

Weight/dose normalised AUC and C_{max} of 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 C_{max} values were the same in girls and boys following single doses of 30-70 mg.

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

Biotransformation

Lisdexamfetamine dimesylate is converted to dexamfetamine and l-lysine, which occurs 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 hematocrit levels. Lisdexamfetamine is not metabolised by cytochrome P450 enzymes.

Amfetamine is 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 norephedrine, respectively. Norephedrine and 4-hydroxy-amfetamine are both active and each is subsequently oxidised to form 4-hydroxy-norephedrine. 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.

Elimination

Following the oral administration of a 70 mg dose of radiolabelled lisdexamfetamine dimesylate 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% 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 one hour in studies of lisdexamfetamine dimesylate in volunteers. The half-life of dexamfetamine is 11 hours.

Special populations

The pharmacokinetics of dexamfetamine, as evaluated by clearance, is similar in children (aged 6 to 12) and adolescents (aged 13 to 17) ADHD patients, and healthy adult volunteers after correcting for body weight.

Systemic exposure to dexamfetamine is similar for men and women given the same mg/kg dose.
Formal pharmacokinetic studies for race have not been conducted. There is no evidence of any impact of ethnicity on the pharmacokinetics of dexamfetamine.

In a pharmacokinetic study of 40 subjects (8 subjects in each of five renal functional groups: normal, mild impairment, moderate impairment, severe impairment, and end stage renal disease) dexamfetamine clearance was reduced from 0.7 L/hr/kg in normal subjects to 0.4 L/hr/kg in subjects with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m^2 or CrCl < 30 mL/min).

Mean steady state exposure of dexamfetamine was approximately 44% higher in paediatric patients ages 4 to 5 years compared to the paediatric population patients ages 6 to 11 years receiving the same dose (30 mg/day), based on a population pharmacokinetic analysis.

In a study of 47 subjects aged 55 years of age or older dexamfetamine clearance was approximately 0.7 L/hr/kg for subjects 55 to 74 years of age and 0.55 L/hr/kg for subjects ≥ 75 years of age. This is slightly reduced compared to younger adults (approximately 1 L/hr/kg for subjects 18 to 45 years of age).

5.3 Preclinical safety data

Non-clinical abuse liability studies indicate that lisdexamfetamine dimesylate can produce subjective effects in rats and monkeys that are similar to those of the CNS stimulant dexamfetamine, but that are delayed in onset and transient while the rewarding effects as determined in self-administration studies are lower than those of methylphenidate or cocaine.

In repeat dose toxicity studies the major findings were changes in behaviour, such as increased activity typical of stimulant administration, with associated reductions in body weight gain, growth measurements and food intake, considered to be a consequence of an exaggerated pharmacological response.

Lisdexamfetamine dimesylate was not genotoxic when tested *in vitro* in the Ames test and the mouse lymphoma assay or *in vivo* in the mouse bone marrow micronucleus test. Carcinogenicity studies of lisdexamfetamine dimesylate have not been performed. No evidence of carcinogenicity was found in studies in which *d-, l-* amfetamine (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.

Lisdexamfetamine dimesylate had no effect on embryofoetal development or survival when administered orally to pregnant rats at doses up to 40 mg/kg/day, and rabbits at doses up to 120 mg/kg/day.

Acute administration of high doses of amfetamine (d- or d,l-) has been shown to produce long lasting neurotoxic effects in rodents, including irreversible nerve fibre damage. However, in definitive juvenile toxicity studies with lisdexamfetamine dimesylate in rats and dogs, adverse central nervous system changes were not apparent. The significance of these findings to humans is unknown.

Amfetamine (*d- to l-* enantiomer ratio of 3:1) did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amfetamine (*d-* or *d,l-*) at doses similar to those used clinically can result in long-term neurochemical and behavioural alterations. Reported behavioural effects include learning and memory deficits, altered locomotor activity, and changes in sexual function. Similar studies have not been

conducted for lisdexamfetamine dimesylate . However, an assessment of fertility following cessation of treatment with lisdexamfetamine dimesylate was included in a juvenile rat toxicity study, with no adverse effects on fertility observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Content

Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Magnesium stearate (E572)

Capsule shells

Gelatin

20 mg: titanium dioxide (E171) and yellow iron oxide (E172).
30 mg: titanium dioxide (E171) and erythrosine (E127).
40 mg: titanium dioxide (E171), brilliant blue FCF (E133), black iron oxide (E172) and yellow iron oxide (E172).
50 mg: titanium dioxide (E171) and brilliant blue FCF (E133).
60 mg: titanium dioxide (E171) and brilliant blue FCF (E133).
70 mg: titanium dioxide (E171), brilliant blue FCF (E133) and erythrosine (E127).

Printing ink

Shellac (E904)
Potassium hydroxide (E525)
Black iron oxide (E172)
Propylene glycol (E1520)
Ammonia solution, concentrated (E527)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

High density polyethylene bottle and a polypropylene child resistant cap with a foil inner seal.

Pack sizes: 28 or 30.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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