ELVANSE UK SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Elvanse 30 mg capsules, hard.

Elvanse 50 mg capsules, hard.

Elvanse 70 mg capsules, hard.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

30 mg Capsules: Each capsule contains 30 mg lisdexamfetamine dimesylate, equivalent to 8.9 mg of dexamfetamine.

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

70 mg Capsules: Each capsule contains 70 mg lisdexamfetamine dimesylate, equivalent to 20.8 mg of dexamfetamine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

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

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

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

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Treatment must be under the supervision of a specialist in childhood and/or adolescent behavioural disorders. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptom.

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. A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children 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.

Elvanse is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age and potential for abuse, misuse or diversion.

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. The use of Elvanse 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 childhood and/or adolescent behavioural disorders.

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 Elvanse.

For all patients, either starting treatment for ADHD or switching from another medication, the starting dose is 30 mg taken once daily in the morning.

The dose maybe increased by 20 mg increments, at approximately weekly intervals. Elvanse 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

Elvanse may be taken with or without food.

Elvanse may be swallowed whole, or the capsule opened and the entire contents dissolved in a glass of water. If the contents include any compacted powder, a spoon may be used to break apart the powder in the water. The contents should be stirred until completely dispersed. The patient should consume the full glass of water 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 once the water 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, Elvanse dosing can resume the next day. Afternoon doses should be avoided because of the potential for insomnia.

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 height and weight on a growth chart (see section 4.3 and section 4.4).

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

Ongoing monitoring

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

- Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and at least every six months.
- Height, weight, and appetite should be recorded at least six-monthly with maintenance of a growth chart.
- 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.

Patients should be monitored for the risk of diversion, misuse, and abuse of Elvanse.

Long-term use

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

Adults

In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood (see sections 4.4 and 5.1).

Children Under 6 years

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

Elderly

Dexamfetamine clearance is reduced in the elderly so dose adjustment may be required (see section 5.2).

Patients with renal or hepatic impairment

No studies have been conducted in patients with renal or hepatic impairment. There was no relationship between creatinine clearance and amfetamine pharmacokinetics in elderly subjects (see section 5.2). Dosage reduction may be required in renally impaired patients.

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 Elvanse have a potential for abuse, misuse, dependence, or diversion for non-therapeutic uses that physicians should consider when prescribing this product. Stimulants should be prescribed cautiously to patients with a history of substance abuse or dependence.

Tolerance, extreme psychological dependence, and severe social disability have occurred with the abuse of stimulants. There are reports of patients who have increased the dosage of amfetamine to levels many times higher than recommended; abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression. Changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amfetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

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.

The use of Elvanse is contraindicated in patients with symptomatic cardiovascular disease and also in those patients with moderate to severe hypertension (see section 4.3).

Cardiomyopathy

Cardiomyopathy has been reported with chronic amfetamine use. It has also been reported with Elvanse.

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 Elvanse. 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 suppression of growth (height and weight)

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 Elvanse, +0.87 (1.102) kg for placebo, and -1.36 (1.552) kg for methylphenidate hydrochloride.

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 Elvanse feasible should be prescribed or dispensed in order to minimise the risk of possible overdose by the patient.

Use with other sympathomimetic drugs

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

Use in adults

Safety and efficacy have not been established for the routine continuation of treatment beyond 18 years of age. If treatment withdrawal has not been successful when an adolescent has reached 18 years of age continued treatment into adulthood may be necessary. The need for further treatment of these adults should be reviewed regularly and undertaken annually.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro enzyme inhibition

In vitro experiments with human microsomes indicate minor inhibition of CYP2D6 by amfetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites. Although the clinical significance of this interaction is likely to be minimal, consideration should be given when medications metabolised by these pathways are administered.

Agents whose blood levels may be impacted by Elvanse

Extended release guanfacine: In a drug interaction study, administration of an extended release guanfacine in combination with Elvanse 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 Elvanse.

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

clinically meaningful. In this study, no effect on dexamfetamine exposure was observed following co-administration of extended release venlafaxine and Elvanse.

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

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

Agents whose effects may be reduced by amfetamines

Antihypertensives: Amfetamines may decrease the effectiveness of guanethidine or other antihypertensive 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

There are no adequate and well controlled studies of Elvanse in pregnant women. Dexamfetamine, the active metabolite of lisdexamfetamine, crosses the placenta.

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 Elvanse treatment with female patients who have started menstruation. Elvanse 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. Elvanse should not be used during breast-feeding.

Fertility

Amfetamine has shown no harmful effects on fertility in a rat study (see section 5.3). The effect of Elvanse on human fertility has not been investigated.

4.7 Effects on ability to drive and use machines

Elvanse can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia 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 Elvanse treatment mainly reflect side effects commonly associated with stimulant use. Very common adverse reactions include decreased appetite, insomnia, dry mouth, headache, weight decreased and upper abdominal pain.

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	Frequency not known	Uncommon
Metabolism and Nutrition Disorders	Decreased appetite	Very common	Very common	Very common
	Anorexia	Common	Common	Common
Psychiatric Disorders	*Insomnia	Very common	Very common	Very common
	Agitation	Uncommon	Uncommon	Common
	Anxiety	Uncommon	Uncommon	Common
	Logorrhea	Uncommon	Uncommon	Uncommon
	Libido decreased	Not applicable	Not reported	Common
	Depression	Uncommon	Uncommon	Uncommon
	Tic	Common	Uncommon	Uncommon
	Affect lability	Common	Common	Uncommon
	Dysphoria	Uncommon	Frequency not known	Uncommon
	Euphoria	Frequency not known	Uncommon	Uncommon
	Psychomotor hyperactivity	Common	Uncommon	Common
	Dermatillomania	Uncommon	Uncommon	Uncommon
	Psychotic episodes	Frequency not known	Frequency not known	Frequency not known
	Mania	Uncommon	Frequency not known	Uncommon
	Hallucination	Uncommon	Uncommon	Frequency not known
	Aggression	Common	Uncommon	Frequency not known
Nervous System Disorders	Headache	Very common	Very common	Very common
	Dizziness	Common	Common	Common
	Restlessness	Uncommon	Uncommon	Common
	Tremor	Uncommon	Common	Common
	Somnolence	Common	Uncommon	Uncommon
	Seizure	Frequency not known	Frequency not known	Frequency not known
	Dyskinesia	Frequency not known	Frequency not known	Uncommon
Eye Disorders	Vision blurred	Uncommon	Frequency not known	Uncommon
	Mydriasis	Common	Uncommon	Frequency not known
Cardiac Disorders	Tachycardia	Uncommon	Common	Common
	Palpitation	Uncommon	Common	Common
	Cardiomyopathy	Frequency not known	Frequency not known	Frequency not known
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Uncommon	Common	Common
Gastrointestinal Disorders	Dry mouth	Common	Common	Very common
	Diarrhoea	Common	Common	Common
	Upper abdominal pain	Very common	Common	Common
	Nausea	Common	Common	Common
	Vomiting	Common	Common	Uncommon
Hepatobilary Disorders	*Eosinophilic Hepatitis	Frequency not known	Frequency not known	Frequency not known
Skin and	Hyperhidrosis	Uncommon	Frequency not	Common

System/Organ Class	Adverse Reaction	Children (6 to 12 years)	Adolescents (13 to 17 years)	Adults
Subcutaneous Tissue Disorders			known	
	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	Irritability	Common	Common	Common
	Fatigue	Common	Common	Common
	Feeling jittery	Uncommon	Uncommon	Common
	Pyrexia	Common	Uncommon	Uncommon
Investigations	Blood pressure increased	Uncommon	Common	Common
	*Weight decreased	Very Common	Very Common	Common

Description of selected adverse reactions

Insomnia

Includes insomnia, initial insomnia, and middle insomnia.

Weight decreased

In a 4 week controlled trial of Elvanse 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 Elvanse 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 Elvanse 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 Elvanse 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 Elvanse 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 Elvanse 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.

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.

4.9 Overdose

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

Manifestations of acute overdosage with amfetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, 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.

Management of acute amfetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic, and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amfetamine excretion but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amfetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Elvanse 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 Elvanse in the treatment of ADHD has been demonstrated in three controlled trials in children aged 6 to 12 years, one controlled study in adolescents aged 13 to 17 years, one controlled study in children and adolescents (6 to 17 years), 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 Elvanse 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 to 17 years were evaluated in the pivotal Phase 3 European Study SPD489-325. In this seven-week randomised double-blind,

dose-titrated, placebo- and active-controlled study, Elvanse 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 Elvanse 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 Elvanse when compared to placebo. The endpoint of this study is defined in Table 1. The results were also significantly higher for Elvanse 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 Elvanse significantly improves functional outcomes. Specifically, in Study SPD489-325, 75.0% of subjects on Elvanse 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 ($p<0.001$).

Elvanse 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. Elvanse demonstrated a significant improvement from baseline compared to placebo (Elvanse: 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 Endpoint[1] (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.

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 Elvanse 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 Elvanse 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 Elvanse 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.

Adult population

The effectiveness of Elvanse in the treatment of ADHD was established in a double-blind, randomised, placebo-controlled, parallel-group study conducted in 420 adult patients aged 18 to 55 years who met DSM-IV criteria for ADHD. Significant improvements in ADHD symptoms, based upon investigator ratings on the ADHD-RS with adult prompts total score, were observed for all Elvanse doses compared to placebo. Treatment with Elvanse significantly reduced the degree of functional impairment as measured by improvement on the CGI-I rating scale compared to placebo.

In addition, maintenance of effect was demonstrated in a double-blind, placebo-controlled, randomised withdrawal design study that enrolled adults (n=123) who met DSM-IV criteria for ADHD and who, at study entry, had been treated with Elvanse for a minimum of 6 months. A significantly lower proportion of patients treated with Elvanse met relapse criteria (8.9%) compared to patients receiving placebo (75.0%) in the double-blind randomised withdrawal phase. Relapse was defined as a ≥50% increase from randomisation in ADHD-RS-IV Total Score and a ≥ 2 point increase in CGI-S score relative to the CGI-S score at randomisation.

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 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 Cmax of dexamfetamine in healthy adults after single-dose oral administration of Elvanse 70 mg capsules but prolongs Tmax 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 Tmax 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 Tmax 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 Cmax 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.

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-hydroxy-amfetamine, 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 is similar in children (aged 6 to 12) and adolescents (aged 13 to 17) ADHD patients, and healthy adult volunteers. Any differences in kinetics seen after oral administration are a result of differences in mg/kg dosing.

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 Elvanse.

In a study of 47 subjects aged 55 years of age or older amfetamine 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). Reduced amfetamine clearance does not appear to be related to kidney function as measured by creatinine clearance.

5.3 Preclinical safety data

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.

No adverse effects on nervous system development or reproductive function were observed following repeat dose administration of lisdexamfetamine dimesylate to juvenile rats and dogs.

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 Elvanse.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose.

Croscarmellose sodium.

Magnesium stearate.

Capsule shells

Gelatin.

Black ink (shellac and black iron oxide E172).

Capsule shell colourants:

30 mg: titanium dioxide (E171) and erythrosine (E127).

50 mg: titanium dioxide (E171) and brilliant blue FCF (E133).

70 mg: titanium dioxide (E171), brilliant blue FCF (E133) and erythrosine (E127).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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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Chineham, Basingstoke

Hampshire

RG24 8EP

UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)

PL 08081/0050-0052

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/02/2013

10 DATE OF REVISION OF THE TEXT

01/02/2013