Public Assessment Report

Decentralised Procedure

Elvanse Adult 30, 50 and 70 mg capsules, hard

(Lisdexamfetamine dimesylate)

Procedure No: UK/H/5567/001-03/DC

UK Licence No: PL 08081/0059-0061

Shire Pharmaceutical Contracts Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY
Elvanse Adult 30, 50 and 70 mg Capsules, hard
(lisdexamfetamine dimesylate)

This is a summary of the public assessment report (PAR) for Elvanse Adult 30, 50 and 70 mg Capsules, hard (PL 08081/0059-0061; UK/H/5567/001-03/DC). Elvanse Adult 30, 50 and 70 mg Capsules, hard will be termed Elvanse Adult 30, 50 and 70 mg Capsules throughout this PAR for ease of reading. It explains how Elvanse Adult 30, 50 and 70 mg Capsules were assessed and their authorisations recommended as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Elvanse Adult 30, 50 and 70 mg Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Elvanse Adult 30, 50 and 70 mg Capsules and what are they used for?
Elvanse Adult 30, 50 and 70 mg Capsules are treatments for 'attention deficit hyperactivity disorder' (ADHD) in adults.

For children and adolescents aged 6 to 17 years, another product containing lisdexamfetamine dimesylate is available. Elvanse Adult is not used as a treatment for ADHD in children under 6 years of age because it is not known if it is safe or of benefit in such young people.

How are Elvanse Adult 30, 50 and 70 mg Capsules used?
Elvanse Adult 30, 50 and 70 mg Capsules should be taken in the morning before breakfast with or without food. There are two ways to take Elvanse Adult:

- Swallow the capsule whole with a drink of water
- Open the capsule and empty the contents into a soft food (such as a yogurt), or a glass of water or orange juice.
  Use a spoon to completely break up any bits and stir the Elvanse Adult and yogurt, water or orange juice until they are completely mixed together. Eat all the yogurt or drink all the water or orange juice immediately after mixing – do not store it.

The recommended dose at the start of treatment is 30 mg and this may be increased by a doctor.

Elvanse Adult 30, 50 and 70 mg Capsules can only be obtained on prescription from a doctor.

For further information on how Elvanse Adult 30, 50 and 70 mg Capsules are used, please see the Summaries of Product Characteristics and package leaflet available on the MHRA website.

How do Elvanse Adult 30, 50 and 70 mg Capsules work?
Elvanse Adult 30, 50 and 70 mg Capsules contain the active substance lisdexamfetamine dimesylate. They improve the activity of certain parts of the brain which are under-active. These medicines can help improve attention, concentration and reduce impulsive behaviour. Elvanse Adult 30, 50 and 70 mg Capsules are long-acting medicines which work gradually over time.

What benefits of Elvanse Adult 30, 50 and 70 mg Capsules have been shown in studies?
Studies have shown that Elvanse Adult 30, 50 and 70 mg capsules improve symptoms of ADHD in adults. In clinical studies conducted in adults the effects of these products were ongoing at 14 hours in adults when the product was taken once daily in the morning. In adults it has been shown that continued long term treatment is beneficial.

What are the possible side effects of Elvanse Adult 30, 50 and 70 mg Capsules?
Like all medicines, these medicines can cause side effects, although not everybody gets them.

The most common side effects with Elvanse Adult 30, 50 and 70 mg Capsules (which may affect more than 1 in 10 people) are decreased appetite, being unable to sleep, dry mouth and headache.

The most common side effect with Elvanse Adult 30, 50 and 70 mg Capsules (which may affect up to 1 in 10 people) is palpitations (uneven heartbeat).

For the full list of all side effects reported with Elvanse Adult 30, 50 and 70 mg Capsules, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why are Elvanse Adult 30, 50 and 70 mg Capsules approved?
It was concluded that Elvanse Adult 30, 50 and 70 mg Capsules have shown to have a positive benefit/risk and could be approved for use.

What measures are being taken to ensure the safe and effective use of Elvanse Adult 30, 50 and 70 mg Capsules?
A risk management plan has been developed to ensure that Elvanse Adult 30, 50 and 70 mg Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Elvanse Adult 30, 50 and 70 mg Capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Elvanse Adult 30, 50 and 70 mg Capsules
Denmark, Sweden and the UK agreed to grant Marketing Authorisations for Elvanse Adult 30, 50 and 70 mg Capsules on 13th January 2015. Marketing Authorisations were granted in the UK on 3rd February 2015.

The full PAR for Elvanse Adult 30, 50 and 70 mg Capsules follows this summary. For more information about treatment with Elvanse Adult 30, 50 and 70 mg Capsules, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in April 2015.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Elvanse Adult 30 mg, 50 mg and 70 mg capsules, hard (PL 08081/0059-0061; UK/H/5567/001-03/DC), are approvable.

These products are prescription only medicines indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in adults.

Elvanse Adult is not indicated in all adult patients 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.

Treatment must be under the supervision of a specialist in behavioural disorders. 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 symptom. In adults, the presence of symptoms of ADHD that were pre-existing 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. A comprehensive treatment programme typically includes psychological, educational, behavioural, occupational and social measures as well as pharmacotherapy and is aimed at stabilising the adult patient with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, impulsivity and hyperactivity.

The drug product, Elvanse, is referred to as SPD489 throughout this report. The proposed marketed formulation of SPD489 contains 30, 50, or 70 mg of lisdexamfetamine dimesylate, equivalent to 8.9, 14.8, or 20.8 mg dexamfetamine, respectively.

These are line extension applications submitted via the decentralised procedure in accordance with Article 8.3 (known active substance) of Directive 2001/83/EC, as amended, for a full indication for treatment of adults. The United Kingdom acted as RMS and Denmark and Sweden were CMSs.

Following decentralised procedures (UK/H/3326/001-03/DC) completed in December 2013, SPD489 is already indicated in the EU as part of a comprehensive treatment programme for ADHD in children aged 6 to 17 years of age. The purpose of these applications is to obtain a stand-alone Marketing Authorisation indicated for adult patients. The formulation is identical to that which was approved in the procedure for Elvanse 30 mg, 50 mg and 70 mg capsules hard (PL 08081/0050-0052, UK/H/3326/001-03/DC).

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 central nervous system (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*.

Most of the non-clinical data submitted with these applications were from the previous decentralised dossier (UK/H/3326/001-03/DC). Some new data have been generated since submission of the original Marketing Authorisation. These studies are not specific to adults, but were conducted to enhance the package or to provide information supporting potential alternative indications.

No new clinical data were submitted, however the applicant has provided clinical data, including package of trials in adults, which were submitted with the original dossier. All clinical studies were conducted in accordance with Good Clinical Practice (GCP)

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

All involved Member States agreed to grant Marketing Authorisations for the above products at the end of the procedure (Day 210 – 13th January 2015). After a subsequent national phase, the UK granted Marketing Authorisations (PL 08081/0059-0061) for these products on 3rd February 2015.

II QUALITY ASPECTS

II.1 Introduction

These are line extension applications submitted under Article 8.3 (known active substance) for a full indication for treatment of adults. They are distinct from the existing products for Elvanse 30, 50 and 70 mg Capsules (PL 08081/0050-2; UK/H/3326/001-03/DC) as the paediatric indication has been deleted from the new products.

These products are capsules and contain 30, 50 and 70 mg lisdexamfetamine dimesylate (equivalent to 8.9, 14.8 and 20.8 mg of dexamfetamine), as active ingredient. The excipients present are microcrystalline cellulose, croscarmellose sodium and magnesium stearate making up the capsule fill, the capsule shell consists of gelatin, black ink (shellac and black iron oxide E172), titanium dioxide (E171), erythrosine (E127) (30 mg and 70 mg) and brilliant blue FCF (E133) (50 mg and 70 mg).

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of gelatin and titanium dioxide which comply with the United States Pharmacopeia.
The excipients erythrosine (E127) and brilliant blue FCF (E133) comply with in-house specifications and black iron oxide with the United States Pharmacopeia-National Formulary requirements.

The only excipient used that contains material of animal origin is gelatin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

The applicant has also confirmed that the magnesium stearate used is a vegetable origin.

None of the excipients are sourced from genetically modified organisms.

The finished product is packaged in high density polyethylene bottle and a polypropylene child resistant cap with a foil inner seal containing 28 or 30 capsules. Not all pack sizes may be marketed.

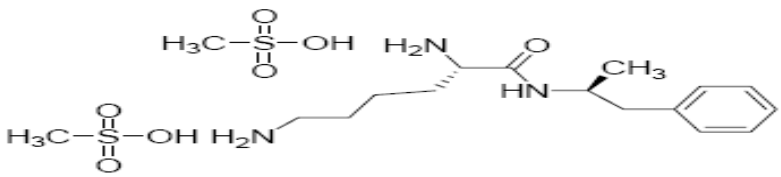
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: **Lisdexamfetamine dimesylate**

Chemical name(s): (2*S*)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide dimethanesulphonate

Structure:



Lisdexamfetamine dimesylate

Molecular formula: $C_{17}H_{33}N_3O_7S_2$
Molecular weight: 455.6 g/mol

Lisdexamfetamine dimesylate is a specific stereoisomer: L-lysine D-amphetamine.

Appearance: A white to off-white solid.

Full details of lisdexamfetamine dimesylate synthesis, control of materials and process validation are provided in the dossier.

Satisfactory controls of materials are in place. The routes of synthesis are adequately described and characterised, and the structure of lisdexamfetamine dimesylate has been confirmed by analytical evidence by both the active pharmaceutical ingredient manufacturers.

The proposed drug substance specification is satisfactory.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed and the proposed retest period of 4 years is justified and a storage statement in line with CHMP guidelines has been proposed.

II.3 Medicinal Product

Pharmaceutical Development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory.

Satisfactory product development data were submitted.

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing process has been validated at commercial scale and has shown satisfactory results.

Finished Product Specifications

The finished product specifications are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results a shelf-life of 2 years with a storage condition ‘Do not store above 25°C’ is set. This is satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

These are line extension applications for a known active substance, lisdexamfetamine dimesylate (LDX), submitted via the decentralised procedure in accordance with Article 8.3 of Directive 2001/83/EC, as amended.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

All non-clinical studies were conducted in accordance with good Laboratory Practice (GLP).

III.2 Pharmacology

Lisdexamfetamine dimesylate is claimed to be pharmacologically inactive, with its biological actions appearing to be due to *d*-amfetamine released into the systemic circulation following intestinal absorption and metabolism by erythrocytes. The counter-moiety, *l*-lysine, which is also released upon enzymatic hydrolysis of lisdexamfetamine is a naturally occurring amino acid, and the amount generated is a small amount of the required daily amount. The systemic delivery of *d*-amfetamine after administration of lisdexamfetamine has been shown to alter its pharmacodynamics and improve the therapeutic index in preclinical models. The mode of action is the ability to increase synaptic concentrations of the catecholamine neurotransmitters noradrenaline and dopamine in the prefrontal cortex (PFC), and in the striatum.

In vitro radioligand binding screens demonstrated that lisdexamfetamine has no affinity for dopamine reuptake transporter (DAT) or norepinephrine reuptake transporter (NET) sites, nor significant affinity for 62 receptors, transporters, ion channels, second messengers, steroids, prostaglandins, growth factors / hormones, brain / gut peptides and enzymes for a range of neurotransmitters, neuropeptides and hormones from a range of species. These data indicate that lisdexamfetamine is pharmacologically inactive and its effects *in vivo* are mediated via its metabolite, *d*-amfetamine.

The data presented show that lisdexamfetamine was efficacious in a rodent model of ADHD. It also enhanced catecholaminergic neurotransmission in the brain *in vivo*. Results from head-to-head comparison experiments indicate that lisdexamfetamine may have equivalent or greater efficacy in ADHD than *d*-amfetamine or methylphenidate with less potential to induce stimulant adverse events than either drug.

Lisdexamfetamine reduced impulsive behaviour in a delay discounting paradigm in juvenile male Wistar rats, and systemic administration of lisdexamfetamine to rats enhanced catecholaminergic neurotransmission in the brain *in vivo*.

Dual-probe microdialysis in the PFC and the striatum of freely-moving rats along with simultaneous measurement of locomotor activity showed that doses of lisdexamfetamine that are not overtly stimulant can, nevertheless, potentiate noradrenergic and dopaminergic function in the PFC and dopaminergic function in the striatum.

In comparative studies, lisdexamfetamine was less behaviourally stimulant than *d*-amfetamine even though it produced substantial increases in striatal dopamine efflux, suggesting that it may have greater differentiation between its therapeutic actions and its unwanted stimulant effects.

The results of the behavioural despair test in the mouse suggest that the drug has modest antidepressant activity on its own, and that there was evidence of augmentation of the efficacy of some anti-depressant drugs. The effects of lisdexamfetamine on food intake, satiety, water intake and bodyweight have been investigated in normal male rats. Lisdexamfetamine reduced food intake throughout a 24-hour study

period in a dose-dependent manner. In dietary-induced obese female rats lisdexamfetamine dose-dependently reduced food intake, which was most marked in the first week of dosing which was due to specific loss of body fat, with no effect on body protein. Plasma levels of insulin, cholesterol and triacyl glycerol (TAG) were not altered. However, there were significant reductions of plasma glycerol, non-esterified fatty acids (NEFA) and leptin compared with vehicle-treated animals.

There was negligible binding affinity of lisdexamfetamine *in vitro* for a range of receptors, ion channels, enzymes, allosteric binding sites and transporters that are known to mediate the pharmacological action of drugs of abuse.

Lisdexamfetamine was resistant to enzymatic metabolism. Incubation of lisdexamfetamine with various rat and human tissues and cells indicate that hydroylysis of lisdexamfetamine is primarily due to enzymatic activity in red blood cells.

Overall, the data show that lisdexamfetamine can produce effects in rats and monkeys that are similar to those of *d*-amfetamine. However, the potential of lisdexamfetamine for abuse appears to be lower than that of *d*-amfetamine or methylphenidate because of the prerequisite for metabolic activation which results in slower delivery of *d*-amfetamine to the brain and a slower onset of its pharmacological effect. As activation occurs in the blood, the potency of lisdexamfetamine is not increased by switching from the oral to the parenteral route of administration.

Additional studies reported since the submission of the original Marketing Authorisation Application (MAA) include neurochemical interaction studies between lisdexamfetamine and *S*-citalopram in the PFC of freely moving rats which revealed that 5-HT, dopamine and norepinephrine were increased in the PFC and hippocampus, the effect being greater than additive. A neurochemical interaction study in freely moving rats revealed that lisdexafetamine potentiated the effect of olanzapine on dopaminergic and noradrenergic neurotransmission in the PFC and nucleus accubens. An investigation into the effect of lisdexamfetamine in a rat model of binge eating behaviour revealed that the compound reduced, as also did *d*-amfetamine and sibutramine, intermittent hyperphagia of food.

III.3 Pharmacokinetics

The non-clinical data indicate that lisdexamfetamine is absorbed intact via an active transport process likely mediated by peptide transporter -1 (PEPT-1). It is then hydrolysed primarily by peptidase(s) associated with red blood cells to the naturally occurring amino acid, l-lysine, and active drug, *d*-amfetamine. This mechanism of activation appears to prevent the rapid release of a bolus of *d*-amfetamine and provides a pharmacokinetic profile that appears to support once-daily administration. The delivery of *d*-amfetamine to the blood and brain after administration of lisdexamfetamine appears to alter its pharmacodynamics and improve the therapeutic index in preclinical models.

Systemic exposures to both lisdexamfetamine and *d*-amfetamine were broadly linear across a wide range of doses except possibly at those that exceeded the Maximum Tolerated Dose (MTD). As expected for a polar compound, lisdexamfetamine did not penetrate the brain and *d*-amfetamine levels in the brain reflect those in the systemic circulation in a manner that parallels *d*-amfetamine derived from administration of amfetamine sulphate.

The major metabolite of lisdexamfetamine is *d*-amfetamine and there are no significant alternate metabolic pathways. Elimination occurs primarily by metabolism, the major excretory products being *d*-amfetamine and a glucuronide metabolite of *d*-amfetamine in the urine. Lisdexamfetamine itself has no clinically relevant interactions with cytochrome (CYP) P450s or membrane transporter proteins and therefore drug-drug interactions mediated by these enzymes/proteins are considered not to be important for lisdexamfetamine. Although *d*-amfetamine has been reported to inhibit CYP2D, *in vitro* studies suggest that this only occurs at exposures far greater than those expected from the clinical use of lisdexamfetamine.

Additional studies submitted with this submission, not available in the original MAA included *in vitro* studies in human hepatocytes and liver microsomes which revealed no indication of inhibition of the CYP P450 tested. The interaction of lisdexamfetamine with an extensive range of membrane transporter protein indicated only weak interactions.

III.4 Toxicology

The programme with lisdexamfetamine dimesylate omitted fertility, pre and post-natal development studies and carcinogenicity testing. The applicant submitted an acceptable rationale for the lack of reproductive toxicity and carcinogenicity studies.

Single dose toxicity studies suggest that lisdexamfetamine is less acutely toxic than *d*-amfetamine at equivalent amfetamine doses.

In the repeated dose rat studies there were some early deaths in particular in the 6-month study. Most deaths on this study were considered to be incidental but the causes were not always established; behaviour changes associated with treatment, leading to broken teeth, may have been contributory.

The most consistently observed overt signs of toxicity were increased activity following oral dosing in both rats and dogs and in all studies. In the rat, self-mutilation was reported in the short-term studies at ≥80mg/kg, often resulting in premature sacrifice. In dogs increased activity was almost always accompanied by various forms of abnormal behaviour and by panting. Salivation, ocular discharge, bloodshot eyes and self-mutilation were reported in the short term studies at ≥6mg/kg/day.

All of these overt signs of toxicity were attributed to the *d*-amfetamine moiety and a very similar range of signs was observed in both rats and dogs in reference control groups treated with equivalent doses of *d*-amfetamine sulfate. None of the observed signs except thin build was persistent for more than about a day on withdrawal from treatment. The signs in 3 of the pivotal studies were subject to a detailed post hoc analysis to confirm the absence of any signs of tolerance or withdrawal. Consistent with the lack of abuse potential, there were no similar signs in dogs following intranasal dosing at 7 mg/day.

At all doses in both rats and dogs and in all studies, there were dose-related reductions in body weight gain that persisted throughout treatment. Body weight gain increased during withdrawal from treatment showing substantial recovery from this effect. Also in all studies and at all doses in both species there were initial temporary significant reductions in food intake. Similar changes in food intake and bodyweight were observed in rats treated with *d*-amfetamine sulfate at equivalent doses. Appetite suppression and associated weight loss is a well-known pharmacological effects of *d*-amfetamine.

There were no treatment-related findings in either gross necropsy observations or microscopic histopathology on any of the repeat dose toxicology studies. In a specific assessment for potential proliferative changes in the rat 6-month study, the number of hepatocyte nuclei immunolabeled by anti-Ki-67 antibodies was unaffected by treatment with lisdexamfetamine.

All of the observed changes could be ascribed to the pharmacological actions of *d*-amfetamine. There was no evidence of neurotoxic changes in any of the studies sponsored by the applicant.

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. The applicant states that in view of

the metabolism of lisdexamfetamine to release amfetamine, the transient nature of plasma exposure in humans to lisdexamfetamine ($t_{½}$ about 1 hour), and the absence of treatment related microscopic tissue changes following administration of either lisdexamfetamine or amfetamine in the rat 6-month study, life-span carcinogenicity studies with lisdexamfetamine were not considered necessary. This is considered to be an acceptable explanation for the lack of carcinogenicity studies.

Lisdexamfetamine dimesylate had no effect on embryo-foetal development or survival when administered orally to pregnant rats and rabbits and effects were consistent with those expected for *d*-amfetamine. As a comprehensive reproduction toxicity package, including fertility, embryo-foetal development and pre- and post-natal development studies has been conducted on mixed amfetamine salts to modern testing standards, further studies with lisdexamfetamine were not considered necessary to support its safety. 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.

Juvenile toxicity evaluations demonstrate no significant irreversible toxicities. The changes observed in developmental and behavioural characteristics were those expected from exposure to *d*-amfetamine and there was no evidence of significant irreversible change.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Based on a maximum daily dose for lisdexamfetamine of 70 mg, *d*-amfetamine is considered unlikely to represent a risk for the environment following the prescribed usage of the product.

III.6 Discussion on the non-clinical aspects

In conclusion, all of the observed changes could be ascribed to the pharmacological actions of *d*-amfetamine. Noteworthy, there appeared to be no evidence of neuro-toxic changes in any of the studies sponsored by the applicant.

The applicant has provided an acceptable explanation for the absence of carcinogenicity studies with dexamfetamine mesylate.

The new non-clinical studies submitted since submission of the original Marketing Authorisation Application were not specific to adults, but were stated to have been conducted to enhance the package or to provide information supporting potential alternative indications.

The new data do not raise any new toxicological concerns. There are no changes proposed to the maximum clinical dose, of 70 mg, therefore safety margins in adults are greater than those previously presented for children and adolescents.

The new data does not raise any non-clinical concerns.

There are no objections to the approval of these products from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction

These are line extension applications submitted under Article 8.3 (known active substance) for a full indication for treatment of adults. These products are distinct from the existing products for Elvanse 30 mg, 50 mg and 70 mg capsules hard (UK/H/3326/001-03/DC) as the paediatric indication has been deleted.

ADHD is a chronic heterogeneous neurobehavioural disorder characterised by "inattention and/or hyperactivity-impulsivity that is more frequent and severe than expected in individuals at a comparable level of development." Its' onset is in early childhood and in many cases (reports indicate about 50% to 75% although there is not universal consensus) it persists into adolescence and adulthood where it is associated with adverse long term outcomes in academic and social function. The core symptoms may evolve over time, with decreases in hyperactive and impulsive symptoms relative to inattentive symptoms. It is especially important to note that the presence of ADHD in childhood and adolescence (by the age of 12 years according to DSM 5) is a prerequisite for the diagnosis to be made in adults.

Adult ADHD is a somewhat controversial condition. There is not complete consensus amongst expert opinion regarding diagnosis or treatment and clinical practice shows considerable geographic variation. The current UK National Institute for Health and Care Excellence (NICE) guideline states that drug treatment is the first-line treatment for adults with ADHD with either moderate or severe levels of impairment and that methylphenidate is the first-line drug. The latter is potentially problematic as no methylphenidate product is currently approved for the treatment of ADHD in adults in the UK. Strattera (atomoxetine) is a non-stimulant and is currently the only product with a full approved indication for treatment of adult ADHD.

IV.2 Pharmacokinetics

A total of 16 studies have been conducted to characterise the pharmacokinetic and pharmacodynamic properties of lisdexamfetamine and the associated release of *d*-amfetamine following SPD489 administration. The package of studies, all of which were conducted in the US, is as follows:

- 3 bioavailability studies (Studies NRP104.101, NRP104.102, SPD489-111)
- 1 dose proportionality study in children with ADHD (Study NRP104.103)
- 1 efficacy and safety study in children with ADHD with a secondary objective to evaluate PK profile and PK/PK relationship with multiple dosing (Study NRP104.201)
- 1 ADME study in healthy adults (Study NRP104.106)
- 1 dose-escalating, PK study in healthy adults (Study SPD489-109)
- 1 special populations (elderly) study in adults ≥55 years of age (Study SPD489-116)
- 1 steady-state dosing study in healthy adults (Study NRP104.104)
- 3 drug-drug interaction studies in healthy adults (Study SPD489-113 – co-administration with omeprazole, Study SPD489-117 - co-administration with venlafaxine and Study SPD503-115, co-administration with the ADHD medication guanfacine)
- 3 abuse potential studies in adults with a history of stimulant abuse (Studies NRP104.A01, NRP104.A02 and NRP104.A03)
- 1 exploratory study designed to evaluate the sensitivity and responsiveness of a standardised, validated, neuropsychometric tests to the potential effects of SPD489 in adults with ADHD (Study SPD489-115).

<u>Absorption and activation of parent drug</u>

After oral administration and absorption, lisdexamfetamine is absorbed intact, as evidenced by relatively high plasma concentration of unconverted drug in the portal blood of rats. *In vitro* studies indicated that the intestinal peptide transporter PEPT-1 is likely to be involved in the uptake of lisdexamfetamine in the intestine. The absolute oral bioavailability of lisdexamfetamine is close to 100% (96.4% of radioactivity was recovered in a human 0-120hr urine collection). Bioequivalence was shown for both the fed vs. fasting state. The bioavailability of lisdexamfetamine clearly meets the biopharmaceutics classification system (BCS) criteria for a highly permeable drug.

After absorption, lisdexamfetamine is rapidly converted to *d*-amfetamine (the active substance) and *l*-lysine with a T½ of less than 1 hour. The major site of the metabolic activation for lisdexamfetamine to

d-amfetamine is believed to be in red blood cells (hydrolysis). Both intra-and inter-subject pharmacokinetic variability in *d*-amfetamine C_{max} and AUC_0 were demonstrated to be low (<20%). AUC of lisdexamfetamine is non dose-linear, with a greater than proportional increase in AUC and C_{max} with increasing dose. This would appear to be due to differences in the clearance of lisdexamfetamine (*i.e.* conversion to dexamfetamine) and not to dose non-linearity of bioavailability. If absorption kinetics were not linear we would expect to see comparable differences in dose adjusted AUC also for the metabolite dexamfetamine but this was not the case. Presumably there is a degree of saturation of the metabolising enzymes in the red blood cells that reduces the clearance of lisdexamfetamine at the higher dose. This is not problematic as kinetics for the active drug are essentially dose linear.

Non-clinical studies demonstrated that the hydrolysis of lisdexamfetamine to *d*-amfetamine occurred primarily by red blood cells. The capacity of this process was investigated *in vitro* by incubating lisdexamfetamine with various dilutions of red blood cells. Lisdexamfetamine was hydrolysed to *d*-amfetamine at all red blood cell dilutions, and the rate of hydrolysis was not substantially affected until the red blood cells were diluted to 25% of normal haematocrit. Thus the conversion of lisdexamfetamine to *d*-amfetamine is a high capacity and linear process that is unlikely to be saturated at higher doses. This is confirmed when single doses of lisdexamfetamine up to 250 mg demonstrated linear dose proportionality of *d*-amfetamine.

Further study of the enzyme(s) responsible for the hydrolysis of lisdexamfetamine to *d*-amfetamine, with a view to identifying any potentially significant drug-drug interactions at this level, is under investigation.

At steady-state, peak levels are about 90 ng/ml and trough levels are about 20 ng/ml. That is not a small degree of peak-to-trough fluctuation and is greater than that seen for many prolonged release products where low peak-to-trough fluctuation is considered advantageous. The situation is a little more complicated for stimulant treatments for ADHD as therapeutic drug levels at night may not be required or even desirable (*e.g.* insomnia as an undesirable effect). The situation is further complicated by the possibility suggested in the literature that a phase of rapid increase in plasma levels is necessary to achieve full therapeutic effect. This is said to be the reason a conventional monophasic prolonged release methylphenidate was found to lack efficacy but newer biphasic formulations such as Concerta XL and Equasym XL were more successful.

The PK profile for *d*-amfetamine after dosing of SPD489 70 mg to steady state might meet these criteria for a successful stimulant treatment for ADHD. The initial rise in plasma levels is reasonably sharp; not as rapid probably as a biphasic prolonged release formulation with a substantial immediate release component but this could have advantages for undesirable effects and abuse potential. Ultimately whether the PK profile of SPD489 is preferable to the currently marketed products containing *d*-amfetamine can only be established by comparative clinical efficacy and safety data.

Oral administration of SPD489 resulted in generally predictable pharmacokinetic parameters for lisdexamfetamine and *d*-amfetamine (AUC and C_{max}). AUC and C_{max} values were generally higher in children than in adults, broadly proportional to their weight differences.

Plasma concentrations of unconverted lisdexamfetamine are low and transient. Plasma levels are very low after 3 to 4 hours and are generally non-quantifiable by 8 hours after administration. Both lisdexamfetamine and *d*-amfetamine are eliminated in the urine but very little of the former is found in urine as most of an administered dose is hydrolysed to *d*-amfetamine. Only 2.2% of the administered dose was detected as lisdexamfetamine in the 0-48h urine sample. T_{max} values for lisdexamfetamine after oral administration were extremely consistent with mean values in the range 1.0 hours to 1.3 hours. The exceptions were the delayed T_{max} in the fed state (2.1 hours in adults, attributed to delayed gastric emptying) and in the elderly aged over 75 years (1.8 hours).

For dexamfetamine mean T_{max} values after oral administration were also consistent, in the range 3.3 hours to 4.6 hours. In the very elderly (over 75 years) T_{max} was prolonged to about 5 hours.

The data for the parent lisdexamfetamine are consistent with a drug that is reliably well absorbed and the data for the active dexamfetamine are consistent with a predictable and consistent rate of conversion from the pro-drug parent. These findings are generally reassuring.

Metabolism
It has been sufficiently established that lisdexamfetamine has a single primary metabolite, dexamfetamine. Dexamfetamine is a very old long established drug and its metabolic pathway is reasonably well-established hence further work to characterise its metabolic pathway is not required. Sufficient information has been provided on the enzyme systems responsible for the various metabolic steps, on the pharmacokinetics of the main metabolites, the pharmacological activity of the metabolites and the potential for drug – drug interactions.

Elimination
The primary metabolites, dexamfetamine and hippuric acid, are excreted in urine. After oral administration of 14C-radiolabeled SPD489 70mg, approximately 67% of the dose was excreted as *d*-amfetamine (41.5%) or hippuric acid (24.8%) in the 0-48hr urine sample. Very little (2.2%) was excreted as unmetabolized lisdexamfetamine. Neither biliary nor faecal excretion played a major role in elimination. After 7 days of once-daily dosing of SPD489 70mg, there was no accumulation of lisdexamfetamine. Steady-state for *d*-amfetamine was achieved by Day 5, with a mean t½ on Day 7 that was essentially the same as after a single dose.

No studies in impaired renal function are provided and information in the Summary of Product Characteristics (SmPC) is based on the PK data in normal subjects. This is acceptable given the well-established nature of dexamfetamine and the pharmacological inactivity of lisdexamfetamine.

Interactions
No human tissue *in vitro* interaction studies have been performed. There are data in the literature from *in vitro* studies that suggest that CYP2D6, CYP1A2, and CYP3A4 may be weakly inhibited by *d*-amfetamine or other metabolites. However, in a study conducted with extended release (ER) mixed amfetamine salts, *d*- and *l*-amfetamine at concentrations 4- to 30-fold in excess of those anticipated clinically did not produce notable inhibitory effects on the marker reactions of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, the major human CYP forms involved in the metabolism of most clinically used drugs. It is agreed that there is a low potential for CYP mediated drug-drug interactions. Additional human tissue *in vitro* interaction studies investigating the potential for drug-drug interactions relating to hepatic metabolism are not considered necessary.

IV.3 Pharmacodynamics

Lisdexamfetamine dimesylate is the l-lysine conjugate of *d*-amfetamine (dex-amfetamine), a well-known centrally acting non-catecholamine sympathomimetic amine. The stimulant activity of *d*-amfetamine appears to relate to blockade of norepinephrine and dopamine reuptake in the central nervous system thereby increasing the availability of these naturally occurring neurotransmitters.

Lisdexamfetamine is an inactive parent drug. *In-vitro* studies showed that lisdexamfetamine does not bind to the sites responsible for the reuptake of norepinephrine or dopamine. In receptor binding studies, lisdexamfetamine at concentrations up to 10^{-5}M had no detectable binding affinity to the human recombinant norepinephrine transporter or the dopamine transporter. It is difficult to prove a negative i.e. that the parent lisdexamfetamine has no pharmacological activity. Nevertheless the package of *in-vitro* studies is fairly comprehensive and seems sufficient for the purpose of this application to justify the contention that lisdexamfetamine is unlikely to have major pharmacological activity that would need to be further addressed in the clinical safety evaluation.

Although not fully understood, the mechanism of action of stimulants including *d*-amfetamine in the treatment of ADHD is reasonably well characterised and further data are not required.

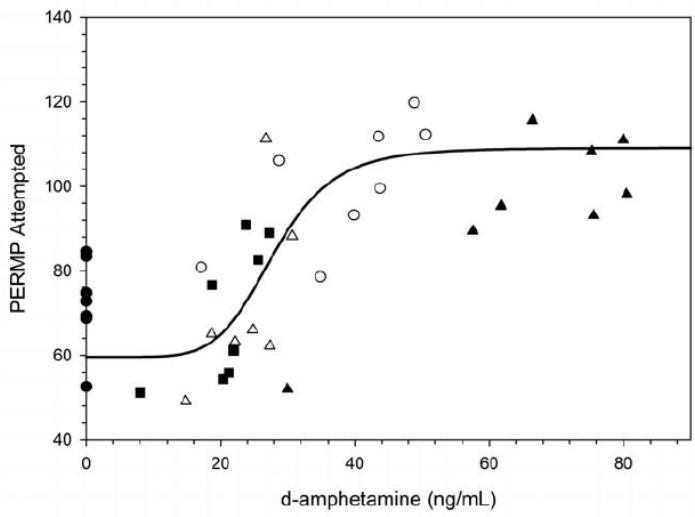
The potential cardiovascular effects of lisdexamfetamine have been evaluated. In the human Ether-à-go-go related gene (hERG) assay, 50µg/mL lisdexamfetamine produced no inhibition of hERG tail current. The available data showing little or no potential for dexamfetamine to prolong QT interval are sufficient and no further data are required.

The effects of a single 50 mg oral dose of lisdexamfetamine on blood pressure and pulse rate were investigated in study SPD489-116, which was primarily a pharmacokinetic study in healthy elderly male and female subjects in three age groups studied (55-64, 65-74 and ≥75 years). These data indicated that SPD489 causes increases in blood pressure and pulse rate that if maintained with maintenance long term treatment might be expected to be associated with significantly increased risk of serious cardiovascular and cerebrovascular adverse events in susceptible patients. This would be an important consideration in the benefit-risk assessment for adults especially and is considered further in the clinical safety section.

PK-PD relationship

Population pharmacokinetic/pharmacodynamic models for the change in plasma *d*-amfetamine concentration over time have been developed based on an analogue classroom assessment of an immediate release (IR) mixed amfetamine salts (MAS) product, an extended release MAS product, and placebo administered to children with ADHD (McCracken *et al*. 2003). The pharmacodynamic parameters were based on the Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale (SKAMP) and Permanent Product Measure of Performance (PERMP) scores. The data best fit a sigmoid model in which the *d*-amfetamine plasma concentration required to achieve 50% maximum effect is approximately 24-28 ng/mL and lower plasma concentrations can be considered as sub-therapeutic. Maximal treatment effect was seen at plasma concentrations about 50 ng/ml.

Figure 1



Abuse Potential

The results from three single-dose, abuse potential studies are provided.

In Study NRP104.A01 (oral administration) the applicant's claim that, compared to *d*-amfetamine sulfate 40mg, SPD489 doses of 30-150mg produced less drug liking.

In Study NRP104.A02 (intravenous administration) reduced drug liking compared to *d*-amfetamine was shown. As might be expected because of the pro-drug nature of lisdexamfetamine, and its need for

metabolic activation even after IV administration, the initial rise in plasma levels after injection of SPD489 prepared for injection is much slower than for *d*-amfetamine sulfate. C_{max} is also substantially lower for SPD489. Both of these factors would be expected to substantially reduce abuse potential by the intravenous route and indeed the data show this.

In Study NRP104.A03 (oral administration) the applicant's claim that SPD489 showed less abuse potential than *d*-amfetamine sulfate at an equimolar dose of amfetamine free base is much more reasonable in this study than in study NRP104.A01. Fast rate of initial increase in plasma levels (fastest with intravenous use) is generally desired for drugs of abuse so it is to be expected that the slower delivery of active drug into the circulation from SPD489 would make it less desirable for abuse than immediate release *d*-amfetamine.

Combining the two oral administration studies it can be concluded that there is reasonable evidence that SPD489 does indeed have slightly or moderately reduced abuse potential compared to an equivalent dose of *d*-amfetamine, although the evidence is inconsistent and statistically rather weak.

The applicant has demonstrated a significantly lower potential for non medical use (abuse and misuse). The most compelling reason is that the gradual bioconversion from prodrug to active dexamfetamine in red blood cells makes it impossible to achieve the rapid rise in plasma levels that many abusers of dexamfetamine desire, and obtain by using the transmucosal or intravenous routes of administration. The applicant has shown that there is significant additional morbidity when the drug is abused in this way. As diversion and abuse of amfetamines is a very real concern this represents a significant advantage for lisdexamfetamine over dexamfetamine, even though the former remains a highly abusable drug.

IV.4 Clinical efficacy

Elvanse Adult (lixdexamfetamine dimesylate) is intended to be indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD), in adults. The proposed starting dose is 30 mg taken once daily in the morning, which may be increased by 20 mg increments at weekly intervals to a maximum of 70 mg. This is the same posology as in children and adolescents.

The CHMP 'Guideline on the clinical investigation of medicinal products for the treatment of attention deficit hyperactivity disorder (ADHD)' is applicable here.

- It states that dose finding should be conducted, comparing at least three doses to placebo for a duration of at least 4 weeks on stable medication. Confirmatory trials for short-term efficacy should be randomised, double-blind, parallel group comparisons to placebo and active control. The duration of these trials should be at least 6 weeks on stable dose (8-12 weeks if maintenance of effect is to be demonstrated with a randomised-responder design). Long term efficacy (maintenance of effect) can be demonstrated using either a 6-month placebo controlled study or a randomised withdrawal design.

- Studies should show both a reduction of symptoms (using a scale such as the Conner's rating scale or the ADHD Symptoms Rating Scale (ADHD-SRS)) and an improvement in functioning (CGI could be used). For both endpoints a responder analysis should be presented as well as difference in mean scores.

- Efficacy should be shown separately in children and adolescents (and adults if applicable). Adult indications can only include patients where it can be verified the symptoms were first present in childhood.

The completed double blind randomised controlled clinical efficacy trials in adults are summarised below:

Controlled efficacy studies in adults
Study 303 - 4 week placebo controlled parallel group trial (dose finding study)
Study 316 - 2 week placebo controlled crossover trial (workplace environment)
Study 401 - 9 week (maximum) placebo controlled randomised withdrawal trial
Study 403 - 10 week placebo controlled parallel group trial

There is also a 52-week, open label, extension trial in adults that primarily assesses safety and tolerability (study 304) and trials (all in adults) in major depressive disorder, schizophrenia (negative symptoms), acute sleep deprivation and binge eating disorder.

The adult programme is generally in-line with the guideline, including a 4-week dose short term efficacy trial, a pivotal 10 week efficacy trial and a randomised withdrawal trial to show maintenance of efficacy. The lack of an active comparator in the adult 10-week confirmatory trial is a disadvantage although at the time there was no approved treatment in this population.

Efficacy measures
The measures of ADHD symptomatology defined as primary efficacy endpoints were the ADHD Rating Scale (ADHD-RS) with Adult Prompts and the Behaviour Rating Inventory of Executive Function – Adult Version (BRIEF-A). In addition the Conner's Adult Rating Scale – Observer: Short Version was used as a secondary efficacy measure in study 403. The ADHD-RS with Adult Prompts is a well-known and established ADHD efficacy measure validated for use in adults and is a suitable primary efficacy measure. The BRIEF-A is less well established but was the primary efficacy measure in the pivotal adult short term study 403. The ADHD-RS with Adult Prompts was a key secondary efficacy endpoint in this study which alleviated any uncertainties about the validity and usefulness of the BRIEF-A.

The main measures of functional outcome were the Clinical Global Impression Scales of Severity and Improvement (CGI-S and CGI-I). The Permanent Product Measure of Performance (PERMP) was a key functional outcome measure in the non-pivotal workplace environment study 316.

The validity and reliability of a number of other rating scales that were used as secondary efficacy measures in the short term efficacy studies have been sufficiently justified.

General methodological aspects
All Phase 3 trials studied the 30, 50, and 70 mg doses of SPD489 for which registration is being sought. Of the three short/medium term, double-blind, randomised studies in adults, two were parallel-group designs (303 and 403) and the workplace environment study 316 was a crossover design. A crossover design is acceptable in principle for the exploratory trial 201 and for the studies in controlled settings, since there is unlikely to be significant carryover of pharmacological activity into the second period. For confirmatory trials randomised, double-blind, parallel-group studies are necessary and the applicant has complied with this requirement.

Of the parallel-group designs, the three dose finding study 303 had 4-week randomised treatment duration, while the pivotal efficacy study 403 had a treatment duration of 10 weeks. According to the ADHD guideline the randomised treatment periods in the pivotal short term trials should be of at least 6 weeks duration. The pivotal trial 403 meets this requirement. The 4-week treatment duration in the dose finding studies is satisfactory.

All studies have included a placebo control. None of the adult trials included an active comparator arm. An active comparator is generally considered to be important in trials of drugs in psychiatry because assay sensitivity of trials varies considerably and without an active comparator of known efficacy it can be difficult to draw conclusions on the clinical relevance (in the context of existing treatment options) of an observed difference from placebo.

Patient populations

The inclusion criteria in the adult trials are generally satisfactory. In particular the exclusion of a major comorbid psychiatric diagnosis but not of mild to moderate psychiatric comorbidity strikes a reasonable balance between ensuring that the study population is truly an ADHD population and excluding so many patients that the wider applicability of the studies could be questionable. The exclusion from the pivotal efficacy study 403 of subjects that had previously failed to respond to amfetamine therapy is probably reasonable. Very few patients screened for inclusion in the trial had previously tried and failed amfetamine therapy so this exclusion criterion is not a concern.

The applicant has provided satisfactory details of how the presence of first symptoms in (early) childhood was verified (*e.g.* by medical records/school reporting *etc*) in the adult patients studied, which is considered mandatory for the diagnosis of ADHD in adults.

The CHMP scientific advice in 2005 stated that data from an EU population would be required as significant differences between the populations in US ADHD trials and the EU ADHD population can be expected. The two European clinical studies 325 and 326 in paediatric populations were considered sufficient in principle to meet this requirement for the previous submission, which resulted in approval of lisdexamfetamine for the treatment of ADHD in children and adolescents.

However all of the controlled studies in adults were conducted in the US. In all studies the majority of subjects were white. In the original submission the applicant provided insufficient justification of the applicability to the EU adult ADHD patient population of the exclusively US adult clinical trial programme. The company provided a detailed comparison of the diagnosis and treatment of adult patients with ADHD in the US and the EU, supported by a comprehensive set of literature references. The RMS considers that sufficient justification has now been provided that the US data can be accepted as applicable to adult patients diagnosed with ADHD in the EU according to the DSM-IV-TR and/or DSM 5 diagnostic criteria. This is discussed further below in the conclusion on efficacy.

Dose finding study – Study 303

Study design and analysis

This study compared Elvanse 30 mg daily, 50 mg daily and 70 mg daily to placebo. It was conducted over approximately 6 weeks. Six visits were scheduled, one to screen candidates (Visit 1: Screening), one to randomise subjects to double-blind treatment (Visit 2: Baseline), and four at weekly intervals to assess the result of treatment (Visits 3, 4, 5, 6). After the screening visit eligible subjects discontinued any psychoactive medications they were currently taking and entered the (at least) 7 day washout period. Patients were required to have a baseline (after washout) ADHD-RS score ≥ 28 to continue in the trial. Eligible subjects were then randomised and received 4 weeks treatment. A forced titration was employed in the Elvanse arms. The table below shows the doses of Elvanse that were taken during the treatment phase of each study.

Figure 2
Titration of Elvanse by treatment group

	Week 1	Week 2	Week 3	Week 4
Elvanse 30mg	30mg	30mg	30mg	30mg
Elvanse 50mg	30mg	50mg	50mg	50mg
Elvanse 70mg	30mg	50mg	70mg	70mg

Results - Primary endpoint

The primary efficacy endpoint was the change from baseline to the patient's final assessment in the ADHD-RS total score (this is equivalent to analysing the change from baseline to week 4 using last observation carried forward (LOCF) to impute missing data). This was analysed using analysis of covariance with baseline score, treatment and site as covariates (site was not included in study 305). To account for the multiplicity of comparing three treatment groups to placebo, Dunnett's test was used to calculate p-values and 95% confidence intervals.

	Placebo	Elvanse 30mg	Elvanse 50mg	Elvanse 70mg
n	62	115	117	120
Baseline - mean (sd)	39.40 (6.42)	40.52 (6.21)	40.81 (7.30)	41.02 (6.02)
Endpoint	31.60 (11.24)	24.26 (12.69)	23.31 (12.16)	22.23 (11.61)
Change from baseline	-7.81 (9.28)	-16.26 (12.67)	-17.50 (11.65)	-18.78 (11.85)
Adjusted change*	-8.20	-16.24	-17.36	-18.61
Difference*		-8.04	-9.16	-10.41
95% CI**		(-12.14,-3.95)	(-13.25,-5.08)	(-14.49,-6.33)
p-value vs. placebo**		p<0.0001	p<0.0001	p<0.0001

*from ANOVA ** from Dunnett's test

The study demonstrated a highly statistically significant advantage over placebo for all three doses of Elvanse and the differences were seen from week 1. A dose response is seen, though the additional benefit of increasing dose was small compared to the benefit of initiating treatment.

Responder analysis for the symptom scores (with the denominator all patients randomised and treated) were presented and confirmed clinically and statistically significant efficacy.

To observe for an improvement in functioning, CGI Improvement (CGI-I) was included as a secondary endpoint. A highly statistically significant improvement in functioning was shown for Elvanse patients compared to placebo. The results were highly consistent with those for the primary endpoint.

Confirmatory study – Study 403

The confirmatory efficacy study in adults was a randomised, double-blind, placebo-controlled, parallel-group study. Elvanse 30-70 mg daily (the flexible dosing scheme proposed in the SmPC) was compared to placebo. As previously discussed there was no active comparator.

The full analysis set (FAS) was defined to include all randomised patients who received treatment and at least one post-baseline ADHD-RS assessment. This was the primary population for efficacy analysis. The FAS was not appropriately defined. In a double-blind trial it is acceptable to include only all treated patients, but the exclusion of patients with no post-treatment data creates a potential bias, as these withdrawals may be treatment related. There were a larger number of patients excluded in the Elvanse group. This could have been a concern if the results had been borderline.

Study 403 was otherwise generally well designed.

There are no obvious baseline differences between treatment groups. Patients were predominantly white so race / ethnicity in this US patient population is not markedly different from an EU population.

The primary efficacy measure was the Subject reported Behavioural Rating Inventry of Executive Function - Adult Version Global Executive Composite T-Score (BRIEF-A GEC T-score). The Adult Attention-Deficit/Hyperactivity Disorder Rating Scale with Prompts (Adult ADHD-RS with prompts) was used as a secondary endpoint. These scales were assessed using change from baseline to the patient's final assessment (equivalent to analysing the change from baseline to week 10 using LOCF to impute missing data).

Change from baseline to last observation in subject reported BRIEF-A GEC T-score

	Placebo	Elvanse
n	75	79
Baseline - mean (sd)	79.4 (8.68)	79.5 (8.01)
Endpoint	68.3 (17.12)	57.2 (14.11)
Change from baseline	-11.1 (16.19)	-22.3 (14.19)
Adjusted change*	-11.1	-22.3
Difference*		-11.2
95% CI**		(-15.9,-6.4)
p-value vs. placebo**		p<0.0001

*from ANOVA

Change from baseline to last observation in Adult ADHD-RS with prompts (Investigator assessed) Total score

	Placebo	Elvanse
n	75	79
Baseline - mean (sd)	39.9 (6.83)	39.9 (7.37)
Endpoint	29.6 (14.32)	18.5 (12.31)
Change from baseline	-10.3 (12.70)	-21.4 (11.27)
Adjusted change*	-10.3	-21.4
Difference*		-11.1
95% CI**		(-14.9,-7.3)
p-value vs. placebo**		p<0.0001

*from ANOVA

A highly statistically significant advantage over placebo was seen both for the primary endpoint, and for the ADHD-RS (used as primary in the previous trials).

A large number of secondary endpoints also showed highly statistically significant results. Responder analyses (in which responders were defined as a >30% reduction from Baseline in ADHD-RS-IV Total Score and a CGI-I value of 1 or 2) confirmed statistically significant and clinically relevant superiority of active treatment over placebo for the key efficacy measures.

The lack of data showing the treatment effect in comparison with an established product is a weakness of the dossier. The NICE guideline recommends that drug treatment is the first-line treatment for adults with ADHD with either moderate or severe levels of impairment, and that methylphenidate is the first-line drug. No stimulant currently has a licensed indication for adult ADHD although section 4.2 of the SmPC for Concerta XL states "*In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood. However, start of treatment with CONCERTA XL in adults is not appropriate*". Concerta XL could have been an appropriate active comparator as it is recommended in established guidelines, albeit not currently an approved indication. More recently (May 2013) Strattera (atomoxetine) has been approved for adult ADHD and this would now also be a suitable active comparator. The lack of an active comparator in the adult study 403 is non-compliant with the ADHD guideline, although the lack of another product approved for the adult indication is a substantial mitigating factor. It is at least reassuring that the results of study 403 seem to be of clear clinical relevance.

Long-term efficacy (adults) – Study 401

Study 401 was a randomised withdrawal study. Patients were recruited who had been on stable treatment with Elvanse 30, 50 or 70 mg daily for at least 6 months and were responding (Adult ADHD-RS with prompts total score < 22 and CGI-S ≤ 3 at screening) with acceptable tolerability.

Eligible patients went into a 3-week open-label treatment phase where they continued on the same dose of Elvanse they were already receiving. Patients who had ADHD-RS score ≥22 or CGI-S score > 3 at visit 3 (week 3) were withdrawn from the study.

The remaining patients continued into the double-blind treatment phase and were randomised to either continue on the same dose of Elvanse or switch to placebo for a maximum of 6 weeks, which was considered to be sufficient to observe a meaningful difference between treatments in ADHD symptom.

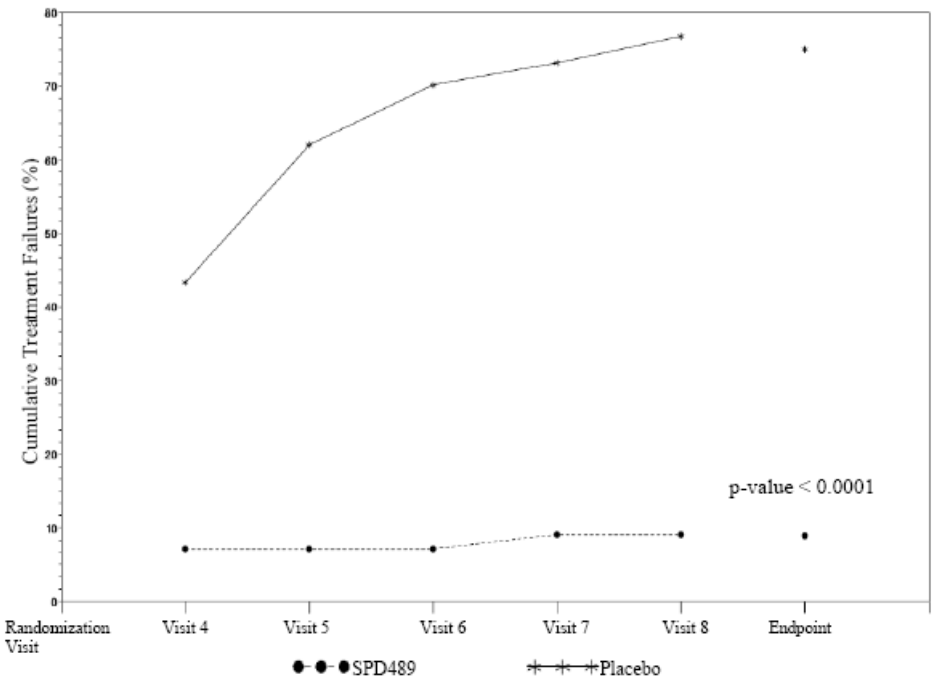
During the double-blind randomised withdrawal phase, patients who had both a ≥50% increase in ADHD-RS and a ≥2 point increase in CGI-S relative to visit 3, were discontinued from the trial and classified as a treatment failure. The primary end-point compared the proportion of patients with treatment failure across the two groups.

Results

	Placebo	Elvanse
n	60	56
Relapsed		
Visit 4	26	4
Visit 5	10	0
Visit 6	4	0
Visit 7	1	1
Visit 8	2	0
Visit 9	0	0
Withdrew without providing data at withdrawal visit	2	0
Total	45 (75.0%)	5 (8.9%)
p-value		p<0.0001
Any withdrawal = failure	47 (78.3%)	6 (10.7%)
		p<0.0001

The relapse rate was clearly higher for those who had treatment withdrawn. Hence it seems clear that in patients who respond to short-term treatment, there is benefit in continuing treatment to the long-term.

Figure 3: Cumulative Proportion of Treatment Failures by Visit (FAS)

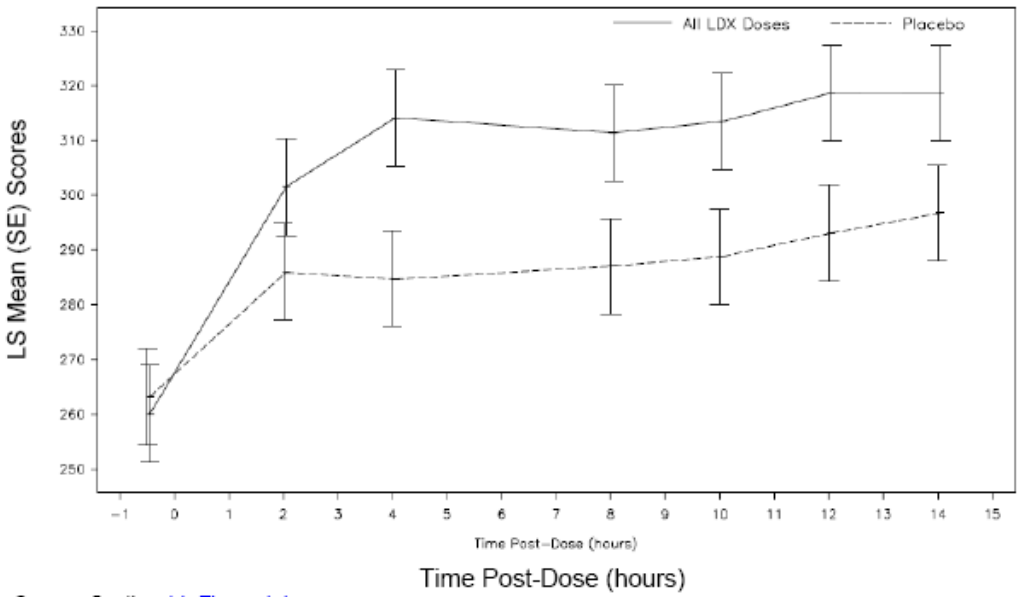


There is clear evidence in adults that patients receiving clinically important benefit from Elvanse can expect to receive further benefit in terms of symptoms (ADHD-RS score) or CGI-S score if treatment is continued. However this trial was not designed to provide evidence that a beneficial effect on functioning (including behavioural, occupational educational and social) is maintained with long term treatment.

Supportive study – Study 316

Study 316 was a randomised, double-blind, two-way crossover study comparing Elvanse to placebo in adults aged 18-55 years. It was conducted in the controlled setting of an Adult Workplace Environment (AWE) to give a picture of efficacy throughout the day. Although no substitute for studies in the natural setting, this study in a controlled setting provides useful additional information on which aspects of mental functioning and behaviour respond positively to treatment.

Figure 3: LS Mean (SE) PERMP Total Score by Time Point (ITT Population)



Highly statistically significant differences are seen right from the earliest time-point (in this case 2 hours after treatment). The treatment effect initially grows, and is then maintained for the rest of the day right out to hour 14. This study shows that the onset of effect is quick and is maintained long enough to cover the working day.

Assessor's overall conclusions on clinical efficacy (adults)

A clear short-term effect is seen in both symptoms (on standard validated symptom rating scales) and improvement on clinical global impression scores. This effect is produced quickly after treatment initiation and maintained for the working day. It is also shown that there is maintenance of efficacy with continued long-term treatment In all trials the differences from placebo are highly statistically significant and robust to choices of analysis and handling of missing data. The magnitude of the difference from placebo appeared to be consistently of clear clinical significance for all strengths and for functional measures as well as ADHD symptom scores.

An effect purely on symptom scores does not readily translate into a clearly relevant clinical benefit. Demonstration of an effect on functioning (work, social, family *etc*) is therefore considered an important aspect of the development of products for the treatment of ADHD. Only the 10-week confirmatory study 403 included true functional efficacy measures. These were the Adult ADHD Impact Module (AIM-A), the Adult ADHD Quality of Life scale, the Marital Impact Checklist, the Marital Satisfaction Inventory and the Alabama Parenting Questionnaire. In general Elvanse showed statistically and clinically significant superiority to placebo on a range of functional measures in study 403.

There is clear evidence from the randomised withdrawal trial 401 that adult patients receiving clinically important benefit from Elvanse can continue to receive benefit from continuing treatment in terms of symptoms (ADHD-RS score) or CGI-S score. However this trial was not designed to provide evidence that a beneficial effect on functioning (including behavioural, occupational educational and social) is maintained with long term treatment.

It remains the case that considerably more patients (as % of the total population) are treated with drugs for ADHD in the US than in most of Europe, both adults and children. However the applicant has provided substantial reassurance that the controlled inclusion / exclusion criteria of the clinical trials will have minimised any effects of these regional differences. DSM-IV-TR diagnostic criteria and strict structured interview procedures were used for entry into the studies supporting these applications. This should minimise any differences between the US trial populations and comparable EU patients.

It is worth noting that including a wide range of patients with milder ADHD symptoms and/or prominent co-morbidities or personality disorders (which is what is believed to happen more in US practice) might be expected to reduce the overall measured efficacy rather than exaggerate it, as stimulants are expected to be more effective as a treatment for patients with "pure" ADHD than for the aforementioned other categories.

The clinical and statistical significance of the efficacy demonstrated in the trials supporting this application was consistently high, both on standard validated rating scales and on measures of functioning. It remains possible that results in an EU population might differ to some degree from the US data but the well referenced arguments presented by the applicant are sufficient to reassure that large differences would not be seen. Given the substantial treatment effect seen in the US trials it can therefore reasonably be concluded that clinically significant efficacy will be seen in EU patients.

A key conclusion is that the differences between the US and the EU are in clinical practice rather than in the patients *per se*. The Company's statement that "ADHD is not a diagnosis rooted in cultural characteristics" is agreed. Because of trial standardisation procedures, the known differences between the US and the EU in terms of general clinical practice (diagnosis and treatment) are not likely to translate into important differences between the clinical trial populations studied in the US and those that might have been studied in EU trials. This conclusion is indirectly supported by the demonstration that the baseline illness characteristics were similar for EU and US patients in the trials in children and adolescents using similar screening and inclusion/exclusion criteria to those in the adult trials.

It is agreed that the US data can be accepted as applicable to adult patients diagnosed with ADHD in the EU according to the DSM-IV-TR and/or DSM 5 diagnostic criteria.

No stimulant had a licensed indication for adult ADHD at the time of conduct of the pivotal trials. In view of the substantial treatment effect seen in the clinical trials on standard validated rating scales and measures of functioning, the clinical relevance of the demonstrated efficacy can be accepted without reference to an active comparator.

Finally, the supplied references provide clear justification that there is a need for treatment of ADHD in adults with significant impairment of functioning (social, occupational *etc*) both for the benefit of individual patients and to society (*e.g.* unemployment). An additional therapeutic option for these patients is therefore highly desirable. In this context the observation that stimulants have repeatedly been shown to be more effective for ADHD than non-stimulants (Moriyama *et al.* 2013; Bitter *et al.* 2012) is pertinent and is reflected in the NICE guidance that stimulants are the pharmacotherapy of first choice in adult ADHD. The cross trial comparisons and meta-analyses presented by the applicant need to be interpreted with caution but there is a strong indication that SPD489 is at least as effective as alternative treatments, if not more so.

In conclusion the efficacy of the product in the requested indication is considered to be adequately demonstrated.

IV.5 Clinical safety

Stimulants have been used as pharmacological treatments for ADHD over many years and two are currently approved in the UK for this indication, methylphenidate and dexamfetamine. Of these methylphenidate is the preferred first line pharmacological treatment choice in children and adolescents. More recently the non-stimulant atomoxetine (Strattera) has been available as an alternative treatment option. NICE (2007) recommends that dexamfetamine is reserved for patients showing insufficient response to a maximum tolerated dose of methylphenidate and atomoxetine (as part of a comprehensive treatment programme). In adults pharmacological treatment is the treatment of choice and methylphenidate is the first line drug. The reasons for preferring methylphenidate over dexamfetamine

include issues relating to undesirable effects and abuse potential.

The common adverse effects of stimulant therapies for ADHD including dexamfetamine are fairly well defined after years of clinical experience. The applicant has provided reasonably persuasive data indicating that lisdexamfetamine is pharmacologically inactive. The safety profile of Elvanse might therefore be expected in general terms to reflect that of the marketed dexamfetamine, perhaps with some differences attributable to the different PK profile for the active dexamfetamine.

Amfetamines cause increases in pulse and blood pressure and awareness and management of cardiovascular undesirable effects is an important part of managing these patients (NICE 2007). The applicant states that recent published studies have not demonstrated any increased risk of QT prolongation, torsades de point or sudden death for stimulants.

Overall, in the Phase 2-4 Studies, 1941 subjects received at least 1 dose of SPD489. The median duration of exposure was 52 days (range 1 to 431 days). Total exposure to SPD489 in the safety population was 809.6 subject-years. Given the well-established use of dexamfetamine for the treatment of ADHD in children and adolescents the extent of patient exposure in this population is sufficient. There is much less experience with dexamfetamine for the treatment of ADHD in adults. The extent of SPD489 exposure in adults is reasonably substantial but numbers treated long-term are likely to be insufficient to detect for example any increase in cardiovascular risk. The extent of SPD489 exposure in adults is sufficient.

Adverse events

Of the 1941 subjects who received SPD489 in the 13 Phase 2-4 studies, 82.0% had at least 1 treatment emergent adverse event (TEAE), and 70.8% had at least 1 TEAE that was considered by the investigator to be related to the investigational product. In subjects participating in double-blind, parallel-group studies, the incidence of any TEAE was greater among SPD489-treated subjects (72.8%) than among placebo-treated subjects (52.3%). The majority of all TEAEs were mild or moderate in severity; 6.6% of SPD489-treated subjects had 1 or more severe TEAEs. In double-blind, parallel-group, placebo-controlled studies, the percentage of SPD489 subjects with at least 1 severe TEAE (3.7%) was slightly higher than for placebo subjects (2.2%).

In Phase 2-4 studies, the most commonly occurring TEAEs were those typically associated with stimulant therapy, including decreased appetite, insomnia, headache, dry mouth, irritability, upper abdominal pain, and weight decrease. In placebo-controlled, parallel-group studies, these events occurred more frequently among SPD489-treated subjects than among placebo-treated subjects, in line with expectations. Commonly occurring TEAEs not typically associated with stimulant therapy, such as upper respiratory tract infection and nasopharyngitis, occurred with similar frequency in the SPD489 and placebo groups. They are not likely to be treatment related.

It is potentially misleading to compare the data for children and adolescents with those in adults because these are cross trial comparisons. Nevertheless there is a suggestion that decreased appetite and weight loss might be less of an issue in adults than in the paediatric populations. Dry mouth and anxiety might be more of an issue in adults although this cannot be established with any degree of certainty.

The results for study 325 are of particular interest as it provides a comparison with a standard treatment of first choice, Concerta XL (OROS methylphenidate). The numbers of individual adverse events (AEs) in this study is too small to draw clear conclusions on causality or relative incidence. The following observations can be made regarding the most common known stimulant related AEs in the SPD489 (n=77) and Concerta XL (n=80) groups:

- Weight decrease seemed to be more common for SPD489 (10 reports) than Concerta XL (4). The same trend was seen for anorexia (8 reports for SPD489 vs. 3 for Concerta XL) and decreased

appetite (19 vs. 14). This is a potentially important difference if verified.

- Insomnia seemed to be more common for SPD489 (12 reports) than Concerta XL (6 reports).

There were 12 reports of nasopharyngitis in the Concerta XL group and 4 in the SPD489 group. As this is not a treatment related AE (in the full placebo controlled population it was numerically more common for placebo) it serves as a salutary reminder not to read too much into differences in AE rates when numbers are small and some large looking differences can be expected to arise by chance.

In like for like comparisons, there was a trend to a higher incidence of AEs at the 70 mg dose than 30 mg or 50 mg. Adverse events (AEs) leading to discontinuations were more common for 50 mg and 70 mg than for 30 mg, although numbers are too small to be sure that this difference is attributable to dose. Overall there was no clear dose-response relationship for stimulant related side effects although there is a suggestion from study 303 that there might be a moderately increased incidence at the 70 mg dose. This would be in line with expectations as stimulant related undesirable central nervous system (CNS) effects are likely to be dose related to some extent. There do not seem to be particular concerns with the 70 mg dose.

Among the 1941 subjects in the Phase 2-4 studies, there was 1 death (a 22-year-old male). It is agreed that this death appears to be unrelated to study medication.

Twenty seven of the 1941 subjects (1.5%) treated with SPD489 in the Phase 2-4 studies reported one or more serious treatment-emergent adverse events (SAEs). In the double-blind parallel-group studies the incidence of serious TEAEs was not higher for the SPD489 group (4 subjects, 0.4%) than for placebo (4 subjects, 0.9%). SAEs that occurred in more than 1 subject included syncope (5 subjects), aggression (2 subjects), and foot fracture (2 subjects). In each of the 3 age groups, the majority of SAEs reflected intercurrent illnesses, accidental injuries, or potential comorbidities of ADHD. The majority of SAEs were considered by the investigator to be unrelated to SPD489 treatment. Six reports of syncope (plus 2 more in adults not reported as SAEs), two of aggression (in adolescents) and one each of sinus arrest and mania (both in children) were identified as potential concerns.

Discontinuation rates were generally reasonable and in line with expectations. Provided there is adequate monitoring of blood pressure, weight and clinical response the events leading to discontinuations should be manageable without major safety problems arising.

Adverse Events of Special Interest

The integrated AE database was systematically searched for AEs of special interest in the areas of psychiatric events (including suicidality), neurological syndromes, cardiovascular events, growth and development, and sexual dysfunction. This covers the less common AEs that are of most interest for stimulant treatment in ADHD patients. More common AEs of particular interest are covered in the general AE section. The potential for abuse and drug diversion is covered separately.

Most of these AEs of interest were in the open label studies, which is to be expected as the duration of treatment is much longer in these studies than in the placebo controlled studies. The numbers of individual AEs in the placebo controlled studies are for the most part too small for clear conclusions on causality to be drawn although the total frequency of 2.8% for SPD489 compared with 0.9% for placebo is suggestive that some of these AEs are treatment related. The sexual dysfunction AEs make up most of the difference between the active and placebo groups.

Myocardial ischemia: There was no indication of treatment related events of myocardial ischemia in the clinical trial programme. Nevertheless amfetamines do have known cardiovascular effects that can be expected to increase the risk of such events in susceptible patients, almost all of whom will be middle aged or older adults. Patients with known ischaemic heart disease were excluded from clinical trials and

the extent of exposure of adults of an age at risk of coronary events is insufficient to quantify the increased risk associated with amfetamine treatment.

Arrhythmias: ECG analyses showed no sign of treatment related QT interval prolongation. Syncope was experienced by a total of 9 (0.5%) SPD489-treated subjects in the completed SPD489 Phase 2-4 studies, including 4 children (0.5%), 3 adolescents (0.9%), and 2 adults (0.3%). There is no indication that these episodes of syncope are treatment related. The narrative summaries do not reveal features suggesting a serious underlying cause such as serious arrhythmias. Total exposure to SPD489 in the safety population was 810 subject-years and the number of reported events of syncope is not likely to represent an excess over the expected event rate. There was no excess incidence for SPD489 over placebo. It is considered that there is no need to include syncope in the SmPC section 4.8. One event of sinus arrest seems to be related to a pre-existing medical condition (presumably sick sinus syndrome) although the possibility that it might have been precipitated by stimulant treatment in a susceptible patient cannot be excluded.

Psychosis: The only serious psychiatric AE in SPD489-treated subjects in the Phase 2-4 clinical trial programme was one event of mania. The temporal relationship (after 6 months of treatment) does not suggest a causal relationship to SPD489 treatment. Nevertheless there are historical reports that administration of stimulants may exacerbate symptoms of behaviour disturbance and thought disorder in patients with pre-existing psychotic disorders and this is stated in the SmPC.

Depression / suicidality: Suicide and related events (SREs) were systematically examined across the full SPD489 development programme using multiple sources of information including spontaneously reported AEs (events coding to suicidal ideation or behaviours), a retrospective analysis of controlled clinical trial data using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) and prospectively obtained information on suicidal ideation and behaviours of clinical trial subjects using the Columbia-Suicide Severity Rating Scale (C-SSRS). In addition one item (Item 6) from the BPRS-C, collected in Study SPD489-325, assessed suicidal ideation and behaviours. In Phase 2-4 studies, there were no serious cases of depressed mood or flat/blunted/restricted affect and no reported suicide attempts. In the controlled clinical trials there were no cases of suicidal behaviour or ideation in SPD489 treated patients but there was one case in a placebo-treated subject (0.2%). Suicidal ideation was reported for two SPD489 treated children and one adolescent in the open label trials (0.2%). The applicant has provided a well-reasoned argument, supported by a thorough review of the SPD489 safety data and literature references, that the available evidence suggests that SPD489 does not increase the incidence of suicide and related events (SREs). The fact that there were no reports of completed suicides, no suicide attempts (either interrupted or aborted), and no suicidal preparatory acts or behaviours in the safety database covering 810 subject years would seem to be reassuring. The three reported brief and self-limited episodes of suicidal ideation without associated behaviours reported in 3 children or adolescents treated with SPD489 in the long-term open-label trials represented the same incidence as in the placebo treated population (0.2%) and does not suggest an association with SPD489 treatment. Nevertheless caution is required in patients showing evidence of suicidal ideation and the SmPC warnings reflect this.

Behavioural undesirable effects: Two subjects (Subjects 032-006 and 041-003, both in Study 306) experienced SAEs of aggression, both rated as moderate in intensity. Such events can occur in adolescents with ADHD and there is no evidence to attribute them to treatment with SPD489.

Tics: Patients with tic disorders were excluded from the clinical trials so there are limited data on the effect of SPD489 and Concerta XL on inducing or exacerbating tics. However the SmPC appropriately reflects clinical experience that dexamfetamine can exacerbate motor and phonic tics and Tourette's syndrome.

Seizures: No subject in a Phase 1-4 study reported a seizure or other epilepsy-related TEAE.

Sexual dysfunction: A total of 24 SPD489-treated subjects (1.2%) had sexual dysfunction TEAEs of special interest, including libido decreased (12 subjects [0.6%]), erectile dysfunction (11 subjects [0.6%]), libido increased (1 subject [0.1%]), and painful erection (1 subject [0.1%]). In the double-blind, parallel-group studies, TEAEs of special interest relating to sexual dysfunction occurred in 1.6% of subjects in the SPD489 group and in no placebo subjects.

Growth and Development: Mean decreases from baseline in weight in SPD489-treated subjects seemed to be small in the short term studies but became much more significant in the long-term studies. The presented mean values for decreases in weight from baseline in the long-term trials are likely to underestimate the situation in patients treated *de novo* with stimulants as many patients would have been taking another stimulant (most commonly methylphenidate) prior to being recruited into the trials. It will be important to investigate whether SPD489 seems to cause more weight loss than methylphenidate. The applicant addressed this by presenting the equivalent analyses for treatment-naïve patients and in patients who were effectively switched to SPD489 in the clinical trial having previously been on a stable regimen of methylphenidate. Weight loss is of more concern in patients starting with a low body mass index (BMI) at baseline. The data on the proportions of patients who shift from a "normal" BMI (5th to <85th centile) to a below normal BMI (below the 5th centile), 2.1% for SPD489 and 0.7% for placebo, are reasonably reassuring that a serious weight loss problem in the trial populations was not common. This is a well-known issue and as advised in the SmPC patients need to be appropriately monitored. If significant appetite suppression persists and growth delay becomes a concern, consideration should be given to alternative treatments. Major problems relating to these effects of treatment should not arise if patients are appropriately managed.

Cardiovascular parameters: The results for blood pressure did not indicate either a substantial mean increase for SBP or DBP and nor was there a clear or consistent excess of potentially clinically important blood pressure changes in SPD489 treated subjects compared with placebo. Given the known effect of amfetamines on cardiovascular parameters this might seem surprising but at least it does not raise new concerns. The effect of SPD489 on pulse rate was clearer. From these data it was not of a magnitude that would represent a major safety problem although it is likely to represent an additional risk factor for serious cardiovascular and cerebrovascular events in susceptible patients, in particular older adults. This is an important risk management issue.

Laboratory findings: There is no signal of an adverse effect of SPD489 treatment on any clinical chemistry or haematology values. There is no evidence of hepatotoxicity.

<u>Long-term Safety</u>

As long-term treatment of ADHD in adults is proposed, it is important to consider the safety implications of long-term treatment. Although evidence suggests that the long-term effects of ADHD stimulant medication on blood pressure, heart rate, and growth are limited, and that occurrences of suicidal, psychotic and manic symptoms are rare (van de Loo-Neus *et al.* 2011), the potential for side effects that may develop after many months of exposure, or side effects that are rare and of significant clinical concern warrants exploration.

Evidence for the long-term safety of SPD489 comes from the three 1 year, open-label studies (1 each in children [study 302], adolescents [306], and adults [304]). As in the short-term studies, the most frequently occurring TEAEs in the long-term, follow-on studies were events typically associated with stimulant treatment, as well as nasopharyngitis and upper respiratory tract infection. In the 3 long-term safety studies, there were no clinically concerning trends in laboratory results. Increases in blood pressure and pulse rate were small and there were no concerning trends in ECG results. Mean weight decreases from baseline appeared to be maximal after about 4-5 months of treatment and declined thereafter.

Long-term effects on cognitive ability and academic outcomes have not been examined in the SPD489 programme. However it is noted that the efficacy of SPD489 was demonstrated across multiple outcome measures (symptomatic, functional, and health-related quality of life) administered by multiple raters (clinician and parent) in the 3 long-term safety studies within the limitations of the open-label study design. Although not a long-term study, an improvement in executive function was associated with SPD489 treatment in the 10-week Study SPD489-403.

Study SPD489-404 (ongoing) was designed to further evaluate the long-term effects of SPD489 in children and adolescents over a 2-year treatment period. This open-label study will collect data on specific endpoints such as sexual development and cognition.

In conclusion there is a reasonable amount of open label long-term safety data and no major safety problems have been identified. There are some well-known potential issues such as cardiovascular risk. Evidence for a positive risk-benefit of SPD489 in the long-term is limited by the lack of a control group in the long term studies and the limited extent of exposure beyond one or two years of treatment. This is of particular potential concern for the proposed adult indication for which dexamfetamine is not licensed.

Abuse potential

A review and analysis of treatment emergent adverse events (TEAEs) indicative of potential cases of abuse in the clinical trial programme was conducted. The first Tier search was related to actual behaviours directly coding to MedDRA terms of abuse and misuse. The second Tier search was used to examine drug effects that are potentially indicative of abuse potential (*i.e.*, have face validity, such as "euphoria") and common to some drugs of abuse. In addition similar searches were run to identify cases originated from clinical trials in the Shire Global Safety System within the Pharmacovigilance Department. Overall rates of TEAEs related to misuse and abuse for completed Phase 2-4 clinical studies in Tier 1 and 2 were low, especially in the controlled trials. In the open label trials "any behaviour related to misuse or abuse" was reported in 11 (0.6%) patients, 8 of which were accidental overdose. Only 2 cases of drug misuse behaviour were reported as TEAEs.

These results will inevitably represent considerable under-reporting of potential cases of abuse of SPD489 in the clinical trial programme and the true extent in the controlled settings of clinical trials is likely to be less than what may occur in a more general clinical setting. Abuse and diversion of dexamfetamine is a well-recognised problem and is one of the reasons methylphenidate is preferred as first line treatment. These data are not considered to provide much information on the abuse potential of SPD489 in comparison with other stimulants. This information must come from the abuse liability studies which are reported in the pharmacodynamics section of this report.

Withdrawal and Rebound

Data from the randomised withdrawal study 401 in adults were evaluated for AEs related to drug withdrawal and rebound effects associated with cessation of SPD489 treatment in the placebo group at the beginning of the randomised withdrawal phase. However, no AEs related to drug withdrawal or rebound were reported.

The SPD489 Phase 2-4 AE database was examined for the occurrence of possible withdrawal and rebound events. Rebound effect was reported for 6 subjects (7 events) in the 2 paediatric, open-label studies (Studies 310 and 302). One event described as a rebound effect in Study 310 (which was severe and considered not related to investigational product) occurred after treatment with SPD489 had been discontinued. Of the remaining 6 events of rebound effect, none were serious, none led to discontinuation, and all were mild or moderate in intensity. It is unclear to what extent the events described as rebound in studies 310 and 302 represent true rebound *i.e.* a return of symptoms worse than baseline upon cessation of treatment. It is hard to see how a true rebound event might be considered not treatment related. At least some of these events seemed possibly to represent a loss of efficacy with

falling plasma levels at the end of the day.

The best way to look for true rebound is to evaluate symptoms at baseline (off treatment), during a short period (*e.g.* 4 weeks) of SPD489 treatment and after treatment cessation. A return to near-baseline symptoms upon treatment cessation might be expected and the occurrence of episodes of true rebound could be explored. The applicant provided these analyses from the appropriate short term studies and no evidence of rebound symptoms was seen.

The randomised withdrawal design, Study SPD489-326 showed no evidence of rebound symptoms in children and adolescents.

Safety related to drug-drug interactions
No AEs relating to drug interactions have been reported.

Post marketing experience
LDX was first approved in the United States (US) on 23 Feb 2007 for Attention Deficit Hyperactivity Disorder (ADHD) and is currently approved and marketed in the US, Canada and Australia for use in children, adolescents and adults with ADHD. In Europe, LDX is indicated for use in children and adolescents with ADHD and in Brazil it is indicated for use in children with ADHD.

PSUR number 12 covers a 6-month period of assessment with DLP 23 Feb 2013 to 22 Aug 2013 and has presented a review of all cases within this period of assessment relating to the identified and potential risks currently monitored through the risk management plan (RMP).

The applicant's conclusion that there is insufficient evidence to support a reasonable causal relationship between syncope and SPD489 is reasonable. However, the comment that syncope is a frequent AE in the ADHD population is not supported within the literature or through clinical trials. Syncope is not listed in the SmPC at the present time although it is mentioned as a special warning as a symptom of cardiovascular disease requiring further investigation. This is sufficient.

There are a significant number of reports of off-label use, primarily reported from Brazil, where it was previously supplied on compassionate grounds. Other reports of off-label use include a number of psychotic disorders including autism spectrum disorders. As ADHD is now considered to overlap that of autism spectrum, it is not unexpected that LDX would be used in this population. However, the uses in cases of weight loss or schizophrenia are of concern. It is unclear as to the geographical region that these cases originated from. The on-going DUS described in the RMP will provide further information on the patterns of off-label use in the EU.

Similarly, whilst there are a number of reports of abuse, misuse and diversion, it is again not clear as to the geographical region where these reports are originating. Given that the majority of exposure is currently within the US, and the collation of data from a US data source, it is reasonable to assume that they mainly originate from the US. Controls of amfetamines in the US differ considerably from the EU. Amfetamines are tightly controlled in the EU from manufacture to dispensing. The application of pharmacovigilance measures and supplementary risk minimisation measures is addressed in the RMP, with details of cases through monitoring of these events in the PSURs. The applicant has agreed to stratify these cases by geographical location in future PSURs in order to determine the efficiency of current risk minimisation actions described in the RMP.

Safety conclusions
In general the safety profile described for SPD489 is in line with expectations based on long clinical experience with dexamfetamine for the licensed indication treatment of children and adolescents with ADHD. No new safety concerns have been identified. There are insufficient data to permit a clear and reliable comparison of the safety and tolerability profiles with either of the active comparators used in two studies, Adderal XR (Extended Release mixed amfetamine salts) and Concerta XL (prolonged

release methylphenidate). Weight decrease and insomnia seemed to be more common for SPD489 than for Concerta XL but this could be a chance finding. In the small exploratory study 201, the only study that included dexamfetamine product as an active comparator, the number of subjects reporting any AE was just 8 for SPD489 and 9 for Adderal XR so meaningful comparisons are impossible and the applicant is not able to claim that SPD489 has a superior safety profile to dexamfetamine.

In comparison to the approved paediatric indication there are important additional safety issue in adults, who could potentially require treatment for many years. Although narcolepsy is an approved indication in adults for dexamfetamine there are big differences between the two pathologies in terms of safety issues and benefit – risk considerations. Identified safety issues additional to those that are well known for the paediatric population include cardiovascular events and stroke (related to sympathetic stimulation) and long term effects on various psychiatric and behavioural aspects. Issues of abuse and diversion are generally more problematic in the treatment of adults than in paediatric use.

Although dexamfetamine is not licensed for the treatment of ADHD in adults it is used off label for this indication and the NICE guideline recommends that dexamfetamine (or atomoxetine) can be tried if methylphenidate (the first-line treatment of choice for adults with ADHD with either moderate or severe levels of impairment) is ineffective.

Provided that efficacy is sufficiently demonstrated in adult ADHD, including clinically important benefits in social and employment functioning, the safety profile could be considered acceptable, subject to appropriate clinical monitoring as set out in the SmPC.

IV.6 Risk Management Plan (RMP)

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Elvanse Adult 30, 50 and 70 mg Capsules, hard.

Summary table of Safety concerns

Table 53: Summary of Ongoing Safety Concerns	
Important identified risks	Tachycardia Cardiomyopathy Increased blood pressure Decreased appetite Growth retardation and developmental delay in children and adolescents Hallucinations (auditory, skin sensation, visual disturbance) Psychosis/Mania Hostility/Aggression Depression Tics Intentional drug misuse, abuse and diversion Serious skin reactions Raynaud's phenomenon
Important potential risks	Ischaemic cardiac events Sudden death Withdrawal syndrome Suicidality Migraine Syncope Carcinogenicity Neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory distress/apnoea) Neonatal effects on growth (via lactation) Off-label use Cerebrovascular disorders (ischaemic and haemorrhagic stroke)
Missing information	Long-term safety (cardiovascular, cerebrovascular, and psychiatric effects) in children and adolescents Long-term safety (cardiovascular and cerebrovascular effects) in adults Safety in pregnant women Safety in the elderly

Summary table of risk minimisation measures

Table 61: Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Tachycardia	Cardiac pre-screening stipulation in Section 4.2 of the SmPC Cardiovascular status warning in Section 4.4 of the SmPC Also addressed in Section 4.8 (Undesirable effect) of the SmPC	Educational tools
Cardiomyopathy	This risk is addressed in Sections 4.2, 4.3, and 4.4 of the SmPC	Educational tools
Increased blood pressure	Cardiac pre-screening stipulation in Section 4.2 of the SmPC Hypertension Contraindication in Section 4.3 of the SmPC Blood pressure monitoring Warning in Section 4.4 of the SmPC Pharmacodynamic Interactions detailed in Section 4.5 of the SmPC Also addressed in Section 4.8 (Undesirable effect) of the SmPC	Educational tools
Decreased appetite	Pre-treatment screening for weight and ongoing monitoring of weight and appetite stipulation in Section 4.2 of the SmPC This risk is addressed in Section 4.8 (Undesirable effect) of the SmPC	Educational tools
Growth retardation and developmental delay in children and adolescents	Pre-treatment growth monitoring stipulation in Section 4.2 of the SmPC Growth warning in Section 4.4 of the SmPC This risk is addressed in Section 4.8 (Undesirable effect) of the SmPC	Educational tools
Hallucinations (auditory, skin sensation, visual disturbance)	Pre-treatment screening for psychiatric disorders stipulation in Section 4.2 of the SmPC Psychiatric adverse events warning in Section 4.4 of the SmPC Also addressed in Section 4.8 (Undesirable effect) of the SmPC	Educational tools
Psychosis/Mania	Pre-treatment screening for psychiatric disorders stipulation in Section 4.2 of the SmPC Psychiatric adverse events warning Section 4.4 of the SmPC Also addressed in Section 4.8 (Undesirable effect)	Educational tools

Table 61: Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	of the SmPC	
Hostility/Aggression	Pre-treatment screening for psychiatric disorders stipulation in Section 4.2 of the SmPC Contraindication in Section 4.3 of the SmPC Psychiatric adverse events warning in Section 4.4 of the SmPC Also addressed in Section 4.8 (Undesirable effect) of the SmPC	Educational tools
Depression	Pre-treatment screening for psychiatric disorders stipulation in Section 4.2 of the proposed SmPC Psychiatric adverse events warning Section 4.4 of the SmPC Also addressed in Section 4.8 (Undesirable effect) of the SmPC	Educational tools
Tics	Tics/Tourette syndrome warning in Section 4.4 of the SmPC Undesirable effect in Section 4.8 of the SmPC	Educational tools
Intentional drug misuse, drug abuse and diversion	Misuse and abuse monitoring stipulation in Section 4.2 of the SmPC Drug abuse and misuse warning in Section 4.4 of the SmPC Diversion monitoring stipulation in Section 4.2 of the SmPC Diversion warning in Section 4.4 of the SmPC	Educational tools
Serious skin reactions	This risk is addressed in Section 4.8 of the SmPC	Educational tools
Raynaud's phenomenon	This risk is addressed in Section 4.8 of the SmPC	None
Ischaemic cardiac events	This risk is addressed in Sections 4.2, 4.3, and 4.4 of the SmPC	Educational tools
Sudden death	Cardiac pre-screening stipulation in Section 4.2 of the SmPC Existing cardiac disease Contraindication in Section 4.3 of the SmPC Sudden death warning in the SmPC, Section 4.4	Educational tools
Withdrawal syndrome	This risk is addressed in Section 4.4 of the SmPC	None
Suicidality	This risk is addressed in Sections 4.2 and 4.4 of the SmPC	Educational tools
Migraine	No risk minimisation activities proposed	None
Syncope	Exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease warning in Section 4.4 of the SmPC.	Educational tools

Table 61: Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Carcinogenicity	Preclinical data summary in Section 5.3 of the SmPC	None
Neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory distress/apnoea)	This risk is addressed in Section 4.6 of the SmPC	None
Neonatal effects on growth (via lactation)	This risk is addressed in Section 4.6 of the SmPC	None
Off-label use	Off-label age groups addressed in Section 4.2 (*Special populations*) of the SmPC	None
Cerebrovascular disorders (ischaemic and haemorrhagic stroke)	This risk is addressed in Sections 4.2, 4.3, and 4.4 of the SmPC	Educational tools
Long-term safety (cardiovascular, cerebrovascular, and psychiatric effects) in children and adolescents	Long-term use is addressed in Section 4.2 of the SmPC	Educational tools
Long-term safety (cardiovascular and cerebrovascular effects) in adults	Long-term use is addressed in Section 4.2 of the SmPC	Educational tools
Safety in pregnant women	Pregnancy is addressed in Section 4.6 of the SmPC	Educational tools
Safety in the elderly	Elderly addressed in Section 4.2 (*Special populations*) of the SmPC	None

IV.7 Discussion on the clinical aspects

The grant of Marketing Authorisations is recommended.

V User consultation

User testing of the package leaflet has been accepted, based on bridging reports provided by the applicant making reference to the user-testing of the package leaflet for Elvanse 30 mg, 50 mg and 70 mg capsules, hard (UK/H/3326/001-03/DC). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

Quality

The important quality characteristics of Elvanse 30 mg, 50 mg and 70 mg capsules, hard are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

There appeared to be no evidence of neuro-toxic changes in any of the studies carried out by the applicant. All of the observed changes are attributed to the pharmacological actions of dexamfetamine. The applicant has provided an acceptable explanation for the absence of carcinogenicity studies with dexamfetamine mesylate. All non-clinical points raised for consideration have been addressed

adequately. There are no objections to the authorisation of these products on non-clinical grounds.

EFFICACY

The dossier for lisdexamfetamine dimesylate has been compiled reasonably well and includes an extensive package of data of pharmacology studies, and efficacy studies A clear short-term effect is seen in both symptoms (on standard validated symptom rating scales) and improvement on clinical global impression scores. This effect is produced quickly after treatment initiation and maintained for the working day. It is also shown that there is maintenance of efficacy with continued long-term treatment In all trials the differences from placebo are highly statistically significant and robust to choices of analysis and handling of missing data. The magnitude of the difference from placebo appeared to be consistently of clear clinical significance for all strengths and for functional measures as well as ADHD symptom scores.

The differences between the US and the EU are in clinical practice rather than in the patients per se. The company's statement that "ADHD is not a diagnosis rooted in cultural characteristics" is agreed. Because of trial standardisation procedures, the known differences between the US and the EU in terms of general clinical practice (diagnosis and treatment) are not likely to translate into important differences between the clinical trial populations studied in the US and those that might have been studied in EU trials.

It is agreed that the US data can be accepted as applicable to adult patients diagnosed with ADHD in the EU according to the DSM-IV-TR and/or DSM 5 diagnostic criteria.

No stimulant had a licensed indication for adult ADHD at the time of conduct of the pivotal trials. In view of the substantial treatment effect seen in the clinical trials on standard validated rating scales and measures of functioning, the clinical relevance of the demonstrated efficacy can be accepted without reference to an active comparator.

SAFETY

In general the safety profile described for SPD489 is in line with expectations based on long clinical experience with dexamfetamine for the licensed indication treatment of children and adolescents with ADHD. No new safety concerns have been identified. In the small exploratory study 201, the only study that included dexamfetamine product as an active comparator, the number of subjects reporting any AE was just 8 for SPD489 and 9 for Adderal XR, so meaningful comparisons are impossible and the applicant is not able to claim that SPD489 has a superior safety profile to dexamfetamine.

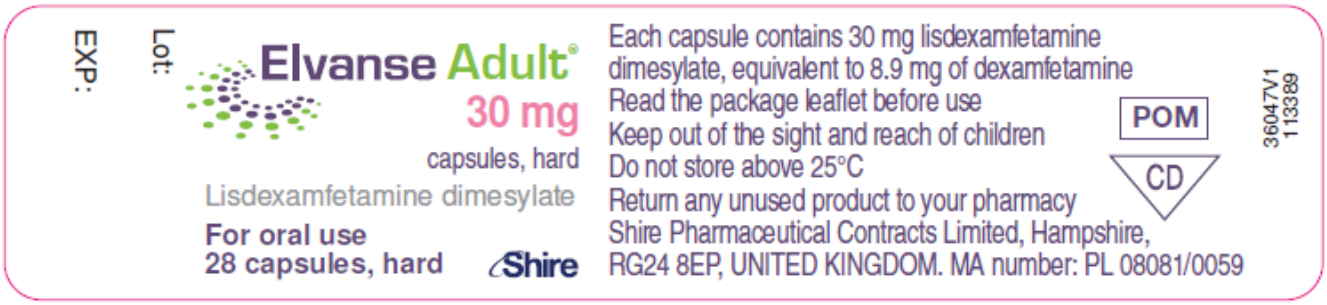
Identified safety issues additional to those that are well known for the paediatric population include cardiovascular events and stroke (related to sympathetic stimulation) and long-term effects on various psychiatric and behavioural aspects.

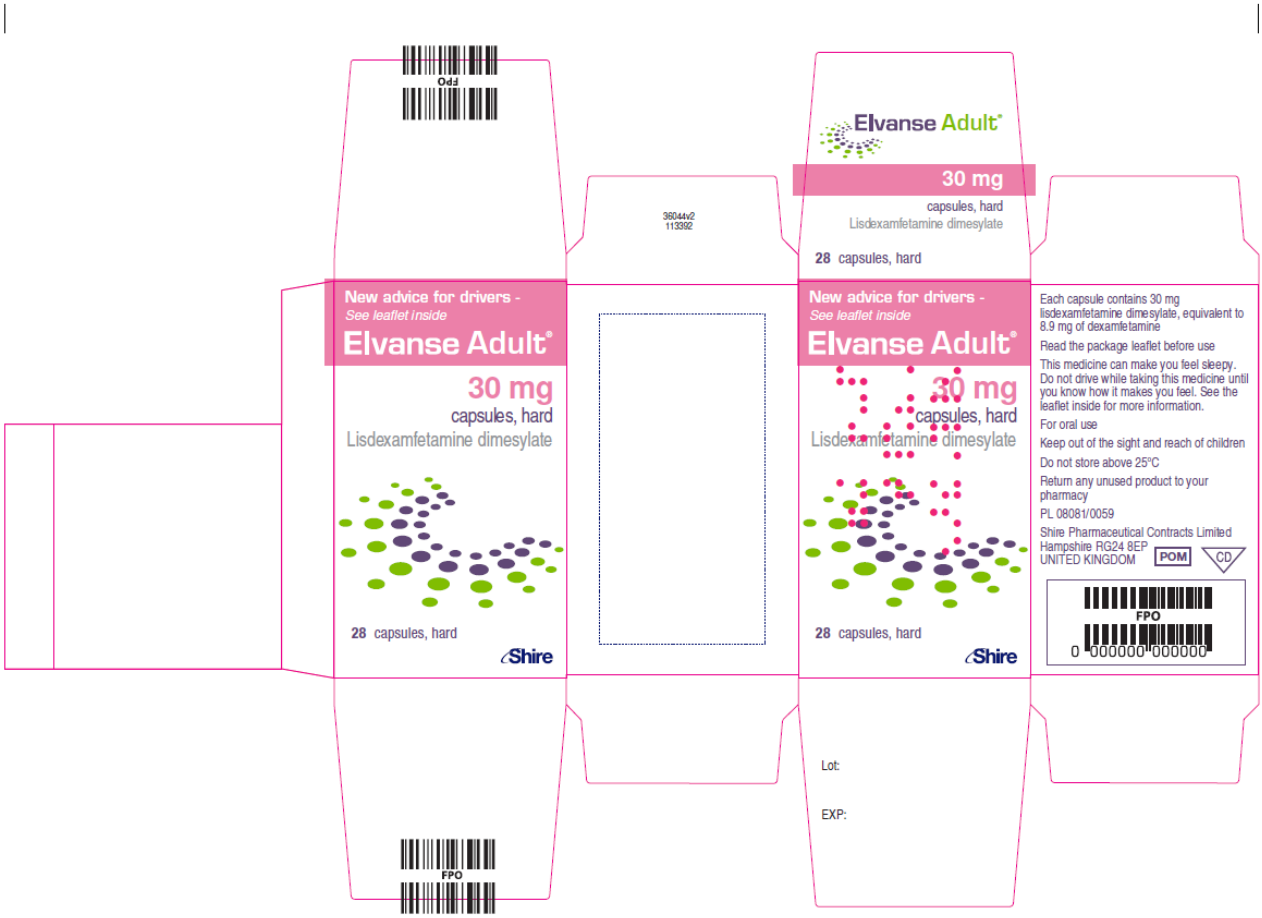
Although dexamfetamine is not licensed for the treatment of ADHD in adults it is used off label for this indication and the NICE guideline recommends that dexamfetamine (or atomoxetine) can be tried if methylphenidate (the first-line treatment of choice for adults with ADHD with either moderate or severe levels of impairment) is ineffective.

Provided that efficacy is sufficiently demonstrated in adult ADHD, including clinically important benefits in social and employment functioning, the safety profile could be considered acceptable, subject to appropriate clinical monitoring as set out in the SmPC.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Labelling





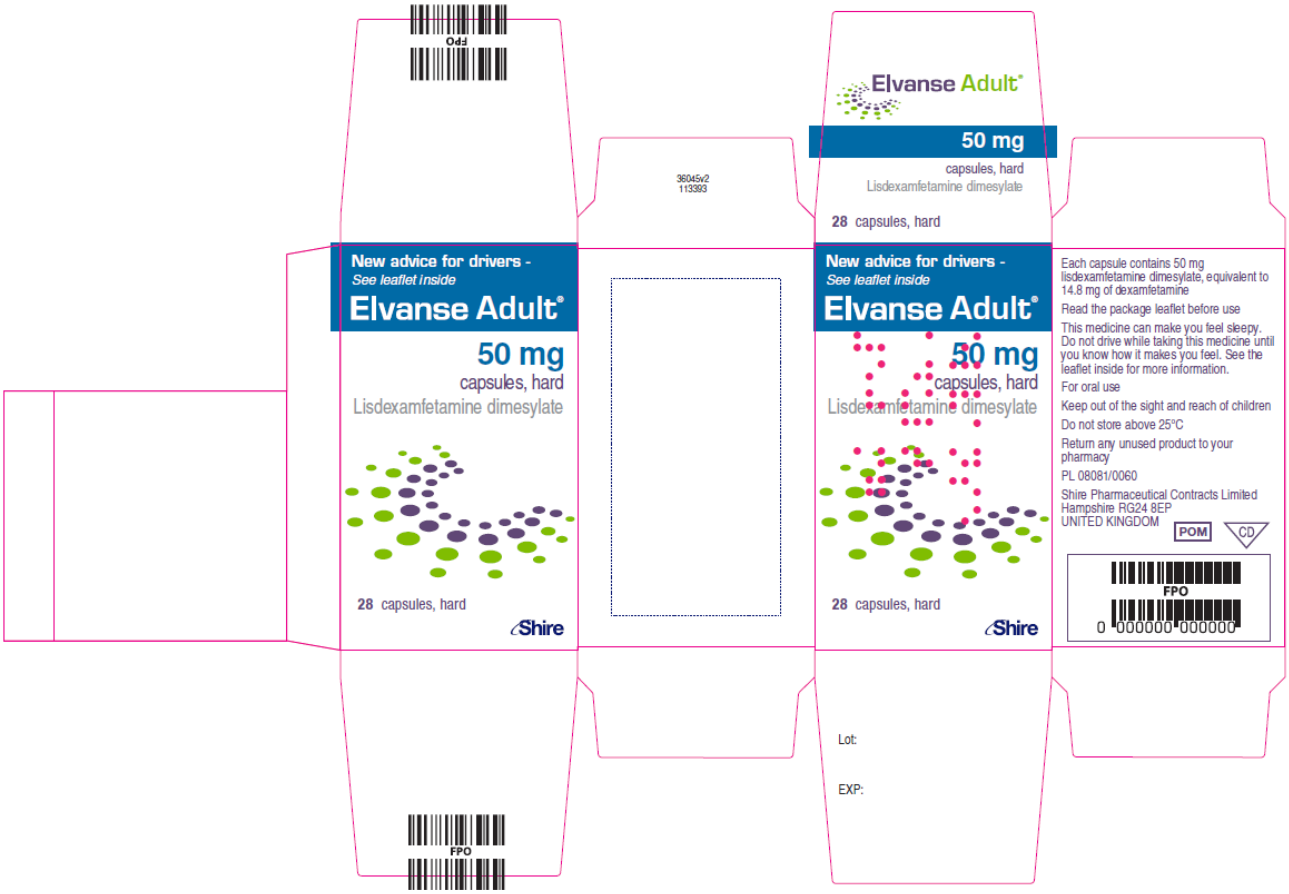
EXP:
Lot:

Elvanse Adult®
50 mg
capsules, hard
Lisdexamfetamine dimesylate
For oral use
28 capsules, hard
Shire

Each capsule contains 50 mg lisdexamfetamine dimesylate, equivalent to 14.8 mg of dexamfetamine
Read the package leaflet before use
Keep out of the sight and reach of children
Do not store above 25°C
Return any unused product to your pharmacy
Shire Pharmaceutical Contracts Limited, Hampshire, RG24 8EP, UNITED KINGDOM. MA number: PL 08081/0060

POM
CD

36048V1
113390



EXP:
Lot:

Elvanse Adult®
70 mg
capsules, hard
Lisdexamfetamine dimesylate
For oral use
28 capsules, hard
Shire

Each capsule contains 70 mg lisdexamfetamine dimesylate, equivalent to 20.8 mg of dexamfetamine
Read the package leaflet before use
Keep out of the sight and reach of children
Do not store above 25°C
Return any unused product to your pharmacy
Shire Pharmaceutical Contracts Limited, Hampshire, RG24 8EP, UNITED KINGDOM. MA number: PL 08081/0061

POM
CD

36050V1
113391


FPO
36048v2
113394
New advice for drivers -
See leaflet inside
Elvanse Adult®
70 mg
capsules, hard
Lisdexamfetamine dimesylate
28 capsules, hard
Shire
FPO
Elvanse Adult®
70 mg
capsules, hard
Lisdexamfetamine dimesylate
28 capsules, hard
New advice for drivers -
See leaflet inside
Elvanse Adult®
70 mg
capsules, hard
Lisdexamfetamine dimesylate
28 capsules, hard
Shire
Each capsule contains 70 mg lisdexamfetamine dimesylate, equivalent to 20.8 mg of dexamfetamine
Read the package leaflet before use
This medicine can make you feel sleepy. Do not drive while taking this medicine until you know how it makes you feel. See the leaflet inside for more information.
For oral use
Keep out of the sight and reach of children
Do not store above 25°C
Return any unused product to your pharmacy
PL 08081/0061
Shire Pharmaceutical Contracts Limited
Hampshire RG24 8EP
UNITED KINGDOM
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Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)