Evidence Review for Prescribing Clinical Network

Treatment: Lisdexamfetamine dimesylate

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Summary page

Lisdexamfetamine dimesylate (Elvanse) received a UK marketing authorisation in February 2013 and was launched in the UK in March 2013. It is licensed for use as part of a comprehensive treatment programme for attention deficit hyperactivity disorder (ADHD) in children aged 6 years and over when response to previous methylphenidate treatment is considered clinically inadequate. Lisdexamfetamine dimesylate is a pharmacologically inactive pro-drug that is converted into the central nervous system stimulant, dexamfetamine.

Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults (NICE clinical guideline 72, published in 2008) recommends that drug treatment for children and young people with ADHD should always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice/interventions. It also recommends that when drug treatment of ADHD is considered appropriate, methylphenidate, atomoxetine and dexamfetamine are suitable options within their licensed indications. The decision regarding which product to use should be based on specific criteria listed in the guideline (such as the presence of comorbid conditions).

This evidence summary is based on the NICE new medicines evidence summary for lisdexamfetamine dimesylate issued in May 2013 and on the Scottish Medicines Consortium (SMC) Advice also issued in May 2013.

The NICE review considers a European, 7-week, randomised controlled trial that compared lisdexamfetamine dimesylate with placebo in children and young people aged 6 to 17 years, who had a diagnosis of moderate ADHD, which found that, compared with placebo, lisdexamfetamine dimesylate treatment resulted in

statistically significantly greater improvements in the symptoms of ADHD as measured using the ADHD rating scale version IV (ADHD-RS-IV, the primary outcome) and the clinician-rated global impression of improvement. The changes compared with placebo (around 50% decrease in score) were also considered to be clinically meaningful (25–30% decrease in score). A modified-release methylphenidate reference arm in the trial showed similar results to the lisdexamfetamine dimesylate treatment arm when both drugs were compared with placebo, but there was no direct comparison between the 2 active treatments. At the time of publication, there are no fully published randomised controlled trials that directly compare lisdexamfetamine dimesylate with other drugs licensed for treating ADHD.

The SMC accepted lisdexamfetamine dimesylate for use in NHS Scotland within its licensed indication. The advice is based on a multi-centre, randomised, double-blind, controlled study in children and adolescents with ADHD, where treatment with lisdexamfetamine was associated with a shorter time to first response compared with a non-stimulant, centrally-acting sympathomimetic agent. A greater proportion of lisdexamfetamine treated patients achieved improvements in symptom scores and functioning than those treated with the active comparator (atomoxetine).

The comparator study is currently awaiting publication. Studies awaiting publication are accepted by both the SMC and in NICE technology appraisals - http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/evidence

Evidence from the European registration RCT suggests that lisdexamfetamine dimesylate produces clinically meaningful benefits in ADHD symptoms compared with placebo. The adverse effect profile appears similar to other stimulant drugs, although theoretical advantages in terms of improved adherence and reduced abuse potential require further evaluation in clinical practice.

Effectiveness	**Safety**
• 1 European, 7-week RCT in around 300 children/young people aged 6-17. Both lisdexamfetamine and methylphenidate provided clinically meaningful and statistically significant benefits compared with placebo in controlling symptoms of ADHD (measured	• Similar to the safety profile of other stimulant agents. Similar monitoring profile to other

using a validated and widely used rating scale - the ADHD RS IV) (published) • 1 multi-centre, randomised, double-blind, controlled study in children and adolescents with ADHD, where treatment with lisdexamfetamine was associated with a shorter time to first response compared with a non-stimulant, centrally-acting sympathomimetic agent. A greater proportion of lisdexamfetamine treated patients achieved improvements in symptom scores and functioning than those treated with the active comparator (atomoxetine).(unpublished)	stimulants
Patient factors • Similar tolerability to methylphenidate (treatment discontinuations ~5% vs 2%) • Monitoring requirements similar to other stimulant medications (cardiovascular height, weight and appetite) • Potential improved adherence and reduced abuse potential require further evaluation in practice • Proposed schedule 2 controlled drug - to be confirmed • Capsule contents can be dissolved in water	**Cost** • Around £750 to £1100 per year at licensed doses (greater than dexamfetamine and methylphenidate, less than atomoxetine)

Key evidence

Coghill D, Banaschewski T, Lecendreux M et al. (2013) European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder. European Neuropsychopharmacology: in press

Clinical trials.gov. Comparison of lisdexamfetamine dimesylate with atomoxetine HCl in attention-deficit/hyperactivity disorder (ADHD) subjects with an inadequate response to methylphenidate. NCT01106430. Last updated 25 January 2013. www.clinicaltrials.gov

Potential advantages in terms of: efficacy, compliance, pharmacokinetics, drug interactions and adverse effects?

- There is an unmet need for a longer acting, second-line, psycho-stimulant within the treatment pathway. The duration of action of lisdexamfetamine is up to 13 hours.
- In a comparative study versus atomoxetine in patients inadequately responding to methylphenidate, lisdexamfetamine demonstrated significantly greater efficacy in terms of shorter time to first response and reduction in symptoms scores.
- Lisdexamfetamine dimesylate is a once a day pro-drug which demonstrates consistent symptom control throughout the day.
- An additional advantage for children who struggle with solid oral dosage forms is that lisdexamfetamine capsules can be opened and the contents dissolved in water and swallowed as a liquid, whereas the marketing authorisation for atomoxetine discourages this.

Is there a clear place in therapy / treatment pathway?
(E.g. patient type / characteristics, and relationship to other therapies)

- Lisdexamfetamine is licensed as a second-line therapy after methylphenidate. It may be used when a patient displays presence of some residual symptoms, has an inadequate duration of response to methylphenidate and/or variability in symptom control.
- Currently, a non-stimulant, atomoxetine, is usually used as a second-line therapy. It is anticipated that in appropriate patients, lisdexamfetamine dimesylate will used instead of atomoxetine in the treatment pathway.
- There is an unmet need for a longer-acting, second-line stimulant medication.

Current pathway:
Methylphenidate IR/ER > (Inadequate response) > Atomoxetine or combination

Proposed pathway:
Methylphenidate IR/ER > (Inadequate response) > Lisdexamfetamine dimesylate > Atomoxetine or combination

Traffic light status

- It is recommended that an amber status is issued and will form part of existing shared care agreements.

Financial implications

- Average yearly acquisition cost is less than atomoxetine (see section 2.4 below for details). It is anticipated that lisdexamfetamine will be used in place of atomoxetine in appropriate patients.

- In CCG's covered by Surrey PCN (approximate population of 1,329,900) – it is anticipated that if used within licensed indication and in place of atomoxetine, a cost saving of £3,332 would be achieved over a 3-year

period. This only assumes a 30% uptake in place of atomoxetine after 3-years and therefore potential savings could be higher in line with increased uptake.

Other issues

- Unlike atomoxetine, which needs to be taken continually as it is not immediately active, lisdexamfetamine can be stopped at weekends and during school holidays. Therefore further cost-savings may be realised.

National Guidance available

- No NICE Single Technology Appraisal will be conducted. NICE ADHD clinical guideline will be updated in 2014.
- Scottish Medicines Consortium (SMC) have accepted lisdexamfetamine dimesylate for use in NHS Scotland within licensed indication.

Recommendations:
Lisdexamfetamine is approved for use within its licensed indication by Surrey Prescribing Clinical Network and is afforded an amber traffic light status, allowing on going prescribing under agreed shared care arrangements.

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
1	May 13	Simon Whitfield	Draft	Comments from SABP CAMHS consultant body and Dr Bozhena Zoritch received and incorporated into document
1.1	June 13	Simon Whitfield	Draft	
2	June 13	Simon Whitfield	Final	Ready for Surrey PCN

1. Purpose of the Review

To enable Surrey Prescribing Clinical Network to make a recommendation on the availability, place in therapy and traffic light status of Lisdexamfetamine within the local health economy.

2. Appropriateness

2.1 The patient:

Lisdexamfetamine dimesylate (Elvanse) received a UK marketing authorisation in February 2013 and was launched in the UK in March 2013. It is licensed for use as part of a comprehensive treatment programme for ADHD in children aged 6 years and over when response to previous methylphenidate treatment is considered clinically inadequate. In young people whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood (see the Elvanse summary of product characteristics).

Treatment must be under the supervision of a specialist in childhood and/or adolescent behavioural disorders. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the child or young person. Diagnosis cannot be made solely on the presence of 1 or more symptoms (see the summary of product characteristics).

The British national formulary (BNF) highlights that dexamfetamine is a controlled drug under Schedule 2 of the Misuse of Drugs Regulations (2001) (and subsequent amendments). Currently, lisdexamfetamine dimesylate is a prescription-only medicine and has not been scheduled as a controlled drug. The Advisory Council on the Misuse of Drugs is reviewing the legal status of lisdexamfetamine dimesylate and will duly advise the Home Office. Interim advice issued by the Royal Pharmaceutical Society is that lisdexamfetamine dimesylate should be treated as a schedule 2 controlled drug (Royal Pharmaceutical Society, 2013). Regard should be given particularly to the requirements around the transportation and holding of stocks, safe custody and supply to patients (Department of Health: personal communication April 2013).

2.2 The problem:

Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults (NICE clinical guideline 72, published in 2008) describes ADHD as a heterogeneous behavioural syndrome characterised by the core symptoms of hyperactivity, impulsivity and inattention. Although these symptoms tend to cluster together, some people are predominantly hyperactive and impulsive, whereas others are principally inattentive. Children with ADHD are also at increased risk of comorbidities; common conditions are oppositional defiant disorder (50% of paediatric cases with ADHD), conduct disorder (35%), anxiety disorder (33%), and depression (33%) (Punja et al. 2012).

Two main diagnostic criteria are in current use for ADHD: the International Classification of Mental and Behavioural Disorders 10th revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV). ICD-10 uses a narrower diagnostic category, which includes people with more severe symptoms and impairment. DSM-IV has a broader, more inclusive definition, which includes a number of different ADHD subtypes (see the NICE clinical guideline on ADHD).

For a person to be diagnosed with ADHD, according to DSM-IV criteria, they should demonstrate at least 6 symptoms of inattention, hyperactivity or impulsivity persisting for at least 6 months to an extent inconsistent with their expected developmental level; some symptoms must have been present before 7 years of age and they should not be explained by another mental health disorder. The resulting impairment should be evident in 2 or more settings, and it should be clinically significant with regard to social, academic or occupational functioning. In addition, symptoms should not occur exclusively during the course of a pervasive developmental disorder, schizophrenia or other psychotic disorder (King et al. 2006).

Severe ADHD corresponds approximately to the ICD-10 diagnosis of hyperkinetic disorder. This is defined as when hyperactivity, impulsivity and inattention are all present in multiple settings, and when impairment is severe, although determining severity is a matter of clinical judgement (see the NICE clinical guideline on ADHD).

Using DSM-IV criteria, ADHD is thought to affect about 3–9% of school-age children and young people in the UK. Based on the narrower criteria of ICD-10, hyperkinetic

disorder is estimated to occur in about 1–2% of children and young people in the UK (see the NICE clinical guideline on ADHD).

In general, ADHD is a persisting disorder. Of the young people with a sustained diagnosis, most will go on to have significant difficulties in adulthood, which may include continuing ADHD, personality disorders, emotional and social difficulties, substance misuse, unemployment and involvement in crime (see the NICE clinical guideline on ADHD).

The NICE clinical guideline on ADHD recommends group-based parent-training/education programmes (and/or psychological treatment for the child or young person) usually as the first-line treatment for parents and carers of children and young people of school age with ADHD and moderate impairment. Drug treatment should be reserved for children and young people with ADHD who have severe symptoms and impairment, or for those with moderate levels of impairment who have refused non-drug interventions, or whose symptoms have not responded sufficiently to parent-training/education programmes or group psychological treatment.

2.3 The Intervention:

Lisdexamfetamine dimesylate is a pharmacologically inactive pro-drug. After oral administration, it is rapidly absorbed from the gastrointestinal tract and hydrolysed primarily by red blood cells to dexamfetamine, which is responsible for the drug's activity (see the Elvanse summary of product characteristics). The mode of therapeutic action of amfetamines is not completely established but they are believed to act as central nervous system stimulants, restoring levels of norepinephrine and dopamine in the brain. In people with attention deficit hyperactivity disorder (ADHD), insufficient production of norepinephrine and dopamine in parts of the brain, including the prefrontal cortex, may lead to symptoms of forgetfulness, distractibility, impulsivity, and inappropriate social behaviours (Punja et al. 2012).

The manufacturer claims that the pro-drug formulation of lisdexamfetamine dimesylate is substantially resistant to commonly available chemical and enzymatic hydrolysis techniques outside the body, making it difficult to tamper with for rapid drug effects (Shire Pharmaceuticals Limited: personal communication October 2013). However, stimulants should be prescribed cautiously to people with a history of

substance abuse or dependence. See also information on safety in the Evidence review section.

Care setting:
Secondary care initiation, primary care continuation.

Frequency:
Lisdexamfetamine dimesylate is available as 30 mg, 50 mg and 70 mg hard capsules.

For all children or young people who are either starting treatment for ADHD or who are switching from another medication, the recommended starting dose of lisdexamfetamine dimesylate is 30 mg taken once daily in the morning. The dose may be increased by 20 mg increments, at approximately weekly intervals, but the lowest effective dose should be used. The maximum recommended dose is 70 mg per day (see the summary of product characteristics).

The summary of product characteristics states that, for long-term use, the usefulness of lisdexamfetamine dimesylate should be evaluated at least yearly, and trial periods off medication should be considered to assess the child or young person's functioning without the treatment.

2.4 Alternative treatments:

The NICE clinical guideline on attention deficit hyperactivity disorder (ADHD) recommends that drug treatment for children and young people with ADHD should always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions. When drug treatment is considered appropriate, methylphenidate, atomoxetine and dexamfetamine are recommended, within their licensed indications, as options for the management of ADHD in children and young people (see Estimated impact for the NHS for more details). The need to continue drug treatment for ADHD should be reviewed at least annually.

Costs of treatment alternatives

	Usual licensed daily dose range [a]	**Annual cost range** [b]
Lisdexamfetamine dimesylate capsules (Elvanse)	30 mg to 70 mg	£759.20 to £1084.05

Atomoxetine capsules (Strattera)	10 mg to 80 mg for weight up to 70 kg[c] 40 mg to 100 mg for weight over 70 kg	£814.21 to £1628.42 £814.21 to £1628.42
Dexamfetamine tablets (generic)[d]	5 mg to 20 mg (According to the BNF, 40 mg daily has been required in some children)	£246.38 to £985.50 (£1971.00)
Methylphenidate tablets (generic)[d]	5 mg to usual maximum of 60 mg	£36.87 to £398.58
Methylphenidate modified release tablets (Concerta XL)	18 mg to 54 mg	£379.48 to £895.71
For the purposes of this evidence summary, licensed doses are quoted. We are aware that for some people higher 'unlicensed' doses are prescribed under the direction of a specialist. [a] Doses taken from the relevant summary of product characteristics; therapeutic equivalence is not implied. [b] Costs taken from the Drug Tariff March 2013. [c] Based on a starting dose of 0.5 mg/kg/day and a usual maintenance dose of approximately 1.2 mg/kg/day. [d] Doses taken from the British national formulary (BNF) April 2013.		

3. Effectiveness

3.1 Clinical effectiveness

Evidence for the use of lisdexamfetamine in the management of ADHD is from 3 pivotal studies.

1. A European, 7-week, phase III trial of lisdexamfetamine dimesylate in children and young people with attention deficit hyperactivity disorder (ADHD; Coghill et al. 2013;

- Design: 7-week, double-blind randomised controlled trial in 48 centres in 10 European countries (Germany, Sweden, Spain, Hungary, France, the UK, Italy, Belgium, Poland and the Netherlands).
- Population: children aged 6–12 years and young people aged 13–17 years who met the DSM-IV-Text Revision (DSM-IV-TR) criteria for a primary

diagnosis of ADHD. Participants had ADHD of at least moderate severity, defined by a baseline ADHD rating scale version IV (ADHD-RS-IV) total score of 28 or higher. Children and young people were excluded if their current ADHD medication provided effective control of symptoms with acceptable tolerability. Exclusion criteria also included those who had a comorbid psychiatric diagnosis with significant symptoms, or a conduct disorder (excluding oppositional defiant disorder).

- Intervention and comparison: once-daily lisdexamfetamine dimesylate (30 mg, 50 mg or 70 mg capsule), once-daily modified-release methylphenidate (18 mg, 36 mg or 54 mg tablet), or placebo. Study drugs were over-encapsulated to appear identical. After a washout period (3–42 days), participants were started at the lowest dose, and titrated upward at weekly intervals during the first 4 weeks of the trial until an acceptable response was achieved (defined as a reduction of at least 30% in ADHD-RS-IV total score from baseline and a Clinical Global Impressions-Improvement [CGI-I] rating of 1 [very much improved] or 2 [much improved] with tolerable adverse effects). The titration period was followed by a 3-week dose maintenance period.
- Outcome: the primary outcome was the change from baseline in the ADHD-RS-IV total score at end point.
- Secondary outcome: the main secondary outcome was the investigator-rated CGI-I rating. Results were categorised as 'improved' (CGI-I score 1 or 2: all participants regarded as 'very much improved' or 'much improved') or 'not improved' (CGI-I scores of 3 to 7). Other outcomes were subscales of the ADHD-RS-IV relating to impulsivity, hyperactivity and inattention.

In Coghill et al. (2013), the improvement from baseline in the ADHD symptom scale was statistically significantly greater in children and young people who received lisdexamfetamine dimesylate or modified-release methylphenidate compared with those who received placebo. The difference in least squares mean change in ADHD-RS-IV total score from baseline was −18.6 (95% confidence interval [CI] −21.5 to −15.7; p<0.001) for lisdexamfetamine dimesylate compared with placebo. This was −13.0 (95% CI −15.9 to −10.2; p<0.001) when modified-release methylphenidate was compared with placebo.

The authors commented that at study end point, the mean ADHD-RS-IV total score in children and young people who were treated with lisdexamfetamine dimesylate decreased by more than 50% compared with baseline. Separate analyses of data from other trials of lisdexamfetamine dimesylate have suggested that a 25% to 30% decrease is clinically meaningful (Goodman et al. 2010). There were also statistically significantly greater improvements for children and young people receiving active treatment (lisdexamfetamine dimesylate or modified-release methylphenidate) in ADHD-RS-IV subscales relating to hyperactivity, impulsivity and inattention compared with placebo treatment.

Statistically significantly more children and young people receiving lisdexamfetamine dimesylate treatment or modified-release methylphenidate treatment were considered to be 'very much improved' or 'much improved' by investigators compared with those receiving placebo treatment. It is important to note that the study was not designed to compare lisdexamfetamine dimesylate with modified-release methylphenidate, only to compare each of these drugs with placebo.

2. A multi-centre, double-blind, randomised, active-controlled phase III study recruited children and adolescents (aged 6 to 17 years) with ADHD of moderate severity, ADHD Rating Scale version IV (ADHD-RS-IV) total score of _28 and who had a historical or current inadequate response to treatment with methylphenidate. (The ADHD-RS-IV assesses the major symptoms of ADHD, grouped into two sub-scales: inattention and hyperactivity/impulsivity with total score ranging from 0 to 54, higher scores indicating more severe symptoms).

Patients were randomised equally to either lisdexamfetamine (30mg to 70mg/day) or atomoxetine (10mg to 100mg/day), with stratification by country. Treatment was administered over nine weeks consisting of a four-week dose optimisation phase (titration schedules as per respective licences) followed by a five-week maintenance phase.

The primary outcome was the time to response, assessed at each weekly visit during the study, defined as attainment of a Clinical Global Impression – Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved) measured on a seven-point scale, ranging from 1 to 7 (very much worse). Patients who did not complete the

study and those who completed the study without response were censored the end of the study.

In the full analysis set (FAS), defined as all randomised patients who had taken at least one dose of randomised treatment, 89% (113/127) of patients in the lisdexamfetamine group compared with 76% (102/135) of patients in the atomoxetine group met the response criterion. The median time to first response was significantly shorter for patients in the lisdexamfetamine group, 12 days (95% confidence interval [CI]: 8 to 16) compared with the atomoxetine group, 21 days (95% CI: 15 to 23), p=0.001.

Secondary outcomes included an alternative assessment of treatment response, defined as a ≥25%, ≥30% or ≥50% reduction in ADHD-RS-IV total score from baseline. Significantly more patients in the lisdexamfetamine group compared with atomoxetine were classed as responders for each threshold at each study visit.

The above study is awaiting publication and reviewed in SMC submission (http://www.scottishmedicines.org.uk/files/advice/lisdexamfetamine_dimesylate__Elvanse__FINAL_April_2013_Amended_26.04.13_for_website.pdf).

3. Randomised controlled trials of lisdexamfetamine dimesylate in children and young people with longer-term follow-up have been published in poster form only (Childress et al. 2011 and Coghill et al. 2012). Two shorter, 4-week randomised controlled trials have also been published that had similar results to the 7-week trial (Findling et al. 2011 and Biederman et al. 2007).

From the SMC submission for lisdexamfetamine, the base case analysis produced a cost per quality adjusted life year (QALY) of £6,969. This was a cost-utility analysis comparing lisdexamfetamine to atomoxetine for the treatment of ADHD in children aged 6 years of age and older when response to previous methylphenidate treatment is considered clinically inadequate.

3.2 Safety

Rates of adverse events leading to discontinuation of the study drug were around 5%. Treatment-emergent adverse events leading to discontinuation of lisdexamfetamine dimesylate were vomiting, anorexia, decreased appetite, angina pectoris, tachycardia, decreased weight and insomnia. The case of angina pectoris occurred in a 13-year-old boy who experienced pre-cardiac pain, which was considered by the study investigator to be of moderate intensity and did not meet the criteria for a serious treatment-emergent adverse event. During the study, the boy had no clinically significant laboratory abnormalities, no treatment or concomitant medications were reported, and all electrocardiograms were normal.

There were no serious adverse events considered to be related to lisdexamfetamine dimesylate treatment, and no deaths were reported during the trial.

Both lisdexamfetamine dimesylate and modified-release methylphenidate were associated with modest increases in mean pulse rate, heart rate, systolic blood pressure and diastolic blood pressure, and decreases in mean body weight from baseline to end point. The Elvanse summary of product characteristics recommends that all people being considered for stimulant medications, such as lisdexamfetamine dimesylate, have their cardiovascular status assessed beforehand. In addition, people taking stimulant medications should be monitored for large changes in heart rate and blood pressure during treatment. Other monitoring recommended during treatment with lisdexamfetamine dimesylate includes recording height, weight and appetite at least 6 monthly, as well as monitoring for the appearance of, or worsening of, aggressive behaviour or hostility in people beginning treatment.

Results of abuse-potential studies carried out in people with a history of drug abuse are described in the Elvanse summary of product characteristics. Lisdexamfetamine dimesylate 100 mg produced positive subjective responses on a scale of 'Drug Liking Effects' (primary end point) that were significantly less than immediate-release dexamfetamine 40 mg. However, oral administration of 150 mg of lisdexamfetamine dimesylate produced increases in positive subjective responses on this scale that were comparable to the positive subjective responses produced by 40 mg of oral immediate-release dexamfetamine and 200 mg of diethylpropion. The summary of product characteristics recommends that stimulants (such as lisdexamfetamine

dimesylate) should be prescribed cautiously to people with a history of substance abuse or dependence.

3.3 Review of evidence

Evidence strengths and limitations

One of the strengths of the trial (Coghill et al. 2013) is that it was carried out in Europe. Also, blinding of treatment was achieved by enclosing all medications in identical capsules. The trial design (double-blind, randomised, placebo-controlled) and analysis of results was appropriate to demonstrate the short-term (7-week) effectiveness of lisdexamfetamine dimesylate compared with placebo. Longer-term randomised control trial data are available but have yet to be published in full (Childress et al. 2011 and Coghill et al. 2012). The results of a 26-week trial that showed maintenance of the treatment effect are referred to in the summary of product characteristics. Given that ADHD is a long-term condition, these data are necessary to form an opinion on the effectiveness of the treatment in usual practice.

There was no direct comparison of the efficacy of lisdexamfetamine dimesylate with modified-release methylphenidate. A comparison of the 2 active treatments would be useful in establishing the place of lisdexamfetamine dimesylate in therapy. At the time of publication, there are no fully published randomised controlled trials that directly compare lisdexamfetamine dimesylate with other drugs licensed for treating ADHD.

Coghill et al. (2013) also noted that a limitation of the trial was that children and young people with comorbid conditions, such as post-traumatic stress disorder, bipolar affective disorder or severe anxiety disorder, were excluded from the trial. Given that comorbid conditions are relatively common in people with ADHD (Punja et al. 2012), this could affect the generalisability of the results.

A limitation of using the ADHD-RS-IV score change from baseline for the primary end point is that it is a subjective measure of ADHD symptoms completed by the investigator. However, the ADHD-RS-IV is a validated rating scale that is used widely as a measure of efficacy in clinical trials of treatments for ADHD in both children and young people (Goodman et al. 2010).

4. Summary of Key Points for Consideration

4.1 National guidance:

The Scottish Medicines Consortium conducted a full review and have accepted lisdexamfetamine dimesylate for use in NHS Scotland within its licensed indication. This advice is based on a multi-centre, randomised, double-blind, controlled study in children and adolescents with ADHD, where treatment with lisdexamfetamine was associated with a shorter time to first response compared with a non-stimulant, centrally-acting sympathomimetic agent. A greater proportion of lisdexamfetamine treated patients achieved improvements in symptom scores and functioning than those treated with the active comparator (atomoxetine).

The NICE clinical guideline on attention deficit hyperactivity disorder (ADHD) recommends that drug treatment for children and young people with ADHD should always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions.

In addition, the NICE clinical guideline on ADHD recommends group-based parent-training/education programmes (and/or psychological treatment for the child or young person) usually as the first-line treatment for parents and carers of children and young people of school age with ADHD and moderate impairment. Drug treatment should be reserved for children and young people with ADHD who have severe symptoms and impairment, or for those with moderate levels of impairment who have refused non-drug interventions, or whose symptoms have not responded sufficiently to parent-training/education programmes or group psychological treatment.

The NICE clinical guideline on ADHD advises that when drug treatment of ADHD is considered appropriate, methylphenidate, atomoxetine and dexamfetamine are recommended, within their licensed indications, as options for children and young people. The decision regarding which product to use should be based on the following:

- the presence of comorbid conditions (for example, tic disorders, Tourette's syndrome, epilepsy)
- the different adverse effects of the drugs

- specific issues regarding compliance identified for the individual child or adolescent, for example problems created by the need to administer a mid-day treatment dose at school
- the potential for drug diversion (where the medication is forwarded on to others for non-prescription uses) and/or misuse
- the preferences of the child/adolescent and/or his or her parent or guardian.

When a decision has been made to treat children or young people with ADHD with drugs, healthcare professionals should consider:

- methylphenidate for ADHD without significant comorbidity
- methylphenidate for ADHD with comorbid conduct disorder
- methylphenidate or atomoxetine when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present
- atomoxetine if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses of methylphenidate.

The NICE clinical guideline on ADHD recommends that dexamfetamine should be considered in children and young people whose ADHD is unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine.

Fully published, long-term randomised controlled trials comparing lisdexamfetamine dimesylate with other drugs in children and young people with ADHD are necessary to confirm its place in therapy.

Prescription Cost Analysis in England show that over the last year (February 2012 to January 2013) in general practice, there were about 664,000 prescription items for methylphenidate (all preparations) costing over £24 million), there were nearly 37,000 prescription items for dexamfetamine costing nearly £3 million (note dexamfetamine is also licensed for narcolepsy) and there were about 83,000 prescription items for atomoxetine (costing over £6 million) (Personal communication. NHS Business Services Authority April 2013).

4.2 Estimated usage

According to the manufacturer, there are about 116 children and young people aged 6–17 years being treated for ADHD per 100,000 of the UK population. The

manufacturer's cumulative estimated uptake of lisdexamfetamine dimesylate is 3 patients per 100,000 in the first year, 7 patients per 100,000 in the second year and 13 patients per 100,000 in the third year (Shire Pharmaceuticals Limited: personal communication January 2013).

4.3 Potential Benefits over existing therapy

- Lisdexamfetamine dimesylate fulfils a clinical need for a longer-acting, second-line stimulant.
- In a second-line setting, lisdexamfetamine dimesylate demonstrates significantly greater efficacy compared to active comparator, atomoxetine.
- Lisdexamfetamine is a once-daily medication.
- An additional advantage for children who struggle with solid oral dosage forms is that lisdexamfetamine capsules can be opened and the contents dissolved in water and swallowed as a liquid, whereas the marketing authorisation for atomoxetine discourages this.

4.4 Budgetary Impact

For the budget impact calculations it is assumed there are an estimated 182,994 children aged 6 to 17 years old in Surrey PCN of whom 1,537 are currently on pharmacological treatment for ADHD.

As lisdexamfetamine dimesylate is indicated as a second-line option, it is anticipated that patients will be treated with it instead of atomoxetine. This is reflected in budget impact. Over a 3-year period it is estimated that ~32% of patients will be started with lisdexamfetamine dimesylate instead of atomoxetine.

Market shares in years 1, 2 and 3 are those estimated by manufacturer.

Prescribing:

Table 1 details the estimated current market shares of ADHD medicines and the effect on market shares of a change in prescribing to lisdexamfetamine dimesylate (Elvanse®) over a 3 year period.

Table 1: Market shares

Medicine	Current market share	Year 1 market share with Elvanse®	Year 2 market share with Elvanse®	Year 3 market share with Elvanse®	Percentage of starting patients changing to Elvanse®
Elvanse®	0.00%	1.34%	2.43%	3.89%	-
Strattera®*	12.20%	10.86%	9.77%	8.31%	31.91%

Concerta® XL	40.50%	40.50%	40.50%	40.50%	0.00%
Equasym® XL	15.80%	15.80%	15.80%	15.80%	0.00%
Medikinet® XL	6.60%	6.60%	6.60%	6.60%	0.00%
Methylphenidate (generic) IR	17.20%	17.20%	17.20%	17.20%	0.00%
Medikinet® IR	0.70%	0.70%	0.70%	0.70%	0.00%
Ritalin® IR	2.10%	2.10%	2.10%	2.10%	0.00%
Dexamfetamine*	4.90%	4.90%	4.90%	4.90%	0.00%

*Patients where response to previous methylphenidate treatment is clinically inadequate
Patients who change to Elvanse® are assumed to change to Elvanse® treatment before starting on Strattera® or Concerta® XL.

The prescribing of Elvanse® would generate the annual budget impacts in years 1, 2 and 3 demonstrated in Table 2

Table 2: Annual budget impact

	Year 1	Year 2	Year 3
Annual budget impact	-£584	-£1,056	-£1,693

In the population of CCG's covered by Surrey PCN there are an estimated 1,537 children currently being treated with medication for ADHD. Moving 3.89% of these patients where response to methylphenidate has been clinically inadequate over to Elvanse®, phased in over a 3 year period, would result in a decrease in the prescribing cost of -£3,332.23. This gives the total cumulative budget impact of -£3,332.23 over the 3 years

4.5. Cost:
Annual cost range: £759.20 to £1084.05 (30mg, 50mg, 70mg doses).

4.6 Precedent setting:

Lisdexamfetamine dimesylate was launched in the UK in March 2013 and to date has been approved by the Sussex Partnership NHS Foundation Trust and subsequently Coastal West Sussex Area Prescribing Committee.

The medicine has also been accepted by Norfolk and Suffolk Area Prescribing Committees.

In addition, South London & Maudsley, Oxford Partnership NHS Foundation Trust and Avon and Wiltshire Partnership Trust have also approved lisdexamfetamine with subsequent Area Prescribing Committee decisions pending.

5. Conclusions and Recommendations

There is sufficient evidence to support the recommendation that Lisdexamfetamine is approved for use within its licensed indication by Surrey Prescribing Clinical Network and is afforded an amber traffic light status, allowing on going prescribing under agreed shared care arrangements.

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