

**lisdexamfetamine dimesylate, 30mg, 50mg and 70mg hard capsules
(Elvanse Adult[®])** SMC No. (1079/15)

Shire Pharmaceuticals Ltd.

10 July 2015 (*Issued 7 August 2015*)

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

lisdexamfetamine dimesylate (Elvanse Adult[®]) is accepted for use within NHS Scotland.

Indication under review: as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in adults. Based on clinical judgment, patients should have ADHD of at least moderate severity.

Three phase III and two phase IV clinical studies in adults with ADHD demonstrated that lisdexamfetamine improves the symptoms of ADHD compared with placebo.

Overleaf is the detailed advice on this product.

**Vice Chairman,
Scottish Medicines Consortium**

Indication

As part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in adults. Based on clinical judgment, patients should have ADHD of at least moderate severity.

A comprehensive treatment programme typically includes psychological, educational, behavioural, occupational and social measures as well as pharmacotherapy.

Treatment must be under the supervision of a specialist in behavioural disorders. Refer to the summary of product characteristics (SPC) for further information.

Dosing Information

The starting dose is one 30mg capsule, taken orally, once daily in the morning. The dose may be increased by 20mg increments, at approximately weekly intervals, to a maximum of 70mg daily. Treatment should be administered at the lowest effective dose, and should be individualised according to the therapeutic needs and response of the patient. Careful dose titration is necessary at the start of treatment.

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

Product availability date

28 July 2015.

Summary of evidence on comparative efficacy

Attention deficit/hyperactivity disorder (ADHD) is a persistent behavioural syndrome presenting with symptoms of hyperactivity, impulsivity and inattention.¹ Lisdexamfetamine is an inactive prodrug that is rapidly absorbed after oral administration and hydrolysed to the active moiety dexamfetamine. It is thought to exert its effect by blocking the reuptake of norepinephrine and dopamine into the presynaptic neuron and by increasing their release into the extraneuronal space.²

SMC has previously accepted lisdexamfetamine for use within NHS Scotland as part of a comprehensive treatment programme for ADHD in children aged six years of age and over when response to previous methylphenidate treatment is considered clinically inadequate. The marketing authorisation for lisdexamfetamine has now been extended to include treatment initiation in adults diagnosed with ADHD. Atomoxetine (Strattera®) is currently the only licensed treatment in Scotland for ADHD in adults when pre-existing symptoms in childhood can be confirmed,³ and has been accepted by SMC for use within NHS Scotland for this indication.

Clinical evidence to support the use of lisdexamfetamine in the treatment of ADHD in adults derives from four multicentre, double-blind, randomised, placebo-controlled studies and one open-label, single-arm study.

Study NRP104.303 was a short-term, phase III, forced-dose escalation study to evaluate the safety and efficacy of lisdexamfetamine in adults with ADHD. A follow-up study (NRP104.304) of open-label, single-arm design, evaluated long-term safety and effectiveness. The studies recruited adults aged 18 to 55 years with a primary diagnosis of moderate to severe

symptomatic ADHD (with a clinician-rated baseline post-washout ADHD rating scale [ADHD-RS] score of ≥ 28), based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision[®] (DSM-IV-TR[®]) criteria. Patients underwent a 7- to 28-day washout period of any prior stimulant, and were then randomised in a 2:2:2:1 ratio to four weeks treatment with lisdexamfetamine 30mg once daily (n=119), 50mg once daily (n=117), 70mg once daily (n=122), or placebo (n=62). In the follow-up study all patients (n=349) were allocated to lisdexamfetamine 30mg once daily which was increased according to response over four weeks, and then continued for up to 11 months in the long-term maintenance phase.^{4,5}

The primary outcome for both studies was the clinician-determined change in ADHD-RS total score from baseline to endpoint (the last post-randomisation treatment week for which a valid score was obtained) using adult DSM-IV-TR[®] prompts. In the short-term study there was a significantly greater decrease (improvement) from baseline to endpoint in the ADHD-RS total score for each of the lisdexamfetamine treatment groups compared with placebo in the intention-to-treat population ($p < 0.0001$). Least square (LS) mean (\pm standard error) adjusted changes in scores in the placebo, lisdexamfetamine 30mg, 50mg and 70mg groups, respectively, were -8.2 (± 1.43), -16.2 (± 1.06), -17.4 (± 1.05), and -18.6 (± 1.03). Analysis of secondary outcomes demonstrated statistically significant improvements for lisdexamfetamine versus placebo for dose response, clinical global impressions (CGI) scores, and a post-hoc analysis of the percentage of patients with a $\geq 30\%$ reduction in ADHD-RS total scores.⁴ The longer-term study also demonstrated a significant decrease in ADHD-RS total score from baseline to endpoint with a mean (standard deviation [SD]) change of -24.8 (11.7) ($p < 0.0001$). In those patients who previously received lisdexamfetamine in the short-term study (n=296), there was a mean (SD) improvement in ADHD-RS total score of 62% (25.1), and of 55% (32.0) in those previously treated with placebo.⁵

A phase IIIb, two-way crossover study (SPD489-316) evaluated the duration of the efficacy, tolerability and safety of lisdexamfetamine throughout the day in adults with ADHD using the simulated adult workplace environment (AWE). The study recruited adults aged 18 to 55 years with a primary diagnosis of ADHD (with a clinician-rated baseline ADHD-RS-IV score of ≥ 28), and an equivalent intelligence quotient of ≥ 80 on the Kaufman Brief Intelligence Test. Patients entered a four-week, open-label, dose-optimisation phase and were initiated on treatment with lisdexamfetamine 30mg once daily (n=142), to be titrated to the optimum tolerable dose (i.e. 30mg, 50mg or 70mg once daily). Patients then entered a two-week double-blind crossover phase and were randomised to seven days treatment with their optimised dose of lisdexamfetamine (n=127), followed by seven days treatment with placebo, or vice versa.⁶

The primary outcome evaluated the efficacy of lisdexamfetamine versus placebo at improving the total permanent product measure of performance (PERMP) scores in the simulated AWE, with higher scores indicating better performance.⁷ The total PERMP score was averaged over all post-dose time points assessed in the simulated AWE sessions during weeks five and six of the double-blind crossover phase. Lisdexamfetamine was associated with a significantly higher average post-dose total PERMP score (LS mean [SD] 312.7 [94.42]) versus placebo (287.6 [81.45]); LS mean difference 23.4 (95% confidence interval [CI]: 15.6 to 31.2), $p < 0.0001$. The key secondary outcome assessed the duration of effect of lisdexamfetamine versus placebo in the simulated AWE with the PERMP administered at -0.5 hours pre-dose, and then two, four, eight, ten, twelve, and fourteen hours post-dose. Lisdexamfetamine demonstrated a significantly greater efficacy compared with placebo at each time point for absolute values ($p \leq 0.0017$) and in change from pre-dose ($p < 0.001$) of the total PERMP scores. Improvements in quality of life (QoL) were assessed in a secondary analysis of the open-label phase of the study using the ADHD Impact Module for Adults (AIM-A). In the questions relating to treatment impact on

overall QoL and improvement in daily symptoms there was a statistically significant subjective improvement from baseline to the end of the open-label phase (week four) ($p < 0.0001$).⁸

A phase IV withdrawal study (SPD489-401) was conducted to evaluate the safety and maintenance of efficacy of lisdexamfetamine in adults with ADHD who were stable on treatment for at least six months. Patients were enrolled to a three-week open-label treatment phase to receive either 30mg, 50mg, or 70mg daily of lisdexamfetamine dimesylate ($n=123$). Patients would then continue with their assigned dose of lisdexamfetamine ($n=56$) or switch to placebo ($n=60$) in a six-week double-blind randomised withdrawal phase.^{9,10}

The primary outcome was the proportion of treatment failures at endpoint (up to six weeks) in the double-blind randomised withdrawal phase. Treatment failure was defined as $\geq 50\%$ increase (worsening) in the ADHD-RS with adult prompts total score and a two point or greater increase (worsening) in CGI-Severity (CGI-S) score. A significantly lower percentage of treatment failures occurred at endpoint in the lisdexamfetamine group (8.9% [5/56]) compared with the placebo group (75% [45/60]) ($p < 0.0001$).⁹

An additional phase IV study (SPD489-403) evaluated the safety and efficacy of lisdexamfetamine on executive function (EF) behaviours in adults with ADHD via self- and informant-reporting. Patients were randomised to ten weeks treatment with placebo ($n=80$) or lisdexamfetamine ($n=79$) titrated over four weeks to the optimum dose (30mg, 50mg or 70mg daily).^{12,13,14}

The primary outcome was the change from baseline to endpoint (up to ten weeks) in the behaviour rating inventory of executive function adult version (BRIEF-A) global executive composite (GEC) test score (T-score) of participant self-rated measures of EF. A statistically significant reduction (improvement) was achieved in the patient-reported BRIEF-A GEC T-score in the lisdexamfetamine group compared with the placebo group from baseline to endpoint (LS mean -11.2; 95% CI: -15.9 to -6.4; $p < 0.0001$). Secondary outcome analysis of the informant-reported score also demonstrated a statistically significant reduction in the lisdexamfetamine group compared with placebo (-4.9; 95% CI: -7.8 to -1.9; $p = 0.0016$). The key secondary outcome was patient perception of QoL using the AIM-A scale which demonstrated a statistically significant improvement for lisdexamfetamine compared with placebo in performance and daily functioning, daily interference of symptoms, bother/concern of symptoms, and relationships/communication.^{12,13,14}

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

The safety profile for lisdexamfetamine is consistent with the known side effect profile for dexamfetamine, and no new safety concerns were identified in the UK public assessment report (UKPAR).¹⁵ No comparative safety data are available from the clinical studies. Refer to the summary of product characteristics for details.

Adverse events reported were similar across all studies. In study NRP104.303, adverse events were reported by 58% (36/62), 76% (90/119), 77% (90/117), and 84% (102/122) of patients, in the placebo, lisdexamfetamine 30mg, 50mg, and 70mg groups, respectively. Severe treatment-emergent adverse events (TEAEs) were reported in 3.2% (2/62) of patients in the placebo group

and in 4.2% (15/358) of patients in the lisdexamfetamine treatment groups (all doses). Treatment discontinuation, as a result of adverse events, was reported in 1.6% (1/62) and 5.9% (21/358) of patients in the placebo and lisdexamfetamine treatment groups respectively.⁴

In the longer-term study (NRP104.304) when all patients received lisdexamfetamine, 88% (306/349) of patients experienced an adverse event. Severe TEAEs were reported in 12% (42/348) of patients. Treatment discontinuation, as a result of adverse events, was reported in 8.0% (28/348) of patients.

Summary of clinical effectiveness issues

Pharmacological treatment is indicated in adults with ADHD presenting with moderate to severe levels of impairment, and should form part of a comprehensive treatment programme to address psychological, behavioural and educational or occupational needs. Methylphenidate is recommended as the first-line treatment according to current UK guidelines, although it is unlicensed for treatment initiation in adults with ADHD. Atomoxetine or dexamfetamine (unlicensed use) are second-line treatment options in patients who are unresponsive or intolerant to an adequate trial (of approximately six weeks) of methylphenidate. Atomoxetine may be considered as first-line treatment when there is concern over the potential for drug misuse or diversion.¹ Lisdexamfetamine is a licensed long acting alternative to the other treatment options available e.g. dexamfetamine and methylphenidate.

The phase III and IV studies demonstrated the efficacy of lisdexamfetamine over the short and long term, and throughout the working day. The UKPAR noted that the magnitude of difference in ADHD symptom scores and functional measures were consistently demonstrated across all strengths of lisdexamfetamine compared with placebo, and were clinically significant.¹⁵ The scoring systems used in the studies were valid measures of study outcomes in line with the European Medicines Agency (EMA) guidance.¹⁶ The studies presented were however placebo-controlled and no comparative study data were provided for lisdexamfetamine versus an active comparator. EMA guidance indicates that short-term studies should have three arms, including placebo and active comparator arms.¹⁶ The UKPAR considered that the efficacy of lisdexamfetamine could be accepted without reference to an active comparator as a result of the substantial treatment effect demonstrated in the clinical studies¹⁵

The baseline mean ADHD-RS scores of the populations in studies NRP104.303 and SPD489.316 were generally high, representing a moderately to severely ill ADHD population. Patients with a co-morbid psychiatric diagnosis (with significant symptoms) and those receiving concomitant medications affecting the central nervous system or blood pressure were excluded from some studies and this may affect the generalisability of the results. A forced dose titration protocol was used in some studies, which may not reflect the use of lisdexamfetamine in clinical practice, and bias may have been introduced as a result of the open-label design and the lack of a control arm in some of the studies.

The majority of studies were conducted over a short duration, ranging from four to ten weeks. The UKPAR noted that the randomised treatment periods should be of at least six weeks duration in the short-term trials, which was only met in the phase IV studies; it was however concluded that the four-week treatment duration of the short-term dose-finding study (NRP104.303) was acceptable. The UKPAR also noted that although the studies were

conducted in a US population, the data can be accepted as being relevant to adults diagnosed with ADHD in Europe.¹⁵

The summary of product characteristics for lisdexamfetamine advises that blood pressure and pulse rate are recorded at each dose adjustment and at least every six months, which is also a requirement for methylphenidate and atomoxetine.^{2,3,17} Current UK Guidelines recommend routine monitoring of heart rate and blood pressure every three months.¹ The development of any new or worsening psychiatric disorders should be monitored at each dose adjustment and at least every six months and patients should be monitored for the risk of diversion, misuse, and abuse (which is also a requirement for methylphenidate).^{1,17} Lisdexamfetamine, dexamfetamine and methylphenidate are schedule II controlled drugs under the Misuse of Drugs Regulations 2001.¹⁸

Bayesian network meta-analyses (NMAs) were presented in the submission to compare lisdexamfetamine, atomoxetine and methylphenidate in adults with ADHD. A total of 21 studies were included, and five efficacy and safety outcomes were assessed: change from baseline in the clinician-rated ADHD-RS-IV scale and the combined ADHD-RS-IV and ADHD Investigator Symptom Rating Scale (AISRS), change from baseline in CGI-Improvement (CGI-I), and safety analyses of study discontinuation due to any cause or adverse effects. The CGI-I score was not reported in the available atomoxetine studies presented in the NMA and so the outcome was derived through regression with CGI-I change estimation mapped to corresponding changes in ADHD-RS-IV scores. The results of the NMA demonstrated a greater efficacy for lisdexamfetamine (superior to atomoxetine and long-acting methylphenidate), in the outcome assessing the change from baseline in the combined ADHD-RS-IV and AISRS scales. It is not clear if combining these two different rating scales is appropriate in clinical practice. For all other outcomes, overlap occurred in the 95% credible intervals, though lisdexamfetamine was shown to have the highest probability of being the most effective treatment with a lower risk of all cause discontinuation. Sensitivity analyses produced results similar to the core NMA. Heterogeneity was observed throughout the NMA in a number of areas including study population, interventions, study duration and primary outcomes but it was considered to be low across the outcomes. The length of follow-up in the included studies was generally too short to draw conclusions on the long-term treatment of adult ADHD.

Summary of comparative health economic evidence

The company submitted a cost utility analysis comparing lisdexamfetamine to methylphenidate and atomoxetine for the treatment of ADHD in adults. A decision tree was used in the analysis where patients received treatment upon entering the model and after an initial titration phase (which was assumed to occur within the first 28 days of treatment and allowed for patient discontinuation) patients could either respond or not respond. Responders and non responders were then attributed costs and utilities associated with being in the respective 'responder' and 'non responder' health states. The time horizon used in the analysis was one year.

The clinical data used to support the economic analysis were taken from a NMA. The analysis, which consisted of 21 studies, was connected via placebo (a common comparator) and a range of assessment scales were used to measure treatment efficacy including change from baseline to endpoint in ADHD-RS-IV, change from baseline to endpoint in AISRS and a score of 1 (very much improved) or 2 (much improved) according to the CGI-I scale. It should be noted that the economic analysis uses patients' CGI-I score to derive response rates, but as CGI-I data were

not available in the atomoxetine studies, the company mapped the total score change from baseline (using the ADHD-RS-IV and AISRS assessment scales) to estimate a CGI-response. The results of the combined outcome scores (ADHD-RS-IV and AISRS) indicated that lisdexamfetamine was the most effective treatment, with a 99.8% probability of being the most effective treatment.

Drug costs, administration costs and monitoring costs were included in the analysis. Drug costs were based on a weighted average of the doses used in the studies included in the indirect comparison. In relation to administration costs, treatment was assumed to be administered under the supervision of a psychiatrist. The quantity of resource use varied depending on whether the patient was in the responder or non responder health state, and consisted of psychiatrist and psychologist visits as well as GP and nurse visits. The cost associated with tests including blood test, ECG, EEG and allergy tests were also included.

Utility values were derived from published literature where the EQ-5D was used to elicit responses in pre identified Canadian subjects with ADHD and a UK social tariff was applied. Responders and non-responders were associated with a utility value of 0.76 and 0.68 respectively. These utility values were applied for the duration of the model.

The base case results indicated that lisdexamfetamine was dominant versus both comparators i.e. more effective and less costly, resulting in incremental savings of £76.78 and an incremental quality-adjusted life-year (QALY) gain of 0.0049 versus methylphenidate and incremental savings of £394.20 and an incremental QALY gain of 0.0117 versus atomoxetine. As lisdexamfetamine is associated with a higher response rate, the cost savings and QALY gains are driven by patients avoid relatively high costs and low health related quality of life associated with being in the non-responder health state.

The company provided both one-way and scenario analysis. For the comparison versus methylphenidate, results of the one-way sensitivity analysis were sensitive to a 30% reduction in non-responder costs, resulting in an incremental cost-effectiveness ratio (ICER) of £461 per QALY. For the comparison versus atomoxetine, results were most sensitive to a change in efficacy. When a response rate of 0.715 was assumed for atomoxetine (derived using the ADHD-RS-IV alone) lisdexamfetamine was dominated.

The following limitations were noted:

- There was uncertainty relating to the choice of comparators used in the analysis. According to SMC expert responses, dexamfetamine is also a relevant comparator. However, prescribing data in an adult population provided by the company demonstrated that methylphenidate is the medicine most commonly prescribed, use of atomoxetine has increased and use of dexamfetamine has declined in recent years. On balance, the Committee concluded that the comparators included in the analysis were reasonable.
- The results of the NMA showed the relative risk of response with lisdexamfetamine compared with methylphenidate was not statistically significant. The company provided an additional analysis which removed the non-significant differences in response rates and this resulted in a small incremental cost with lisdexamfetamine of between £40 and £46 depending on the response rate used.
- In the base case analysis CGI-I response rates were derived by combining two different outcome measurement scores i.e. ADHD-RS-IV and AISRS. Due to limited validation surrounding this approach, it is unclear whether the combination of these two outcome measurement scores is appropriate. In the one-way sensitivity analysis the company

has provided results using the ADHD-RS-IV alone to derive CGI-I response rates. Based on this analysis lisdexamfetamine remained dominant. However it is worth noting that in the NMA, the results (mean change in baseline score) using this assessment tool were not statistically significant.

Despite the weaknesses outlined above the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Group submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) produced clinical guideline 72, 'Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults', in September 2008 (last modified March 2013).¹ The guideline advises that pharmacological treatment of ADHD in adults is indicated first-line in moderate to severe forms of the condition. Methylphenidate is usually recommended as first-line treatment. Atomoxetine or dexamfetamine should be considered if there is no response, or intolerance to, approximately six weeks treatment with methylphenidate. Atomoxetine may be considered as first-line treatment in patients with contra-indications to the use of stimulants or when there may be concern over the potential for drug misuse and diversion^{1,19}. Initial doses of the chosen treatment should be titrated to the optimal dose over four to six weeks according to the patient's symptoms and side effects. Pharmacological treatment for ADHD should be continued for as long as it is clinically effective and reviewed at least annually.

The British Association for Psychopharmacology (BAP) published the guideline 'Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: update on recommendations from the British Association for Psychopharmacology' in 2014.¹⁹ The guideline notes that when treating adults with ADHD, stimulant medications form first-line treatment. In the UK, methylphenidate is usually the drug of first choice, mainly as a result of the limited amphetamine formulations available (extended-release formulations are not available), and the restrictive licence of lisdexamfetamine. The dose of the chosen drug should be increased to obtain optimal management of symptoms. If higher doses are not tolerated by the patient, or if there is inadequate response after a suitable trial of the drug, a switch to a non-stimulant drug is recommended.

The guidelines predate the availability of lisdexamfetamine for adults.

Additional information: comparators

Atomoxetine, methylphenidate*, dexamfetamine[†].

* Methylphenidate is not licensed for treatment initiation in adults with ADHD.

[†] Dexamfetamine is not licensed for use in adults with ADHD.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Lisdexamfetamine	30mg to 70mg orally daily	757 to 1,081
Dexamfetamine [‡]	10mg to 60mg orally daily	644 to 3,861
Atomoxetine	40mg to 100mg orally daily	812 to 1,083
Methylphenidate modified release [§]	10mg to 108mg orally daily	292 to 1,786
Methylphenidate standard release [¶]	10mg to 100mg orally daily	37 to 662

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS on 28/04/15. [‡]Unlicensed use for refractory ADHD in adults, however dose ranges for this unlicensed indication are detailed in the British National Formulary. [§]Methylphenidate is not licensed for treatment initiation in adults with ADHD, however dose ranges for this unlicensed indication are detailed in the British National Formulary. [¶] Costs and dose ranges for both standard release and modified release methylphenidate relate to the range of products available

Additional information: budget impact

The submitting company estimated the population eligible for treatment with lisdexamfetamine to be 5,358 in year 1 and 5,448 in year 5 with an estimated uptake rate of 1% (54 patients) in year 1 rising to 17% (926 patients) in year 5. Patients were assumed to discontinue at a rate of 14.2 % in each year bringing the population treated to 46 in year 1 and 795 in year 5. The gross impact on the medicines budget was estimated to be £40k in year 1 and £688k in year 5. As other medicines were assumed to be displaced the net medicines budget impact was estimated to result in savings of £782 in year 1 and £14k in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 12 June 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*

http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.