New Medicine Policy Recommendation

Lisdexamfetamine dimesylate (Elvanse Adult®) ▼for Attention Deficit/Hyperactivity Disorder (ADHD) in Adults

Recommendation:

Amber 1

Lisdexamfetamine dimesylate is a licensed long acting alternative to the other treatment options available e.g. dexamfetamine and methylphenidate. It is recommended as an option for use as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in adults when used in line with the treatment pathway specified in Appendix 1. Patients should have ADHD of at least moderate severity and treatment must be under the supervision of a specialist in behavioural disorders.

Summary of supporting information:

Background:
Attention deficit/hyperactivity disorder (ADHD) can be defined as a behavioural syndrome presenting with symptoms of hyperactivity, impulsivity and inattention. Lisdexamfetamine is a pharmacologically inactive prodrug that when taken orally is rapidly absorbed and hydrolysed to the active drug 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. Lisdexamfetamine is indicated as part of a comprehensive treatment programme for ADHD in adults with, based on clinical judgment, ADHD of at least moderate severity. A comprehensive treatment programme typically includes psychological, educational, behavioural, occupational and social measures as well as pharmacotherapy.

NICE Clinical Guideline 72 (published in September 2008), "Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults", predates the availability of lisdexamfetamine for adults. It recommends that drug treatment is the first-line treatment for adults with ADHD with either moderate or severe levels of the condition. Methylphenidate (unlicensed in adults) is the first-line drug. If there is intolerance to methylphenidate or it is ineffective, atomoxetine or dexamfetamine can be tried, after six weeks treatment with methylphenidate. Atomoxetine can be considered first line in those with contra-indications to the use of stimulants or where there may be concern over potential for drug misuse and diversion.

Evidence:

- Clinical evidence to support the use of lisdexamfetamine in the treatment of ADHD in adults derives from four double-blind, randomised, placebo-controlled studies and one open-label, single-arm study.
- A short-term forced dose-escalation study and a follow-up long-term open-label single-arm study evaluated safety and efficacy of lisdexamfetamine in adults with moderate to severe ADHD, aged 18 to 55 years old (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).
- Following a washout period of any other stimulant, patients were randomised in a 2:2:2:1 ratio to four weeks treatment with lisdexamfetamine 30 mg once daily (n=119), 50 mg once daily (n=117), 70 mg once daily (n=122), or placebo (n=62). In the follow-up study all patients (n=349) were allocated to lisdexamfetamine 30 mg 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.
- 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 (±standard error) adjusted changes

in scores in the placebo, lisdexamfetamine 30 mg, 50 mg and 70 mg groups, were; -8.2 (±1.43), -16.2 (±1.06), -17.4 (±1.05), and -18.6 (±1.03) respectively.

- 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 the short-term study (n=296) those who previously received lisdexamfetamine, had a mean (SD) improvement in ADHD-RS total score of 62% (25.1) vs. those treated with placebo of 55% (32.0).
- A two-way crossover study initiated adults with ADHD on lisdexamfetamine 30 mg once daily (n=142) and titrated them to the optimum tolerable dose of 30 mg, 50 mg or 70 mg once daily over a 4 week open label period. Patients were then entered into 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.
- The study found that lisdexamfetamine was associated with a significantly higher average post-dose total permanent product measure of performance (PERMP) score (LS mean [SD] 312.7 [94.42]) compared to placebo (287.6 [81.45]); LS mean difference 23.4 (95% confidence interval [CI]: 15.6 to 31.2), ($p<0.0001$).
- In a phase IV withdrawal study, following at least six months stable treatment, patients were continued with their assigned dose of lisdexamfetamine (n=56) or switched to placebo (n=60) in a six-week double-blind randomised withdrawal phase.
- The primary outcome was the proportion of treatment failures (defined as ≥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) at endpoint (up to six weeks) in the double-blind randomised withdrawal phase. 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]) ($p<0.0001$).
- A further phase IV study evaluated the safety and efficacy of lisdexamfetamine on executive function (EF) behaviours via self- and informant-reporting. Adults with ADHD were randomised to ten weeks treatment with placebo (n=80) or lisdexamfetamine (n=79) and titrated over four weeks to the optimum dose (30 mg, 50 mg or 70 mg daily).
- A statistically significant reduction (improvement) was achieved in the primary outcome; patient-reported behaviour rating inventory of executive function adult version (BRIEF-A) global executive composite (GEC) test-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; $p<0.0001$).
- SMC states that other data were also assessed but remain commercially confidential.

Safety:

- All studies reported similar adverse events (AEs). In the short-term forced dose-escalation study, AEs were reported by 58% (36/62), 76% (90/119), 77% (90/117), and 84% (102/122) of patients, in the placebo, lisdexamfetamine 30 mg, 50 mg, and 70 mg 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 AEs, was reported in 1.6% (1/62) and 5.9% (21/358) of patients in the placebo and lisdexamfetamine treatment groups respectively.
- In the longer-term study, when all patients received lisdexamfetamine, 88% (306/349) of patients experienced an AE. Severe TEAEs were reported in 12% (42/348) of patients. Treatment discontinuation, as a result of AEs, was reported in 8.0% (28/348) of patients.
- No new safety concerns were identified in the UK public assessment report (UKPAR). No comparative safety data are available from the clinical studies.

Strengths and limitations:

- The UKPAR noted the magnitude of difference in ADHD symptom scores and functional measures were consistently demonstrated across strengths of lisdexamfetamine compared to placebo, and were clinically significant.
- There is a lack of data comparing lisdexamfetamine with an active comparator. EMA guidance indicates that short-term studies should have three arms, including placebo and active comparator arms. However, 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 studies.
- A Bayesian network meta-analyses (NMAs) comparing lisdexamfetamine, atomoxetine and methylphenidate in adults with ADHD included 21 studies. The results 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.
- 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. In addition open label and a lack of a control arm in some of the studies increase the risk of bias.

- The SPC advises that blood pressure (BP) and pulse rate are recorded at each dose adjustment and at least every six months. Current UK guidance recommends routine monitoring of heart rate and BP every three months. Development and worsening of psychiatric disorders should be monitored at each dose change and at least every six months, in addition to checking for risk of diversion, misuse and abuse.
- Lisdexamfetamine (in addition to dexamfetamine and methylphenidate) is a schedule II controlled drug.

Cost:

- Atomoxetine is currently the only other CNS stimulant licensed for the treatment of ADHD in adults. It costs £1,086 - £1,628 (usual maintenance dose – maximum dose under specialist supervision), in comparison to lisdexamfetamine which costs between £759 and £1,084 annually.
- Methylphenidate is recommended first-line by NICE Clinical Guideline 72 but is unlicensed in adults. It costs £67 annually for the minimum daily dose, rising to £664 when prescribed at the maximum (unlicensed) dose under the supervision of the specialist.

Please note a full new medicine review has not been carried out for the production of the above recommendation. A national body has performed a full assessment of the evidence, safety and cost effectiveness of this medicine and this document has been used in the preparation of the local policy recommendation.

Prices taken from MIMS online (September 2015).

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Appendix 1 – Treatment Algorithm for the treatment of Adults with ADHD