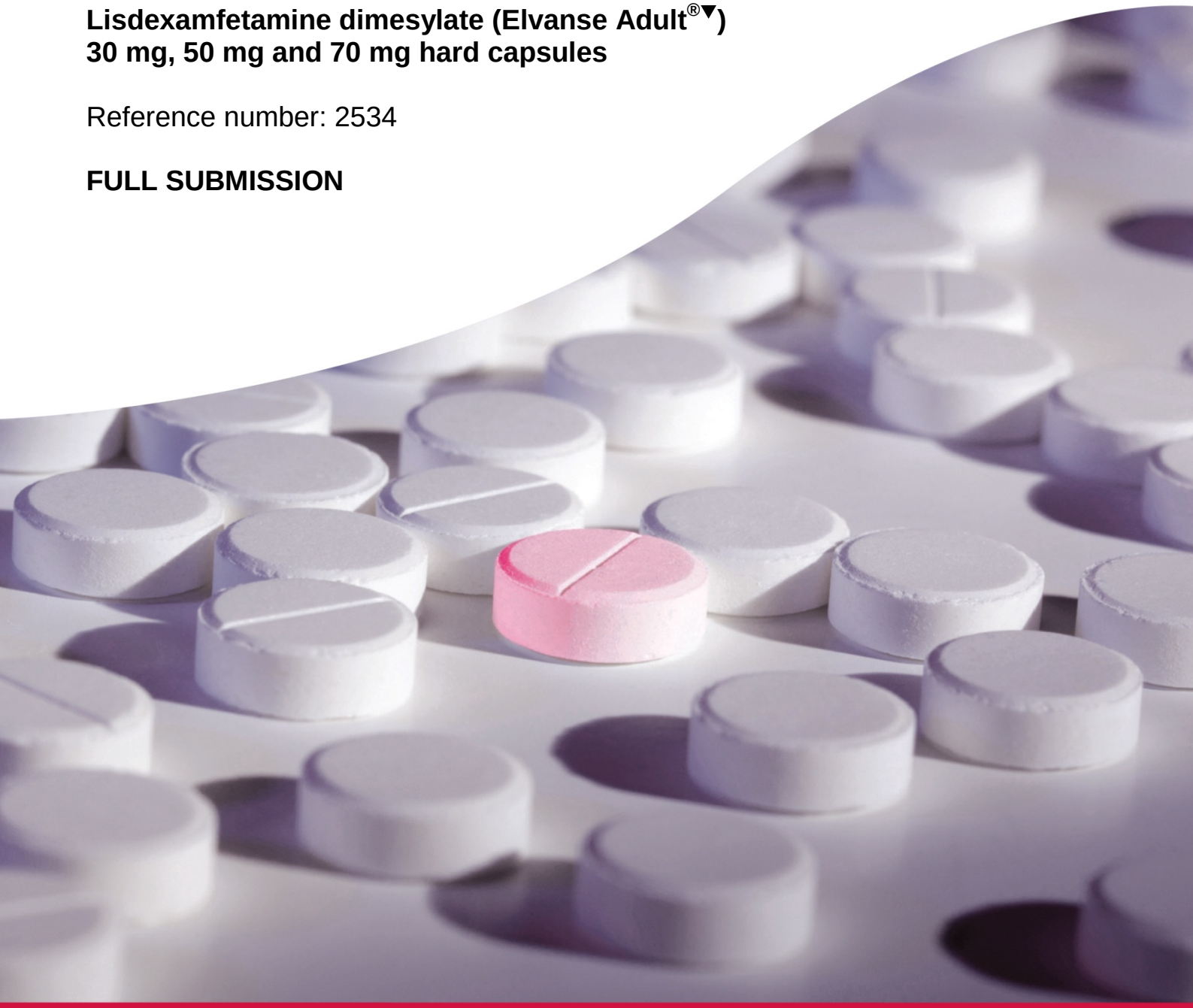
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Lisdexamfetamine dimesylate (Elvanse Adult®▼) 30 mg, 50 mg and 70 mg hard capsules

Reference number: 2534

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Lisdexamfetamine dimesylate (Elvanse Adult®▼) 30 mg, 50 mg and 70 mg hard capsules

This assessment report is based on evidence submitted by Shire Pharmaceuticals Ltd on 26 March 2015[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Lisdexamfetamine dimesylate (Elvanse Adult®▼) is indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in adults. Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2–4].
Dosing	Dosage should be individualised according to the therapeutic needs and response of the patient. Careful dose titration is necessary at the start of treatment with lisdexamfetamine dimesylate. The starting dose is 30 mg taken once daily in the morning. The dose may be increased by 20 mg increments, at approximately weekly intervals. Lisdexamfetamine dimesylate should be administered orally at the lowest effective dosage. The maximum recommended dose is 70 mg/day; higher doses have not been studied. Refer to the SPC for further dosing information[2–4].
Marketing authorisation date	3 February 2015 (licence extension date)[2–4] Originally licensed as part of a comprehensive treatment programme for ADHD in children aged six years and over when response to previous methylphenidate treatment is considered clinically inadequate on 1 February 2013)[5].

2.0 DECISION CONTEXT

2.1 Background

Attention deficit/hyperactivity disorder (ADHD) is a heterogeneous neurobehavioral disorder characterised by hyperactivity, impulsivity and inattention[6]. Prevalence of ADHD, defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR®)[7] is thought to affect about 3–9% of school-age children and young people in the UK[6]. It is estimated that approximately 28,464 adults in Wales have ADHD but only 11% of these are eligible for treatment with pharmacological therapies[8]. In general, ADHD is a persisting disorder[6]. Its onset is in early childhood and, in many cases (reports indicate about 50% to 75%), it persists into adolescence and adulthood where it is associated with adverse long-term outcomes in academic and social function[9]. The presence of ADHD in childhood and adolescence is a prerequisite for the diagnosis to be made in adults[9].

The National Institute for Health and Care Excellence (NICE) clinical guideline 72 (CG72) advises pharmacological treatment as the first-line treatment for adults with ADHD with either moderate or severe levels of impairment[6]. Methylphenidate should normally be tried first; however, if methylphenidate is ineffective or unacceptable,

atomoxetine or dexamfetamine may be considered. Where there may be concerns about the potential for drug misuse and diversion, atomoxetine may be considered as the first-line treatment for ADHD in adults. Pharmacological treatment for adults with ADHD should always form part of a comprehensive treatment programme[6].

Lisdexamfetamine dimesylate (Elvanse Adult®▼; LDX) is a pharmacologically inactive prodrug[2–4,9]. After oral administration, LDX is rapidly absorbed from the gastrointestinal tract and hydrolysed to dexamfetamine, which is responsible for its activity. The mode of therapeutic action of amphetamines is not completely established but they are thought to act as central nervous system stimulants responsible for restoring levels of norepinephrine and dopamine in the brain[2–4,6,9].

2.2 Comparators

The comparators included in the company submission were methylphenidate and atomoxetine (Strattera®).

A clinical expert contacted by AWTTC was in agreement with the comparators suggested by the company[10].

2.3 Guidance and related advice

- British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: update on recommendations from the British Association for Psychopharmacology (2014)[11].
- NICE. CG72. Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults (2013)[6].
- NICE. Evidence summary: new medicine (ESNM) 19. Attention deficit hyperactivity disorder in children and young people: lisdexamfetamine dimesylate (2013)[12].
- Scottish Intercollegiate Guidelines Network (SIGN). Management of attention deficit and hyperkinetic disorders in children and young people. A national clinical guideline 112 (2009)[13].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of lisdexamfetamine dimesylate (Elvanse®▼) in paediatric patients[14] and atomoxetine (Strattera®) in adult patients[15].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

In support of the use of LDX as part of a comprehensive treatment programme for adults with ADHD, the company submission included five randomised, placebo-controlled trials. In the absence of head-to-head studies the company submission included a systematic review and mixed treatment comparison (MTC) providing a comparison of LDX with atomoxetine and methylphenidate as treatments for ADHD in adults[1].

3.1 LDX versus placebo

The company submission included data from five randomised controlled trials (RCTs) in adults that were conducted in the USA[1]. These RCTs included a 4-week placebo-controlled parallel group trial (study NRP104-303); a 2-week placebo-controlled crossover trial (workplace environment; study SPD489-316); a 9-week (maximum) placebo-controlled randomised withdrawal trial (study SPD489-401); and a 10-week placebo-controlled parallel group trial (study SPD489-403). There was also a 52-week, open-label, extension trial in adults that primarily assessed the safety and tolerability of LDX in adults with ADHD (study

NRP104-304; extension of study NRP104-303)[1,9]. See Appendix 1 for an overview of studies.

LDX was demonstrated to be more effective than placebo with statistically significant differences in controlling symptoms of ADHD and overall functioning measured using various validated scales (see Appendix 1). Quality of life was also improved compared to placebo. The long-term follow-up study showed that LDX was significantly more effective than placebo in improving the symptoms of ADHD and this effect was maintained for up to one year[1].

3.2 Systematic review and MTC

In the absence of head-to-head data comparing LDX with other ADHD medications the company submission included a systematic literature review and MTC utilising Bayesian and Frequentist methods to evaluate the relative efficacy of these treatments. The MTCs were performed using fixed and random effects models[1].

A systematic literature review was conducted to identify published papers of RCTs, non-RCTs and systematic reviews concerning the pharmacologic treatment of adults with ADHD[1]. The review identified 6,083 articles; and a total of 21 studies were included in the final review[1].

An MTC model was fitted for each feasible efficacy outcome measure[1]. The efficacy outcomes were: ADHD Rating Scale IV (ADHD-RS-IV); Adult Investigator Symptom Rating Scale (AISRS); Clinical Global Impressions – Improvement (CGI-I) and safety outcomes including all-cause discontinuations and discontinuations due to adverse events (AEs; see Glossary for all endpoint definitions). The results comparing the most relevant outcomes for LDX versus other ADHD medications are presented in Tables 1 and 2. The Bayesian analysis showed that LDX had better efficacy outcomes as measured by ADHD-RS-IV change from baseline and CGI-I response compared to atomoxetine and methylphenidate-extended release (ER); however, these results were not statistically significant. The Bayesian nature of the analysis allowed the company to calculate an additional measure, the probability of being the most efficacious treatment with the aim of providing additional information when no separation in credible intervals was observed. LDX had the highest probability (> 85%) of being the most effective treatment. When efficacy was measured by change from baseline in ADHD-RS-IV or AISRS (ADHD-RS-IV/AISRS) total score, LDX was significantly more effective compared to atomoxetine and methylphenidate-ER. The results of the Frequentist analysis were consistent with the Bayesian analysis. The results were robust with different sensitivity analyses showing the same pattern[1].

Table 1. Effect of LDX on mean change from baseline in ADHD-RS-IV and ADHD-RS-IV or AISRS scores[1]

Core Bayesian analysis: random effects model, combined doses				
	Mean	**95% CrI**	**Probability of the treatment being most effective among all**	**Probability of LDX being more effective compared to each treatment**
Change from baseline in ADHD-RS-IV score				
LDX	¶¶	¶¶	¶¶	¶¶
ATX	¶¶	¶¶	¶¶	¶¶
MPH-ER*	¶¶	¶¶	¶¶	¶¶
Change from baseline in ADHD-RS-IV or AISRS score				
LDX	¶¶	¶¶	¶¶	¶¶
ATX	¶¶	¶¶	¶¶	¶¶
MPH-ER†	¶¶	¶¶	¶¶	¶¶

ATX: atomoxetine; CrI: credible interval; LDX: lisdexamfetamine dimesylate; MPH-ER: methylphenidate extended release

* MPH-immediate release (IR) was not included in the network because no studies with an MPH-IR arm reported ADHD-RS-IV change

† MPH-IR was not included in the network because no studies with an MPH-IR arm reported ADHD-RS-IV or AISRS change

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Table 2. Odds ratio and relative risks for treatment response, as defined by a rating of 1 or 2 in CGI-I score[1]

Core Bayesian analysis: random effects model, combined doses				
	Odds ratio	**95% CrI**	**Probability of the treatment being most effective among all**	**Probability of LDX being more effective compared to each treatment**
LDX	¶¶	¶¶	¶¶	¶¶
ATX	¶¶	¶¶	¶¶	¶¶
MPH-ER*	¶¶	¶¶	¶¶	¶¶
	Relative risk of medicine versus placebo	**95% CrI for relative risk**	**Response rate**	**Placebo risk (95% CrI)†**
LDX	¶¶	¶¶	¶¶	¶¶
ATX	¶¶	¶¶	¶¶	¶¶
MPH-ER*	¶¶	¶¶	¶¶	¶¶

ATX: atomoxetine; CrI: credible intervals; LDX: lisdexamfetamine dimesylate; MPH-ER: methylphenidate extended release

* Methylphenidate-immediate release (IR) was not included in the network because no studies with an MPH-IR arm reported ADHD-RS-IV or AISRS change.

† The placebo risk is the pooled risk of response (CGI-I = 1 or 2) of the placebo arms in the data. The placebo risk uncertainty is measured as the 95% confidence interval around this pooled placebo risk.

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3.3 Safety

In general, LDX was well tolerated and its safety profile was in line with expectations based on clinical experience with dexamfetamine for the treatment of children and adolescents with ADHD[9]. No new safety concerns were identified[9].

In comparison to the approved paediatric indication, there are additional safety issues in adults who could potentially require treatment for many years[9]. 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[9].

The Medicines and Healthcare Products Regulatory Agency (MHRA) concluded that providing 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 Summary of Product Characteristics[1–4,9].

3.3.1 Comparative safety

LDX had a lower relative risk for all-cause discontinuation compared to atomoxetine and methylphenidate[1]. No separation in credible intervals was observed between LDX and atomoxetine or methylphenidate in the Bayesian analysis, and the difference was not statistically significant in Frequentist analyses. Atomoxetine and methylphenidate-ER had a lower relative risk for discontinuation due to AEs than LDX, but there was considerable overlap in the posterior credible intervals. Due to the shapes of the posterior distributions, LDX had the highest probability of being the most tolerable treatment, followed closely by the other treatments. The relative risk of AEs discontinuation for LDX was lower than that for methylphenidate-immediate release (IR), which is currently recommended as a first-line treatment for ADHD in adults[1].

3.4 AWTTC critique

- The MHRA noted that there was a clear clinical significance in the magnitude of difference from placebo for all strengths of LDX for functional measures as well as ADHD symptom scores[9].
- The onset of action of LDX has been established at two hours, which results in fast-acting treatment[1,16]. The long duration of action (at least 14 hours post-dose) allows a once daily administration of LDX with a consistent effect throughout the day[1].
- Only study SPD489-403 included true functional efficacy measures; the MHRA noted that the effect on symptom scores does not readily translate into a relevant clinical benefit and the effect on functioning is considered an important aspect of development of products for ADHD[9].
- In their submission, the company included a systematic literature review and MTC to address the lack of direct comparative evidence. Broadly, LDX was shown to be comparable to atomoxetine and methylphenidate, although MTC results should be interpreted with caution due to heterogeneity of the study with regards to trial population, trial length and prior treatment[1].
- The systematic literature review was based on pre-specified criteria, but excluded trials may have contained important information[1].
- A limitation of using the ADHD-RS-IV score change from baseline for the primary endpoint is that it is a subjective measure of ADHD symptoms completed by the investigator[12]. 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[12,17].
- Following amendments to the Misuse of Drugs Act 1971 in June 2014[18], LDX is considered a schedule 2 controlled drug and is subject to full control drug requirements relating to prescriptions, safe custody and the need to keep

registers[19]; however, the MHRA concluded that the abuse potential of LDX is likely to be lower than that of dexamfetamine[9]. Atomoxetine is not a controlled substance; the abuse potential of LDX versus atomoxetine has not been investigated.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes a cost utility analysis (CUA) of the central nervous system (CNS) stimulant LDX (30 mg, 50 mg or 70 mg) as a first-line pharmacological treatment of ADHD in adults who have been diagnosed with moderate to severe symptoms compared against atomoxetine (10 mg, 18 mg, 25 mg, 40 mg, 60 mg or 80 mg) and long-acting methylphenidate (18 mg, 27 mg or 36 mg)[1].

A decision analytic model is used to estimate the changes in total cost, total quality adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) over a one year time horizon (base case) from an NHS perspective if LDX was to replace atomoxetine and methylphenidate, respectively. The model assumes that every patient will go through a 28-day titration period to achieve optimal balance between AEs from treatment and symptom management. After these first 28 days, the patient cohort was divided into three separate health states comprising “unable to tolerate”, “response” and “no response”. Patients in the “unable to tolerate” group were assumed to discontinue treatment halfway through the titration period (at 14 days) and not to receive any further pharmacological treatment. Patients not responding to treatment were assumed to discontinue treatment after the titration period (at 28 days) without any further pharmacological treatment. Responders continued on their first-line treatment until the end of the time horizon (from day 29 to one year in the base case) and were assumed to maintain their level of response throughout this period.

In the absence of direct comparative data, the company conducted a systematic literature review followed by a Bayesian network meta-analysis using a MTC framework. The MTC provided treatment response and tolerability data for the model as well as withdrawal rates and average dose of treatment. Costs include medicine acquisition, administration and monitoring. Costs of medicine acquisition are based on the weighted average dose of treatment from the clinical trials multiplied by the cost per mg of treatment obtained from the British National Formulary (BNF)[19]. Data on cost and resource use related to administration and monitoring of ADHD treatment programmes of £115.91 per 28 days for responders and £331.88 for non-responders were derived from a survey of UK clinicians treating patients with ADHD as the company states that no data was available from literature. The company undertook a systematic review of studies reporting health-related quality of life in patients with ADHD which identified five studies, three of which did not meet the requirements of the NICE reference case. The model uses data reported by Mitsi et al. (2010) in the base case and data by Matza et al. (2013) in the sensitivity analysis[20,21].

Extensive one-way sensitivity analyses, scenario analyses and probabilistic sensitivity analysis were used to test the robustness of the results to changes in parameter values such as costs (varied by 10% and 30%), utility weights (different data sources), time horizon (five years instead of one year), treatment dose (real-world USA data instead of trial data) and probability of withdrawal (based on 95% confidence interval).

4.1.2 Results

The results of the base case analysis are presented in Table 3. LDX is reported to be less costly per patient over the one year horizon and to result in a greater number of QALYs compared to atomoxetine and long-acting methylphenidate.

Table 3. Results of the base case analysis

	LDX	Comparator treatment	Difference
LDX versus ATX			
Total costs per patient	¶¶	£3,647	¶¶
Total QALYs	¶¶	0.7148	¶¶
ICER (£/QALY gained)	**LDX dominant**		
LDX versus MPH			
Total costs per patient	¶¶	£3,329	¶¶
Total QALYs	¶¶	0.7216	¶¶
ICER (£/QALY gained)	**LDX dominant**		

ATX: atomoxetine; ICER: incremental cost-effectiveness ratio; LDX: lisdexamfetamine dimesylate; MPH: methylphenidate; QALY: quality adjusted life year

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LDX remained the dominant treatment in the majority of the sensitivity analyses and results were insensitive to variations of utility weights, costs and time horizon. LDX was dominated by the comparators in several sensitivity analyses where its efficacy dropped below the efficacy of the comparator treatments or was associated with a high probability of intolerance/discontinuation of treatment. The company claims that these scenarios are unlikely considering the probability of LDX to be more efficacious than atomoxetine and methylphenidate was found to be 92.26% and 97.39%, respectively in the MTC. Probabilistic sensitivity analyses found LDX to be cost-effective in 66.7% of simulations at a £20,000 threshold compared to methylphenidate and 94.3% cost-effective against atomoxetine.

4.1.3 AWTTC critique

The results of the CUA indicate that LDX is the dominant treatment compared to atomoxetine and long-acting methylphenidate, being less costly and more effective than its comparators.

Strengths of the economic analysis are as follows:

- Considering the nature of the clinical pathways and the evidence available in the literature and from clinical experts, the suggested approach generally fits the purpose of the current analysis and answers the question of cost-effectiveness of LDX. The analysis is also supported by Bayesian fixed and random effects modelling.
- The structure of the decision model is based on a previous analysis commissioned by NICE for the Multiple Technology Appraisal (MTA) of long-acting methylphenidate, atomoxetine and dexamfetamine for the treatment of ADHD, and subsequently published in the Health Technology Assessment journal[22]. This model structure was also applied in a previous submission to the AWMSG for LDX as a treatment for ADHD in children and adolescents[14].
- The submission gives a very detailed and transparent account of the methods, data sources and analyses undertaken and the company acknowledges and addresses the main limitations by conducting extensive sensitivity analyses.

Limitations of the economic analysis include:

- The CUA presented by the company does not include dexamfetamine as a comparator. Recommendation 1.7.1.6 of NICE CG72 states that “atomoxetine or dexamfetamine should be considered in adults unresponsive or intolerant to an adequate trial of methylphenidate (this should usually be about six week)”.

The company states that dexamfetamine is usually restricted to use as a final therapy option in patients who are refractory to other pharmacological treatments due to the advantages of long-acting preparations according to a survey of practising psychiatrists in England and Scotland. They also claim that as a short-acting therapy, dexamfetamine (as well as short-acting methylphenidate) are expected to be used by a different patient population and would therefore be inappropriate comparators.

- Methylphenidate (short-acting) is not considered as a comparator as it is not licensed for the treatment of adults with ADHD. As it is one of the cheapest options for treatment, its exclusion from the model could introduce bias in favour of LDX if it is used to a certain proportion in routine practice as an alternative treatment.
- The one year time horizon is short and might be insufficient to pick up all long-term costs and consequences which could introduce bias. However, the company states that there are insufficient long-term follow up data to allow robust assessment of cost-effectiveness after year one and LDX was still the dominant treatment in the sensitivity analysis extending the time horizon to five years. The five year time horizon analysis is, however, limited in that it assumes no further drop-outs beyond the initial 28-day titration period, and also that the health utilities remain constant (excluding discounting) for the duration of the analysis.
- There are limitations to the MTC which include differences in study population (e.g. participant age, inclusion/exclusion criteria, prior treatment, gender, baseline disease severity) and length of trial follow-up. The company acknowledges these limitations in their submission and has submitted sensitivity analyses to address some uncertainty (e.g. differences in population age) which showed no effect on the results of the economic evaluation.
- The CUA does not take into account treatment-related AEs which could potentially affect cost and health-related quality of life. The company justifies this approach on the basis that intolerable AEs during the titration period would be transient in nature, result in discontinuation and resolve upon treatment cessation. The company states that AEs after the titration period are assumed to be minor (dry mouth, decreased appetite and insomnia) and are reflected in the average cost and utilities of the “responder” population. This however, is not described in detail in the submission. They state that these AEs would be expected to be similar across treatment arms and that their approach has been used for other models related to ADHD in children.
- Medicine acquisition costs are based on the weighted average dose of treatment from the clinical trials included in the MTC. It is unclear to what extent these data reflect real-world medicine usage. While the company has provided sensitivity analyses based on USA real-world data which showed no significant effect on the results, generalisability and applicability of these data to the Welsh context is uncertain.
- A sensitivity analysis modelled treatment doses using data obtained from a UK prescription dataset and indicated that LDX is both more costly and more effective than methylphenidate (ICER £12,919 per QALY gained). However, in this scenario, the probability of response to methylphenidate was modelled using efficacy data from the clinical trials, where on average a higher dose of therapy was used. In practice, lower doses of treatment may be used and the probability of response to methylphenidate may be thus overestimating the effectiveness of methylphenidate and the ICER in favour of methylphenidate.
- Resource use and costs of administering and monitoring of the ADHD treatment programmes was derived from a survey of 53 currently practising psychiatrists based in England (62%) and Scotland (38%). It is unclear whether and to what extent the lack of survey response from clinicians based in Wales could bias the results. The company states that their experience with LDX in the children and adolescent population suggests that the clinical practice of treating ADHD

patients does not differ in Wales when compared to England, Scotland or the US.

- Utility data were derived from published literature. As the studies used to populate the model were published as abstracts only, little is known about the methodology and limitations of the studies and hence the quality of the data which will introduce bias. The sensitivity analysis used published utility values that are based on health-state descriptions which is not a recommended method for capturing utilities, as recommended by NICE.
- In the base case analysis, which is first-line treatment, patients who discontinue LDX or atomoxetine do not receive further medicinal treatment if the initial treatment is unsuccessful. Whether this is a plausible assumption in clinical practice is questionable, and could impact the ICER. The company claims that this is due to the limited clinical evidence available beyond first-line treatment.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based upon the UK prevalence for adult ADHD in males (1.81%) and females (0.43%), the company has estimated the prevalence of adult ADHD in Wales to be 1.10068%[23]. Therefore, the company estimate that there are approximately 28,464 adults in Wales with ADHD[24]. The budget impact analysis does not take into account newly diagnosed patients over the first five years, and assumes that the prevalence is fixed over the five year period; the company claims these parameters would be impossible to accurately estimate. Based on NICE CG72, 11.24% of patients will be eligible for treatment resulting in 3,199 adult patients in year one increasing to 3,239 in year five based on general Welsh population growth[24]. The company assumes a fixed discontinuation rate of 14.20% per year and an uptake rate of 1% in year one increasing to 17% in year five which translates to 27 patients being treated with LDX in year one and 472 patients in year five.

5.1.2 Results

The estimated net budget impact is presented in Table 2. The company estimates that cost-savings could be made after introduction of LDX as the cost of the displaced therapies, atomoxetine and long-acting methylphenidate is higher.

Table 4. Company-reported costs associated with use of LDX for the first-line treatment of ADHD in adults

	Year 1 (2015)	Year 2 (2016)	Year 3 (2017)	Year 4 (2018)	Year 5 (2019)
Number of eligible patients (indication covered in this submission)	3,199	3,210	3,210	3,229	3,239
Uptake (%)	1%	4%	8%	13%	17%
Treated patients	32	128	257	420	551
Discontinuation rate	14.2%	14.2%	14.2%	14.2%	14.2%
Patients continuing with treatment after titration period	27	110	220	360	472
Overall net cost	**–£467**	**–£1,874**	**–£3,748**	**–£6,126**	**–£8,036**

No sensitivity analyses or other scenarios were presented by the company.

5.1.3 AWTTC critique

- Compared to the detailed CUA presented by the company, the budget impact analysis is quite minimal and does not give a lot of information on the sources of data and how figures were derived. A budget impact model was not provided. It is therefore difficult to estimate how realistic or biased the analysis is.
- No source or justification is give for the expected uptake rate or the percentage use of different formulations. It is therefore unclear how realistic the potential net savings will be.
- An initial uptake rate of 1% in year one appears to be very conservative and the company does not give an explanation of how these figures were derived. However, as the introduction of LDX is marginally cost-saving in the budget impact analysis, an increased market share would result in higher net cost savings.
- No sensitivity analyses are presented by the company and the extent to which the uncertainties in the data influence the net costs is unknown.

5.2 Comparative unit costs

Weekly acquisition costs for different treatment regimens used for first-line treatment of ADHD in adults with moderate to severe symptoms are shown in Table 5. A titration period of steadily increasing doses until target dose is reached is usually required.

Table 5. Examples of acquisition costs of medicines used for the treatment of ADHD in adults

Regimens	Example doses	Approximate weekly costs per patient
Atomoxetine (Strattera®) 10 mg, 16 mg, 25 mg, 40 mg or 60 mg capsules (7 or 28 pack)	Initially 40 mg daily for 7 days then increased to 80–100 mg daily according to response, given as a single daily dose or 2 divided doses	£15.62
Atomoxetine (Strattera®) 80 mg or 100 mg capsules (28 pack)	Initially 40 mg daily for 7 days then increased to 80–100 mg daily according to response, given as a single daily dose or 2 divided doses	£20.82
Dexamfetamine (non-proprietary)*† 5 mg tablets (28 pack)	Initially 5 mg twice daily, increased at weekly intervals according to response to 60 mg daily given in 2-4 divided doses	£12.14 (10 mg) to £72.84 (60 mg)
Lisdexamfetamine dimesylate (Elvanse®▼)* 30 mg capsules (28 pack)	Initially 30 mg once daily increased if necessary at weekly intervals by 20 mg to 70 mg daily)	£14.56
Lisdexamfetamine dimesylate (Elvanse®▼)* 50 mg capsules (28 pack)	Initially 30 mg once daily increased if necessary at weekly intervals by 20 mg to 70 mg daily)	£17.15
Lisdexamfetamine dimesylate (Elvanse®▼)* 70 mg capsules (28 pack)	Initially 30 mg once daily increased if necessary at weekly intervals by 20 mg to 70 mg daily)	£20.79
Methylphenidate hydrochloride (non-proprietary)* 5 mg tablets (30 pack)	5 mg two to three times daily increased if necessary at weekly intervals according to response to 100 mg daily in 2-3 divided doses	£1.42 (10 mg)
Methylphenidate hydrochloride (non-proprietary)* 10 mg tablets (30 pack)	5 mg two to three times daily increased if necessary at weekly intervals according to response to 100 mg daily in 2-3 divided doses	£6.41 (50 mg)
Methylphenidate hydrochloride (non-proprietary)* 20 mg tablets (30 pack)	5 mg two to three times daily increased if necessary at weekly intervals according to response to 100 mg daily in 2-3 divided doses	£12.74 (100 mg)
Methylphenidate hydrochloride (Ritalin®) 10 mg tablets (30 pack)	5 mg two to three times daily increased if necessary at weekly intervals according to response to 100 mg daily in 2-3 divided doses	£1.30 (10 mg) to £13.00 (100 mg)
Methylphenidate hydrochloride (Concerta XL®)§ 18 mg prolonged-release tablets (30 pack)	Initially 18 mg once daily, adjusted at weekly intervals according to response to 108 mg daily	£7.28 (18 mg)
Methylphenidate hydrochloride (Concerta XL®)§ 27 mg prolonged-release tablets (30 pack)	Initially 18 mg once daily, adjusted at weekly intervals according to response to 108 mg daily	£17.18 (54 mg)
Methylphenidate hydrochloride (Concerta XL®)§ 36 mg prolonged release tablets (30 pack)	Initially 18 mg once daily, adjusted at weekly intervals according to response to 108 mg daily	£29.72 (108 mg)
Methylphenidate hydrochloride (Concerta XL®)§ 54 mg prolonged release tablets (30 pack)	Initially 18 mg once daily, adjusted at weekly intervals according to response to 108 mg daily	£34.36 (108 mg)

* Unlicensed use; † For refractory ADHD; § Initiation in adults unlicensed
Not all regimens may be licensed for use in this patient population. See relevant Summaries of Product Characteristics for full licensed indications and dosing details[5,25–28]
Costs are based on BNF and MIMS list prices as of 3 May 2015[19,29]. Costs of administration are not included. This table does not imply therapeutic equivalence of medicines or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, lisdexamfetamine dimesylate (Elvanse Adult®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that lisdexamfetamine dimesylate (Elvanse Adult®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 20 April 2015
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

ADHD Rating Scale IV (ADHD-RS-IV)

ADHD-RS-IV is a questionnaire used to both diagnose ADHD in children and adolescents and assess treatment response. The scale consists of two subscales: inattention (nine items) and hyperactivity-impulsivity (nine items), and is linked directly to DSM-IV diagnostic criteria for ADHD. The questionnaire is completed independently by the parent and/or teacher and scored by a clinician. Higher scores indicate increased inattention or hyperactivity-impulsivity[30].

Adult Investigator Symptom Rating Scale (AISRS)

The AISRS improves on certain aspects of the ADHD-RS, such as providing a context basis to questions about symptoms and replacing questions that assess two symptom domains with questions that assess only one domain. Symptoms are rated using a four-point Likert-type severity scale (from 0 = none to 3 = severe)[31].

Clinical Global Impressions (CGI) scale

The CGI scale was developed for use in National Institute of Mental Health (NIMH)-sponsored clinical trials to provide a brief, standalone clinician assessment of a patient's global functioning prior to and after initiating study medication. It provides an overall summary measure that takes into account all available information (patient history, symptoms, behaviour etc) and is applicable to all psychiatric conditions. The CGI scale comprises two, one-item measures[32]:

- **Clinical Global Impressions – Severity (CGI-S)**
  A seven-point scale of severity in which, in assessing a patient, the clinician asks him or herself one question: Considering your total clinical experience with this particular population, how mentally ill is the patient at this time? A higher score indicates more severe illness.
- **Clinical Global Impressions – Improvement (CGI-I)**
  A seven-point scale of the change from baseline in which, in assessing a patient, the clinician asks him or herself one question: Compared to the patient's condition prior to medication initiation, this patient's condition is: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse.

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Appendix 1. Pivotal studies of LDX in adult patients with ADHD

Table 1A. Overview of comparative studies versus placebo

Study	Design	Number of patients	Treatment regimen	Treatment duration	Primary endpoint(s)	Results
NRP104-303[33–39]	Phase III, randomised, double-blind, placebo-controlled, forced-dose titration, parallel-group design	N = 420 ITT = 414 Safety = 420 Completers = 349	LDX 30 mg, 50 mg, 70 mg Placebo	4 weeks	Change from baseline to the patient's final assessment in the ADHD-RS total score	LDX was more effective compared to placebo in improving symptomatology of ADHD based on mean change from baseline at endpoint for ADHD-RS total score ($p \leq 0.0002$).
NRP104-304[37,40–42] (extension of study NRP104-303)	Phase III, multicentre, open-label, single-arm study	N = 349 ITT = 345 Safety = 349 Completers = 191	LDX 30 mg, 50 mg, 70 mg	52 weeks	Change from study NRP104-303 baseline ($baseline_{303}$) at endpoint in ADHD-RS total score	LDX was more effective compared to placebo in improving the symptomatology of ADHD based on mean change from baseline at endpoint for ADHD-RS total score ($p \leq 0.0002$). LDX continues to be well tolerated with long-term exposure.
SPD489-316[16,43,44]	Dose optimisation, followed by double-blind, placebo-controlled, cross-over analogue workplace study	N = 142 ITT = 105 Safety = 142 Completers = 103	LDX 30 mg, 50 mg, 70 mg	2 weeks	Average of PERMP total scores	LDX was effective compared to placebo as measured by the PERMP total scores averaged over all post-dose time points for the AWE days ($p < 0.0001$). The duration of effect was 14 hours post-dose as demonstrated by the PERMP total score at the 14 hour post-dose time point of the AWE day.

Table 1A continued

Study	Design	Number of patients	Treatment regimen	Treatment duration	Primary endpoint(s)	Results
SPD489-401[45]	Phase IV, multicentre, double-blind, placebo-controlled, randomised, withdrawal study	N = 123 ITT = 116 Safety = 122 Completers = 63	LDX 30 mg, 50 mg, 70 mg Placebo	9 weeks	The proportion of treatment failures accrued by subjects receiving LDX (all doses) against placebo at endpoint	The proportion of treatment failures on LDX was significantly lower as compared to placebo (8.9% vs. 75%, respectively; $p < 0.0001$) at endpoint during the randomised withdrawal period.
SPD489-403[46,47]	Phase IV, multicentre, randomised, double-blind, placebo-controlled, parallel-group study	N = 161 ITT = 154 Safety = 159 Completers = 115	LDX 30 mg, 50 mg, 70 mg Placebo	10 weeks	The mean change from baseline to week 10/ET for subject-reported BRIEF-A GEC T-score	The mean change from baseline to week 10/ET for subject-reported BRIEF-A GEC T-score was significantly better in the LDX group compared with placebo ($p < 0.0001$).

ADHD: attention deficit hyperactivity disorder; ADHD-RS: attention deficit hyperactivity disorder-rating scale; AWE: adult workplace environment; BRIEF-A: Behaviour Rating Inventory of Executive Function – Adult Version; CGI-S: Clinical Global Impression-Severity; DSM-IV-TR™: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision; EF: Executive Function; GEC: Global Executive Composite; ITT: intention to treat; DX: lisdexamfetamine dimesylate; PERMP: Permanent Product Measure of Performance.