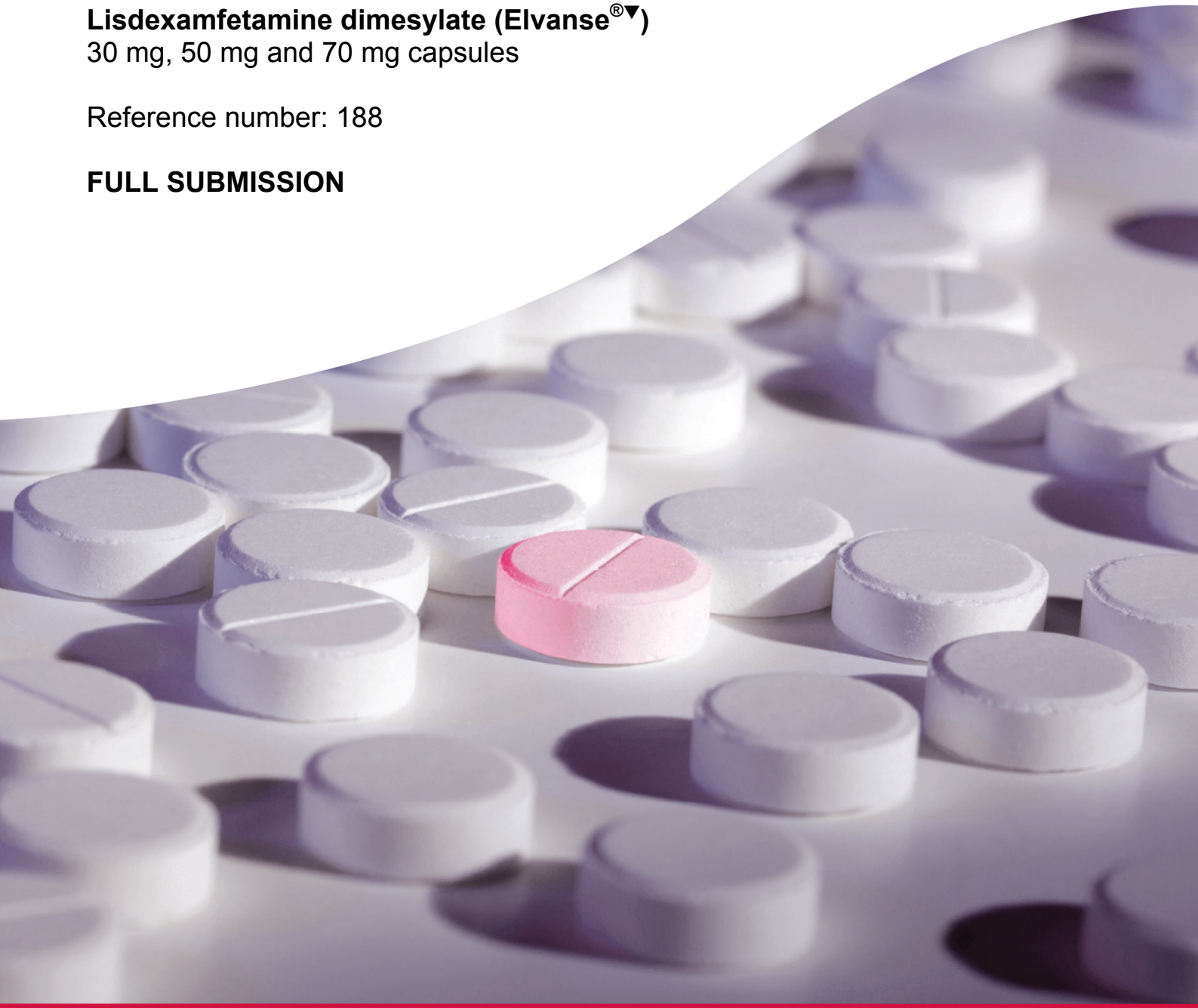
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

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

Reference number: 188

FULL SUBMISSION



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

This assessment report is based on evidence submitted by Shire Pharmaceuticals Ltd on 22 May 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Lisdexamfetamine dimesylate (Elvanse®▼; LDX) is licensed as part of a comprehensive treatment programme for attention deficit/ hyperactivity disorder (ADHD) in children aged six years of age and over when response to previous methylphenidate treatment is considered clinically inadequate. Treatment must be under the supervision of a specialist in childhood and/or adolescent behavioural disorders[2].
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. For all patients, 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. LDX should be administered orally at the lowest effective dosage. The maximum recommended dose is 70 mg/day; higher doses have not been studied[2].
Marketing authorisation date	1 February 2013[2]
UK launch date	4 March 2013[1]

2.0 DECISION CONTEXT

2.1 Background

Attention deficit/hyperactivity disorder (ADHD) is a heterogeneous neurobehavioural disorder characterised by impulsivity, hyperactivity and inattention (either alone or in combination)[1,3,4]. The prevalence of ADHD, defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR®)[5], in school-aged children and adolescents in the UK is estimated at 5.0%[6].

Treatments for ADHD include psychological/behavioural, educational, dietary and/or pharmacological interventions. Where treatment with medication is considered appropriate, methylphenidate, atomoxetine and dexamphetamine are recommended, within their licensed indications, as options for the management of ADHD in children and adolescents[6]. Clinical Guideline 72 (CG72) issued by the National Institute for Health and Care Excellence (NICE) advises that healthcare professionals should consider methylphenidate first-line, or atomoxetine in the presence of some comorbid conditions; where methylphenidate has been tried and has been ineffective at the maximum tolerated dose; or where the child or young person is intolerant to low or moderate doses of methylphenidate. Dexamfetamine should be considered in children and young people whose ADHD is unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine[3].

The mechanism of action of amphetamines for the treatment of ADHD is not fully understood; however, it is thought to be due to the ability to block the reuptake of norepinephrine and dopamine into the presynaptic neuron, and increase the release of these monoamines into the extraneuronal space. Lisdexamfetamine dimesylate (Elvanse®▼; LDX) is a new chemical entity and a pharmacologically inactive prodrug, requiring metabolic activation. After oral administration, LDX is rapidly absorbed from the gastrointestinal tract and hydrolysed primarily by red blood cells to dexamfetamine. The rate-limited bioconversion process attenuates the peak plasma concentrations of the active metabolite (see Section 3.3)[1,2].

2.2 Comparators

The comparator included in the company submission was atomoxetine (Strattera®).

2.3 Guidance and related advice

- NICE Evidence summary: new medicine (ESNM) 19. Attention deficit hyperactivity disorder in children and young people: lisdexamfetamine dimesylate (2013)[7].
- NICE CG72. Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults (2013)[3].
- Scottish Intercollegiate Guidelines Network. Management of attention deficit and hyperkinetic disorders in children and young people. A national clinical guideline (112) (2009)[8].
- British Association for Psychopharmacology. Evidence-based guidelines for management of attention-deficit/hyperactivity disorder in adolescents in transition to adult services and in adults: recommendations from the British Association for Psychopharmacology (2007)[9].
- NICE Technology Appraisal 98 (TA98). Attention deficit hyperactivity disorder (ADHD) - methylphenidate, atomoxetine and dexamfetamine (review) (2006)[6].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company considered three clinical trials as pivotal to the indication under consideration as all included sites in Europe and were completed in children and/or adolescents aged 6–17 years with ADHD. Study SPD489-317 was a head-to-head study of LDX versus atomoxetine. Studies SPD489-325 and SPD489-326 were placebo-controlled trials of LDX; the All Wales Therapeutics and Toxicology Centre (AWTTC) considered these supportive of the head-to-head study and are therefore only discussed briefly below[1].

3.1 Comparative efficacy

3.1.1 LDX versus atomoxetine: Study SPD489-317

Study SPD489-317 was a phase IIIb, randomised, double-blind, multicentre, parallel-group, active-controlled, dose optimisation safety and efficacy study of LDX in children and adolescents aged 6–17 years with at least moderately symptomatic ADHD (defined as an ADHD Rating Scale IV [ADHD-RS-IV; see Glossary] baseline total score of ≥ 28) and who had previously had an inadequate response to treatment with methylphenidate. Inadequate response included, but was not limited to, the presence of some residual symptoms, an inadequate duration of action and/or variability of symptom control, and/or considered by the investigator to have the potential to benefit from an alternative treatment to methylphenidate therapy. Subjects (n = 267) were randomised 1:1 to LDX (as 30 mg, 50 mg or 70 mg capsules; n = 133) or atomoxetine (as 10 mg, 18 mg, 25 mg, 40 mg or 60 mg capsules; n = 134), administered and optimised as described in the Summaries of Product Characteristics (SPCs)[1,2,10].

Study duration was approximately 12 weeks, which was divided into three phases: up to two weeks to screen subjects and allow for the washout of psychoactive medication;

a nine-week double-blind treatment phase, comprised of four weeks of dose optimisation and five weeks of dose maintenance; and a one-week washout and follow-up phase[1].

Subjects included in the efficacy analysis had taken at least one dose of investigational product. One subject had been randomised to receive atomoxetine but actually received LDX. For the efficacy analyses, this subject was included in the atomoxetine treatment group, but was included in the LDX group for the safety analysis. Of the 267 subjects randomised, five (all in the LDX group) did not receive study medication and were excluded from the analysis. Therefore, the full analysis set included 262 subjects (LDX: n = 128; atomoxetine: n = 134)[1].

The primary efficacy endpoint was the time to first response (measured in days), defined as a Clinical Global Impressions - Improvement (CGI-I; see Glossary) score of 1 (very much improved) or 2 (much improved) during any of the double-blind treatment visits, relative to the severity of illness at baseline. For the full analysis set, 113/128 (89%) subjects in the LDX group versus 102/134 (76%) in the atomoxetine group met the response criterion. A statistically significantly shorter median time to response was observed in subjects treated with LDX compared to atomoxetine: 12 days compared to 21 days (p= 0.001)[1].

Secondary endpoints for response-, symptom- and function-related outcomes (including CGI-I, Clinical Global Impressions - Severity [CGI-S; see Glossary], ADHD-RS-IV total and subscale [hyperactivity/impulsivity and inattention] and Weiss Functional Impairment Rating Scale - Parent [WFIRS-P] scores) were supportive of the primary endpoint[1].

3.1.2 LDX versus placebo

3.1.2.1 Study SPD489-325

SPD489-325 was a 14-week, phase III, randomised, double-blind, multicentre, parallel-group, placebo- and active-controlled dose optimisation study designed to determine the safety and efficacy of LDX (maximum 70 mg/day) in children and adolescents aged 6–17 years with ADHD (ADHD-RS-IV baseline score ≥ 28) (n = 336), compared to placebo, with osmotic-controlled release oral delivery system (OROS) methylphenidate used as a reference arm. The study comprised a period of up to six weeks to screen subjects and wash out current psychoactive medication; a seven-week double-blind evaluation phase (comprising a four-week dose optimisation period and a three-week dose maintenance period); and a one-week washout and follow-up phase. LDX was more effective in improving ADHD symptoms compared to placebo for the primary endpoint, defined as change from baseline in ADHD-RS-IV total score; the mean decrease (± standard deviation [SD]) was larger for the LDX and OROS methylphenidate groups when compared to placebo (−24.7 ±10.15 and −18.9 ±12.92, versus −6.3 ±10.02, respectively). The study was not powered to support a comparison between LDX and OROS methylphenidate. Secondary endpoints for symptomatology, functional outcome and quality of life were supportive of the primary endpoint[1].

3.1.2.2 Study SPD489-326

SPD489-326 was a 33-week, phase III, double-blind, randomised withdrawal, long-term extension study, designed to evaluate the long-term maintenance effect of LDX (maximum 70 mg/day) in children and adolescents aged 6–17 years with moderately symptomatic ADHD (ADHD-RS-IV baseline score ≥ 28) (n = 276). The study comprised a four-week open-label, dose optimisation period; a 20-week open-label maintenance period; a two-week open-label fixed dose period; and a six-week, double-blind, randomised withdrawal period. [Commercial in confidence data removed] The primary outcome was treatment failure (a composite endpoint of the ADHD-RS-IV and CGI-S scores via the randomised withdrawal design), defined as a 50% increase in

ADHD-RS-IV total score and a ≥ 2-point increase in CGI-S score observed at any visit during the randomised withdrawal period compared to baseline. Subjects that withdrew from the randomised withdrawal period and did not provide efficacy data at the endpoint visit were also classed as treatment failures. Not all subjects had a value for endpoint, as some subjects did not have an on-treatment assessment after the initial visit post-randomisation. [Commercial in confidence data removed]

3.2 Comparative safety

3.2.1 LDX versus atomoxetine: study SPD489-317

The percentage of subjects that experienced at least one treatment-emergent adverse event (TEAE) was similar between the LDX and atomoxetine treatment groups (92/128 [71.9%] and 95/134 [70.9%], respectively). [Commercial in confidence data removed] This led to discontinuation in eight patients (6.3%) in the LDX arm and ten (7.5%) patients in the atomoxetine arm. Events that were reported more frequently for LDX than for atomoxetine included decreased appetite, weight decrease, insomnia, constipation, dry mouth, irritability and nasopharyngitis. Events reported more frequently for atomoxetine than LDX were fatigue, headache, nausea, vomiting, sedation, somnolence, abdominal pain, upper respiratory tract infection and diarrhoea. No serious TEAEs were reported and no deaths occurred during the study[1].

Changes in body weight, vital signs and electrocardiogram (ECG) results were also monitored as part of the safety analysis in study SPD489-317. At endpoint, the mean (SD) decreases in body weight for the LDX and atomoxetine groups were −1.30 kg (1.806 kg) and −0.15 kg (1.434 kg), respectively. Modest mean increases from baseline in pulse were noted at all double-blind treatment visits in both treatment groups. Mean changes from baseline in systolic blood pressure were not consistent over time for magnitude or direction of change, regardless of treatment group. ECGs were assessed at the screening visit and at visit 4. Although a mean increase in heart rate was observed in both treatment groups at visit 4, this was of lesser magnitude in the LDX group (3.5 bpm) compared to the atomoxetine group (6.4 bpm)[1].

3.2.2 LDX versus placebo

The percentage of subjects that experienced at least one TEAE was increased in the LDX group compared to the placebo group in studies SPD489-325 (72.1% versus 57.3%, respectively) and SPD489-326 (39.7% versus 25.3%, respectively). Serious TEAEs and discontinuation rates were balanced between groups in both studies. In study SPD489-325, the most frequently reported events (occurring in > 10% of patients in any treatment arm) included decreased appetite, headache, weight decrease, insomnia, anorexia, nasopharyngitis and vomiting. The most frequently reported TEAE thought to be related to LDX was decreased appetite. In the randomised withdrawal period of study SPD489-326, nasopharyngitis, headache and upper abdominal pain were reported in > 5% of subjects that received LDX[1].

3.3 AWTTC critique

- The company submission included a comparison of LDX and atomoxetine; they did not consider a comparison to dexamfetamine appropriate. As justification for this, they noted that dexamfetamine is licensed for the treatment of children with refractory hyperkinetic states under the supervision of a physician specialising in child psychiatry, and referred to NICE CG72, which states that dexamfetamine should be considered in children and young people whose ADHD is unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine[1,3,11]. The company states that the licensed indication for LDX (i.e. for the treatment of ADHD when response to previous methylphenidate treatment is considered clinically inadequate) places it alongside atomoxetine in the treatment pathway[1]. It is unclear whether this will be reflected in clinical practice.

- LDX is currently considered a schedule 2 controlled drug[12] until reviewed by the Advisory Council on the Misuse of Drugs. As a prodrug, LDX undergoes gradual bioconversion to dexamfetamine in red blood cells. Time to reach peak plasma concentrations of LDX occurs several hours after administration and, overall, produces smaller peak plasma concentrations than immediate-release dexamfetamine[1]. The Medicines and Healthcare Products Regulatory Agency (MHRA) concluded that due to this, the abuse potential of LDX is likely to be lower than that of dexamfetamine[13]. Atomoxetine is not a controlled substance; the abuse potential of LDX versus atomoxetine has not been investigated.
- Only study SPD489-317 included patients with a history of clinically inadequate response to methylphenidate. However, patients were excluded from this study if they had more than one treatment course of methylphenidate[1]; therefore, applicability to clinical practice is uncertain.
- For children unable to swallow oral dosage forms, LDX capsule contents can be dissolved in water and administered as a solution; by contrast, the atomoxetine SPC states that capsules are not intended to be opened[2,10].
- At the time of licensing, the MHRA stated that, in general, the safety profile for LDX is in line with expectations, based on long clinical experience with dexamfetamine for the treatment of children and adolescents with ADHD. No new safety concerns were identified[13].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submitted a cost–utility analysis comparing LDX to atomoxetine as part of a comprehensive treatment programme for ADHD in children aged six years and over when response to previous methylphenidate treatment was considered clinically inadequate[1]. The analysis uses a decision analytical model to estimate the total cost (drug acquisition, monitoring and treatment programmes), total quality-adjusted life-years (QALYs) and the incremental cost-effectiveness ratio (ICER) for LDX compared to atomoxetine. An NHS perspective is adopted, with the base case having a one-year time horizon.

The modelled response rates among all patients are taken from day 28 measurements in study SPD489-317[1]. This randomised controlled trial was conducted in 51 centres across nine countries (Europe, US and Canada; none were in the UK). A responder was defined as a child gaining a score of 1 (much improved) or 2 (improved) on the CGI-I scale. In the base case, non-responders are assumed to discontinue pharmacotherapy. Response rate was 77.8% for LDX and 60.6% for atomoxetine. Data on those stopping treatment due to adverse events came from week 9 of the trial, with 6.3% ceasing treatment with LDX and 7.5% for atomoxetine. In the model, no treatment effect, costs or utility decrements were attributed to adverse events. These were assumed to occur within 14 days of commencing treatment and resolve when the treatment ceased at 14 days. Medicines usage has also been derived from study SPD489-317, with medication costs provided by the applicant company for LDX and the British National Formulary (BNF) for atomoxetine. [Commercial in confidence data removed] The findings from a survey of 21 specialist clinicians (one practising in Wales) have been used to estimate the resources required to manage responders and non-responders. National quality assured datasets have been used to provide unit costs.

A literature search found six studies reporting utility values. The utility values in the base case were reported to be 0.837 for responders and 0.773 for non-responders or those experiencing an adverse event. These are based on a study of 151 patients with

ADHD in the UK, which uses the EQ-5D tool to elicit preferences, with parents completing the form in consultation with their children[14].

4.1.2 Results

Results of the base case analyses are summarised in Table 1. LDX treatment is estimated to cost £215 per patient per year more than atomoxetine but reduces the costs of managing ADHD by £160 (net cost £55). It is estimated to generate an additional 0.0104 QALYs, giving an incremental cost per QALY of £5,276.

Table 1. Results of the base case analysis.

Base case (per patient)	LDX	Atomoxetine	Difference	Plausibility
Acquisition costs	£689	£474	£215	Further titration of atomoxetine may reduce price difference.
Cost of administrating and monitoring treatment of ADHD	£1,380	£1,540	−£160	Assumes all patients seen by consultant at all visits; if seen by registrar, cost difference much narrower.
Total costs	£2,069	£2,014	£55	Difference may be smaller depending on medical grade
Total QALYs	0.8179	0.8075	0.0104	Values used in base case were not from study SPD489-317, but from published UK study.
ICER (£/QALY gained)	**£5,276**			
ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year				

Probabilistic sensitivity analysis indicates that at cost-effectiveness thresholds of £20,000–£30,000 per QALY, LDX is cost-effective compared to atomoxetine in 77% and 80% of iterations, respectively. The results of sensitivity and scenario analyses are summarised in Table 2. These indicate the model was most sensitive to utility estimates, resource use and costs to manage patients with ADHD. In all cases, the ICER remained below £20,000 per QALY gained. The lowest ICER in the multiway analysis, £619 per QALY gained, occurs when medical costs to manage patients with ADHD are increased by 30%. One scenario includes the use of dexamfetamine after atomoxetine, compared to atomoxetine after LDX in the treatment pathway. This sequence had an ICER of £7,890 per QALY gained.

Table 2. Sensitivity and scenario analyses presented by the company.

Sensitivity analysis and scenarios	ICER (£/QALY gained)	Plausibility
Efficacy using 95% confidence interval for responses to CGI-I scores for LDX and atomoxetine	£2,580–£12,644	Concern is with use of 28-day visit scores rather than those observed at end of trial; adopting 95% CI results does not address this.
Withdrawal due to TEAE using mean + SE for LDX and atomoxetine	£4,841–£5,789	Based on randomised controlled trial evidence.
Utility ranges for responders and non-responders using mean + SE	£3,278 to £13,506	Plausible.
30% change in cost to manage responders and non-responders	LDX dominates if 30% higher cost for non-responders to £15,024	Base case cost difference between responder and non-responder may be overstated; impact not measured by this analysis.
Time horizon extended to five-years	£5,310	Implausible that efficacy at 28 days will apply at year five; i.e. different efficacy at end of study.
Response to treatment measured using ADHD-RS-IV	£6,135	Different measure of benefit but similar magnitude.
Utility weights using HUI-2 data from SPD489-317 (0.926 responder and 0.905 non-responder)	£16,079	The utility values obtained in the randomised controlled trial using the HUI-2 measure of QoL have higher absolute values and narrower differences than the utility values reported in the base case.
Resource use from survey in 2006	£11,462	It is uncertain whether resources used in the base case apply to Welsh setting.
Medical costs associated with managing patients with ADHD increased by 30%	£619	As above.
Treatment sequence: LDX, atomoxetine, no treatment, compared to: atomoxetine, dexamfetamine, no treatment	£7,890	The sequence atomoxetine, LDX, dexamfetamine, using the cheaper, long-acting drug atomoxetine before LDX but after methylphenidate has not been tested as an alternative. This may be because company is making the case for LDX second-line after methylphenidate. This sequence may be more cost-effective than LDX, atomoxetine and no treatment.
HUI-2: Health Utilities Index Mark 2; SE: standard error; QoL: quality of life		

4.1.3 AWTTC critique

The company submission presented no evidence of comparative cost-effectiveness versus dexamfetamine. The choice of comparator was justified by the company based on NICE CG72 (see section 3.2)[3].

The model had two decision points. At day 14, those intolerant to the medication were assumed to discontinue, and at 28 days, the efficacy rates observed in SPD489-317 for responders and non-responders were applied to the remaining cohort for the next 11 months. Thus responders remained responders for one year and likewise non-responders remained non-responders. However, a response (defined as one reported score of a 'very much improved' or 'much improved' score in the CGI-I value from baseline) was not always maintained. [Commercial in confidence data removed]

An alternative sequence of possible clinical relevance that is not modelled is the treatment pathway of atomoxetine, LDX and dexamfetamine compared to LDX, atomoxetine and dexamfetamine. This would use the slightly cheaper medicine (at least at lower doses) first with those not responding switching to LDX and then to dexamfetamine.

Strengths of the economic evidence include:

- The economic model used efficacy data from the appropriate trial and included the correct population and clinical outcome. A sensitivity analysis was available using an alternative outcome.
- The company conducted its own survey of resources used to manage responders and non-responders in 2012, and the results were compared to those obtained in 2006.
- The time horizon of one year was similar to that adopted in other models for ADHD, including a systematic review and economic model conducted by the NHS R&D HTA Programme for NICE[15]. An attempt was made to extend it to five years, recognising that the disorder would continue beyond 12 months, but this was hampered by data limitations.
- The approach to modelling medicine costs was consistent with that used in the aforementioned systematic review and economic model[15]. The results were conservative (favouring the atomoxetine arm marginally) compared to an alternative approach of costing the actual doses for each medicine reported at nine weeks.
- Extensive one-way sensitivity analyses were provided, with acceptable justifications for the ranges selected.

Limitations of the economic evidence include:

- The clinical data came from day 28 of a nine-week trial; the rates were higher than the sustained response rates.
- Only atomoxetine was included as a comparator but dexamfetamine may be an alternative in certain clinical settings.
- There are no long-term data regarding response or discontinuation rates beyond the period observed in study SPD489-317.
- No UK centres were included in the trial, giving rise to potential concerns about generalisability, particularly whether patients in Wales have a similar disease severity to participants in the trial.
- The utility values in the base case were not from study SPD489-317, but used the values adopted in the systematic review and economic model conducted by the NHS R&D HTA Programme[15]. The clinical trial used the Health Utilities Index (HUI), whilst the values used in the NHS R&D model were derived from a study using EQ-5D. Both HUI and EQ-5D are measures of health-related quality of life. HUI has nine dimensions and three to six states for each dimension, whilst EQ-5D has five dimensions and three or five states for each. The results were somewhat different. The HUI scores were 0.926 for responders and 0.905 for non-responders: a gain of 0.021. By comparison, the EQ-5D-derived scores were 0.837 for responders and 0.773 for non-responders: a gain of 0.064.
- Discontinuation due to adverse events is assumed to have the same impact on resource use and quality of life as discontinuation due to poor response.
- The company noted that guidelines and clinical reviews state that a period of four to eight weeks may be required to assess whether patients will respond to atomoxetine. The trial only allowed a four-week titration, with fixed medication thereafter. This may have introduced a bias favouring LDX[1].
- Medication costs are based on mean doses during the five-week maintenance period as well as the doses during four-week titration. However, efficacy is

measured at week 4, when mean doses were lower than during the maintenance period.

- Study SPD489-317 only recruited children with parents/guardians that could supervise the single morning dose; adherence is likely to be poorer in practice.
- The costs assumed all visits to psychiatrists and paediatricians were consultant-led; however, in practice, some patients may be seen by a registrar. The sensitivity of the results to this scenario is tested by substituting a revised unit cost per visit into the model. The unit cost is derived by assuming a cost per registrar of £58 per hour[16], 20 minute appointments and on-costs of 100% of staff costs, giving a cost per visit of £38.67, compared to £228.87 and £166.01 for visits to a psychiatrist and paediatrician, respectively. The additional costs of managing a non-responder compared to a responder fall from £1,000 in the base case to £259. The ICER adopting these values increases to £16,784. In practice, at least one appointment is likely to be consultant-led, thereby reducing the ICER somewhat.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published economic evidence on the cost-effectiveness of LDX in patients with ADHD who have failed treatment with methylphenidates.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company applied annual prevalence and incidence rates of pharmacologically treated ADHD to Welsh population statistics to estimate numbers receiving medication for ADHD. The prevalence data came from a study by McCarthy et al[17]. This used prescription data from 'The Health Improvement Network' (coverage 5.7% of UK population served by GPs) to identify all patients aged over six years with a diagnosis of ADHD/hyperkinetic disorder and a prescription for methylphenidate, dexamfetamine or atomoxetine. Reported prevalence in 2008 was 9.18 per 1,000 in patients aged 6–12 years and 7.40 per 1,000 in those aged 13–17 years, equivalent to 3,532 children and adolescents.

In an evaluation of current treatment patterns among children with ADHD in six countries in Western Europe including the UK, 32% of all physicians reported being 'very satisfied' with their patients' current treatment[18]. The company assumed the remaining 68% (2,402 patients) each year may be eligible for treatment with LDX. Of these, 14% (336 patients) were assumed to be currently treated with atomoxetine. This was based on data from Mitra et al, who reported that 13.6% of prescriptions were for atomoxetine[18]. Of these 336 patients, the company forecast a market share of 11% in year 1 (37 patients), rising to 61% (205 patients) at year 5.

The costs for the two medicines were assumed to be equivalent at £2.45 per day for LDX 50 mg and £2.46 for atomoxetine 40 mg. It was also assumed that 10% of atomoxetine patients would take two 18 mg capsules a day and 90% take one 40 mg capsule a day[19].

5.1.2 Results

The company assumed the budget impact was neutral, as the cost of atomoxetine is equivalent to the cost of LDX. There is also no net increase in the overall market. The company assumed the number of newly diagnosed patients will be roughly equivalent to the number of adolescents turning 18 years and discontinuing treatment.

No additional health or personal service resources were assumed to be required or released as a result of the introduction of LDX. The company-reported costs associated with use of LDX are presented in Table 3.

Table 3. Company-reported costs associated with use of LDX for the treatment of ADHD.

	Year 1 (2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)
Number of patients eligible for LDX	2,402	2,402	2,402	2,402	2402
Number of patients currently receiving atomoxetine	336	336	336	336	336
Uptake (%)	11% (of 336)	24% (of 336)	39% (of 336)	56% (of 336)	61% (of 336)
Treated patients	37	81	131	188	205
Overall net cost	0	0	0	0	0

5.1.3 AWTTC critique

- Prevalence rates are from 2008 and may understate current rates[17]. Applying these rates to 2012 population data gives a 1% lower estimate of the numbers prescribed relevant medication (3,490). Mitra et al reported that physicians identified 21% of patients as 'very good' responders and 52% as 'good' responders to methylphenidates[18]. If the remaining 27% are assumed to switch to second-line, the total number of eligible patients falls from 2,402 to 942. If one assumes 13.6% of all prescriptions are for atomoxetine, consistent with Mitra et al[18], then the market share of that medicine is 475 patients (13.6% of 3,490), somewhat higher than the company estimate of 336 (the company applied 14% to the smaller group of potential switchers). Applying the company's market share forecast of 11% rising to 61% suggests a slightly larger potential market of 52 in 2013, rising to 290 by 2017.
- If one assumes the doses for atomoxetine are those recorded in the clinical study at week 8, the daily cost is £2.28, not £2.46. This is a slight premium on the daily price of £2.23 for doses up to and including 60 mg, reflecting the fact that some patients were prescribed the higher and more expensive doses.
- The company has advised that Welsh clinicians routinely divide a 40 mg dose of atomoxetine into two 18 mg tablets at double the cost to reduce side effects or to deliver a precise dose that cannot be otherwise achieved. This is consistent with the SPC[10].
- Using the 40 mg only dose for LDX is likely to underestimate the mean cost per patient. In study SPD489-317, by week 8, 40% of patients were prescribed LDX 70 mg; the mean daily cost was £2.56. Assuming a mean cost per patient per day of £2.46 for atomoxetine and £2.56 for LDX gives a premium to prescribing LDX of £0.10 per patient day or £36.50 per year. With 52 patients in 2013, the premium is estimated at £1,898, rising to £10,585 in 2017 with 290 patients.

5.2 Table of comparative unit costs

Table 4. Example acquisition costs for ADHD treatments.

Treatment	Example regimen*	Approximate costs per patient per year†
LDX (Elvanse®▼) 30 mg, 50 mg and 70 mg capsules	30–70 mg once-daily	£760–£1,084
Atomoxetine (Strattera®) 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg or 100 mg hard capsules	10–100 mg once-daily	£814–£1,086
Dexamfetamine sulfate (non-proprietary) 5 mg tablets	5–20 mg daily (in 2–4 divided doses)	£246–£986
* Not all regimens may be licensed specifically for the indication under consideration. See relevant SPCs for full licensed indications and dosing details[2,10,11]. † Costs are based on BNF list prices as of 25 July 2013[12]. Costs of administration are not included. This table does not imply therapeutic equivalence of drugs or the stated doses.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, lisdexamfetamine dimesylate (Elvanse®▼) may be appropriate for prescribing within NHS Wales for the indication under consideration with a shared care agreement.

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

6.2 Ongoing studies

The company highlighted one ongoing study relevant to the indication under consideration: SPD489-404 is a phase IV, long-term (two-year), open-label study that includes patients continuing from the EU registration studies SPD489-325, SPD489-326 and SPD489-317. The company stated that results are not expected for at least another 12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 11 June 2013
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[20].

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:

- **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[21,22]?

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