

Attention deficit hyperactivity disorder in children and young people: lisdexamfetamine dimesylate

Evidence summary

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[nice.org.uk/guidance/esnm19](https://www.nice.org.uk/guidance/esnm19)

Key points from the evidence

The content of this evidence summary was up-to-date in May 2013. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#), [BNF for children \(BNFc\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

Limited evidence from 1 RCT suggests that lisdexamfetamine dimesylate produces clinically meaningful benefits in ADHD symptoms compared with placebo. The adverse effect profile appears similar to other stimulant drugs, although theoretical advantages in terms of improved adherence and reduced abuse potential require further evaluation in clinical practice.

<p>Effectiveness</p> <ul style="list-style-type: none"> • 1 European, 7-week RCT in around 300 children/young people aged 6–17 • Both lisdexamfetamine and methylphenidate provided clinically meaningful and statistically significant benefits compared with placebo in controlling symptoms of ADHD (measured using a validated and widely used rating scale - the ADHD RS IV) • No fully published randomised controlled trials directly comparing lisdexamfetamine dimesylate with other drugs licensed for treating ADHD 	<p>Safety</p> <ul style="list-style-type: none"> • Similar to the safety profile of other stimulant agents. Cardiovascular and metabolic effects require monitoring
<p>Patient factors</p> <ul style="list-style-type: none"> • Less well tolerated than methylphenidate (treatment discontinuations ~5% vs 2%) • Monitoring requirements similar to other stimulant medications (cardiovascular height, weight and appetite) • Potential improved adherence and reduced abuse potential require further evaluation in practice • Proposed schedule 2 controlled drug - to be confirmed 	<p>Cost</p> <ul style="list-style-type: none"> • Around £750 to £1100 per year at licensed doses (greater than dexamfetamine and methylphenidate, less than atomoxetine)

Key points

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

Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults (NICE guideline CG72, published in 2008) recommends that drug treatment for children and young people with ADHD should always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice/interventions. It also recommends

that when drug treatment of ADHD is considered appropriate, methylphenidate, atomoxetine and dexamfetamine are suitable options within their licensed indications. The decision regarding which product to use should be based on specific criteria listed in the guideline (such as the presence of comorbid conditions).

This evidence summary is based on a European, 7-week, randomised controlled trial that compared lisdexamfetamine dimesylate with placebo in children and young people aged 6 to 17 years, who had a diagnosis of moderate ADHD. It found that, compared with placebo, lisdexamfetamine dimesylate treatment resulted in statistically significantly greater improvements in the symptoms of ADHD as measured using the ADHD rating scale version IV (ADHD-RS-IV, the primary outcome) and the clinician-rated global impression of improvement. The changes compared with placebo (around 50% decrease in score) were also considered to be clinically meaningful (25–30% decrease in score). A modified-release methylphenidate reference arm in the trial showed similar results to the lisdexamfetamine dimesylate treatment arm when both drugs were compared with placebo, but there was no direct comparison between the 2 active treatments. At the time of publication, there are no fully published randomised controlled trials that directly compare lisdexamfetamine dimesylate with other drugs licensed for treating ADHD.

Treatment-emergent adverse events leading to discontinuation of lisdexamfetamine dimesylate were vomiting, anorexia, decreased appetite, tachycardia, decreased weight and insomnia. Lisdexamfetamine dimesylate and modified-release methylphenidate were both associated with modest increases in mean pulse rate, heart rate, systolic blood pressure and diastolic blood pressure, and decreases in mean body weight from baseline to end point.

Local decision makers will need to consider the place of lisdexamfetamine dimesylate alongside the use of other treatments for ADHD, in the context of the evidence available. There is a greater drug acquisition cost associated with the use of lisdexamfetamine dimesylate compared with dexamfetamine. The NICE guideline on [ADHD](#) states that if there is a choice of more than 1 appropriate drug, the product with the lowest cost (taking into account the cost per dose and number of daily doses) should be prescribed. If its status as a controlled drug under Schedule 2 of the Misuse of Drugs Regulations (2001) is confirmed, this may also influence local decision making.

Key evidence

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

Update

The following information has become available since this ESNM was produced.

September 2015: Availability of lisdexamfetamine for attention deficit hyperactivity disorder (ADHD) in adults

Lisdexamfetamine for ADHD in adults has been launched in the UK as [Elvanse Adult](#). The cost of Elvanse Adult (excluding VAT) is £58.24 for 28×30 mg, £68.60 for 28×50 mg and £83.16 for 28×70 mg capsules. Costs taken from [MIMS](#), September 2015.

June 2014: Amendments to The Misuse of Drugs Act 1971 affecting Tramadol, Zaleplon, Zopiclone and Lisdexamfetamine

On 10 June 2014 [amendments](#) to the Misuse of Drugs Act 1971 came into force. These amendments include specification changes for tramadol hydrochloride, zaleplon, zopiclone and lisdexamfetamine. All of these drugs were previously specified as prescription only medicines and are now specified as controlled drugs. The amendments to legislation were recommended to protect the public from the harms associated with misuse of these drugs. In addition the changes bring the specifications of these drugs in line with those of drugs of a similar structure.

Lisdexamfetamine:

- is now controlled as a Class B drug under the Misuse of Drugs Act 1971
- is now listed under Schedule 2 of the Misuse of Drugs Regulations 2001
- is now subject to regulations for its possession, supply, manufacture, import and export.

These amendments were summarised in a [medicines evidence commentary](#).

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

Relevance to NICE guidance programmes

Lisdexamfetamine dimesylate was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.

Introduction

Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults (NICE guideline CG72, published in 2008) describes ADHD as a heterogeneous behavioural syndrome characterised by the core symptoms of hyperactivity, impulsivity and inattention. Although these symptoms tend to cluster together, some people are predominantly hyperactive and impulsive, whereas others are principally inattentive. Children with ADHD are also at increased risk of comorbidities; common conditions are oppositional defiant disorder (50% of paediatric cases with ADHD), conduct disorder (35%), anxiety disorder (33%), and depression (33%) (Punja et al. 2012).

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

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

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

Using DSM-IV criteria, ADHD is thought to affect about 3–9% of school-age children and young people in the UK. Based on the narrower criteria of ICD-10, hyperkinetic disorder is estimated to occur in about 1–2% of children and young people in the UK (see the NICE guideline on [ADHD](#)).

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

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

Product overview

Drug action

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

The manufacturer claims that the pro-drug formulation of lisdexamfetamine dimesylate is substantially resistant to commonly available chemical and enzymatic hydrolysis techniques outside the body, making it difficult to tamper with for rapid drug effects (Shire Pharmaceuticals Limited: personal communication October 2013). However, stimulants should be prescribed cautiously to people with a history of substance abuse or dependence. See also information on [safety](#) in the Evidence review section.

Licensed therapeutic indication

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

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

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

Course and cost

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

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

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

Table 1 Cost of lisdexamfetamine dimesylate([MIMS online](#); accessed 08 April 2013; subscription required)

Formulation	Dosage	Cost per 28 days	Cost per year
30 mg capsules	30 mg once daily	£58.24	£759.20
50 mg capsules	50 mg once daily	£68.60	£894.25
70 mg capsules	70 mg once daily	£83.16	£1084.05

Evidence review

This evidence review is based on a published, European, 7-week, phase III trial of lisdexamfetamine dimesylate in children and young people with attention deficit hyperactivity disorder (ADHD; [Coghill et al. 2013](#); see table 2).

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

Study: [Coghill et al. \(2013\)](#)

- Design: 7-week, double-[blind](#) randomised controlled trial in 48 centres in 10 European countries (Germany, Sweden, Spain, Hungary, France, the UK, Italy, Belgium, Poland and the Netherlands).
- Population: children aged 6–12 years and young people aged 13–17 years who met the DSM-IV-Text Revision (DSM-IV-TR) criteria for a primary diagnosis of ADHD. Participants had ADHD of at least moderate severity, defined by a baseline ADHD rating scale version IV (ADHD-RS-IV) total score of 28 or higher. Children and young people were excluded if their current ADHD medication provided effective control of symptoms with acceptable tolerability. Exclusion criteria also included those who had a comorbid psychiatric diagnosis with significant symptoms, or a conduct disorder (excluding oppositional defiant disorder).

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

Table 2 Summary of the trial: [Coghill et al. \(2013\)](#)

	Placebo	Lisdexamfetamine dimesylate	Modified-release methylphenidate	Analysis
Randomised	n=111	n=113	n=112	
Efficacy: full analysis set ^a	n=106	n=104	n=107	
Proportion of participants who completed the trial	38% (42/111)	71% (80/113)	66% (74/112)	

Primary outcome: least squares mean change from baseline in ADHD-RS-IV score ^b after 7 weeks' treatment (\pm standard deviation)	-5.7 \pm 1.1	-24.3 \pm 1.2	-18.7 \pm 1.1	Mean difference LDX vs. placebo: -18.6 (95% CI -21.5 to -15.7), $p < 0.001$ Effect size 1.80 ^c Difference MPH vs. placebo: -13.0 (95% CI -15.9 to -10.2), $p < 0.001$ Effect size 1.26 ^c
Selected secondary outcomes:				
Proportion of participants with CGI-I rating ^d 'very much improved' or 'much improved' after 7 weeks' treatment (95% CI)	14% (8 to 21)	78% (70 to 86)	61% (51 to 70)	$p < 0.001$ for LDX vs. placebo $p < 0.001$ for MPH vs. placebo

ADHD-RS-IV hyperactivity/impulsivity subscale, change vs. placebo after 7 weeks' treatment (95% CI)		-8.7 (-10.3 to -7.2)	-6.0 (-7.5 to -4.5)	LDX vs. placebo: p<0.001 Effect size 1.60 MPH vs. placebo: p<0.001 Effect size 1.11
ADHD-RS-IV inattention subscale, change vs. placebo (95% CI)		-9.9 (-11.5 to -8.3)	-7.0 (-8.6 to -5.4)	LDX vs. placebo: p<0.001 Effect size 1.72 MPH vs. placebo: p<0.001 Effect size 1.22
Safety population ^e	n=110	n=111	n=111	
% participants with serious treatment-emergent adverse events	2.7% (3/110)	2.7% (3/111)	1.8% (2/111)	p value not reported
% participants with treatment-emergent adverse events	57.3% (63/110)	72.1% (80/111)	64.9% (72/111)	p value not reported
% participants with treatment-emergent adverse events leading to discontinuation	3.6% (4/110)	4.5% (5/111)	1.8% (2/111)	p value not reported

Abbreviations: ADHD-RS-IV, attention deficit hyperactivity disorder rating scale version IV; CI, confidence interval; CGI-I, Clinical Global Impressions-Improvement; LDX, lisdexamfetamine dimesylate; MPH, modified-release methylphenidate.

^a All participants who were randomised and took at least 1 dose of study drug.

^b ADHD-RS-IV 18-item rating scale of ADHD symptoms. Each item scored on a 4-point: scale from 0 (no symptoms) to 3 (severe symptoms); total possible score ranging from 0 to 54.

^c Effect sizes were based on the difference (active drug–placebo) in least squares mean change in ADHD-RS-IV total score from baseline to end point.

^d CGI-I: 7-point global measure of clinical and functional improvement ranging from 1 (very much improved) to 7 (very much worse).

^e All participants who took 1 dose of any study drug.

Clinical effectiveness

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

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

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

Safety

Rates of adverse events leading to discontinuation of the study drug were around 5%.

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

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

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

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

Evidence strengths and limitations

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

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

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

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

Context

Treatment alternatives

The NICE guideline on [attention deficit hyperactivity disorder \(ADHD\)](#) recommends that drug treatment for children and young people with ADHD should always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions. When drug treatment is considered appropriate, methylphenidate, atomoxetine and dexamfetamine are recommended, within their licensed indications, as options for the

management of ADHD in children and young people (see [Estimated impact for the NHS](#) for more details). The need to continue drug treatment for ADHD should be reviewed at least annually.

Costs of treatment alternatives

	Usual licensed daily dose range ^a	Annual cost range ^b
Lisdexamfetamine dimesylate capsules (Elvanse)	30 mg to 70 mg	£759.20 to £1084.05
Atomoxetine capsules (Strattera)	10 mg to 80 mg for weight up to 70 kg ^c 40 mg to 100 mg for weight over 70 kg	£814.21 to £1628.42 £814.21 to £1628.42
Dexamfetamine tablets (generic) ^d	5 mg to 20 mg (According to the BNF, 40 mg daily has been required in some children)	£246.38 to £985.50 (£1971.00)
Methylphenidate tablets (generic) ^d	5 mg to usual maximum of 60 mg	£36.87 to £398.58
Methylphenidate modified release tablets (Concerta XL)	18 mg to 54 mg	£379.48 to £895.71

For the purposes of this evidence summary, licensed doses are quoted. We are aware that for some people higher 'unlicensed' doses are prescribed under the direction of a specialist.

^a Doses taken from the relevant [summary of product characteristics](#); therapeutic equivalence is not implied.

^b Costs taken from the [Drug Tariff March 2013](#).

^c Based on a starting dose of 0.5 mg/kg/day and a usual maintenance dose of approximately 1.2 mg/kg/day.

^d Doses taken from the [British national formulary \(BNF\) April 2013](#).

Estimated impact for the NHS

Likely place in therapy

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

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

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

- the presence of comorbid conditions (for example, tic disorders, Tourette's syndrome, epilepsy)
- the different adverse effects of the drugs
- specific issues regarding compliance identified for the individual child or adolescent, for example problems created by the need to administer a mid-day treatment dose at school
- the potential for drug diversion (where the medication is forwarded on to others for non-prescription uses) and/or misuse
- the preferences of the child/adolescent and/or his or her parent or guardian.

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

- methylphenidate for ADHD without significant comorbidity
- methylphenidate for ADHD with comorbid conduct disorder

- methylphenidate or atomoxetine when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present
- atomoxetine if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses of methylphenidate.

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

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

Local decision makers will need to consider the place of lisdexamfetamine dimesylate alongside the use of other treatments for ADHD, in the context of the evidence available. There is a greater drug acquisition cost associated with the use of lisdexamfetamine dimesylate compared with dexamfetamine. Theoretical benefits such as increased adherence and decreased abuse potential, require confirmation in longer-term studies and evaluation of clinical experience. The NICE guideline on [ADHD](#) states that if there is a choice of more than 1 appropriate drug, the product with the lowest cost (taking into account the cost per dose and number of daily doses) should be prescribed.

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

Estimated usage

According to the manufacturer, there are about 116 children and young people aged 6–17 years being treated for ADHD per 100,000 of the UK population. The manufacturer's cumulative estimated uptake of lisdexamfetamine dimesylate is 3 patients per 100,000 in the first year, 7 patients per 100,000 in the second year and 13 patients per 100,000 in the third year (Shire Pharmaceuticals Limited: personal communication January 2013).

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About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

For information about the process used to develop this evidence summary, see [evidence summaries: new medicines – interim process statement](#).

Changes after publication

September 2015: Minor maintenance.

November 2014: Minor maintenance.

June 2014: Amendments to the Misuse of Drugs Act 1971 came into force on 10 June 2014, which include specification changes for lisdexamfetamine dimesylate. For details, see our [medicines evidence commentary](#).

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