# New drugs

## Lisdexamfetamine

**Approved indication: attention deficit hyperactivity disorder**

**Vyvanse (Shire)**

**30 mg, 50 mg and 70 mg capsules**

**Australian Medicines Handbook section 18.5**

When attention deficit hyperactivity disorder (ADHD) requires drug therapy as part of its management, dexamphetamine is one of the treatment options.[1] Lisdexamfetamine is a prodrug of dexamphetamine.

After the daily morning dose, lisdexamfetamine is rapidly absorbed from the gut. It is converted to active dexamphetamine by hydrolysis in the blood. Peak concentrations of dexamphetamine occur 3.5 hours after the dose. Only 2% of the dose is excreted as unchanged lisdexamfetamine in the urine. The half-life of the dexamphetamine produced is approximately 10 hours.

In a phase II study 52 children with ADHD took lisdexamfetamine, extended-release amphetamine or placebo. For part of the study they took each treatment for a week then swapped over so that they all had a week of each treatment. The children's symptoms were judged to be significantly better with the active treatments than with placebo on a rating scale of classroom behaviour.[2]

A phase III study randomised 290 children aged 6–12 years to take a placebo or lisdexamfetamine 30 mg, 50 mg or 70 mg. Although the trial was for four weeks, the dose had to be titrated so the children taking 50 mg or 70 mg had a shorter duration of treatment at those doses. All three doses had a significantly greater effect than placebo on a scale which rated the symptoms of ADHD. At least 70% of the children were judged to be much, or very much, improved by lisdexamfetamine compared with 18% of the placebo group.[3]

Lisdexamfetamine has also been studied in 314 adolescents with ADHD. These 13–17 year olds were randomised to take lisdexamfetamine 30 mg, 50 mg, 70 mg or a placebo for four weeks. Again dose titration meant that the adolescents randomised to receive 50 mg or 70 mg took those doses for less than four weeks. Active treatment had a significantly greater effect than placebo on rating scales of inattention, and of impulsivity and hyperactivity.[4]

Another placebo-controlled trial studied 336 children and adolescents (6–17 years old). Those randomised to take lisdexamfetamine started at 30 mg daily and increased the dose weekly up to 70 mg according to their response. After optimising the dose over four weeks there was a three-week maintenance phase. In another arm of the trial the patients were given an osmotic-release formulation of methylphenidate. After seven weeks both lisdexamfetamine and methylphenidate had improved the patients' symptoms significantly more than placebo. The investigators judged that 78% of the lisdexamfetamine group and 61% of the methylphenidate group were much, or very much, improved compared with 14% of the placebo group.[5]

The longer-term effectiveness of lisdexamfetamine was studied in an open-label trial involving 272 children aged 6–12 years. These children took lisdexamfetamine 30 mg, 50 mg or 70 mg for an average of 8.6 months. Compared to their scores on a rating scale at the start of the study, there was a significant improvement in the symptoms of ADHD. Almost 96% of the 139 children who persisted with treatment for 12 months were judged to have improved.[6]

Lisdexamfetamine has also been approved as part of a comprehensive treatment program for adults with ADHD. Similar to the trials in younger patients, a group of 420 adults (mean age approximately 35 years) was randomised to take lisdexamfetamine 30 mg, 50 mg or 70 mg, or placebo for four weeks. All three doses had a significantly greater effect than placebo on an adult ADHD rating scale.[7] A total of 349 patients from this study joined an open-label extension study. This showed that improvements were sustained for up to 12 months in most patients.[8]

Another trial looked at the maintenance of efficacy in 116 adults who had been taking lisdexamfetamine for at least six months. They were randomised, in a double-blind phase of the trial, to continue treatment or switch to a placebo. After six weeks 75% of the patients who took placebo had experienced a relapse of their symptoms compared with 9% of those who continued treatment.[9]

The adverse effects of lisdexamfetamine are similar to those of other stimulant drugs. These include decreased appetite and insomnia. Patients may also develop headaches, dry mouth and nausea. Children may complain of abdominal pain. It is important to check each person's cardiovascular, neurological and psychiatric history before prescribing any stimulant drug. A study of 281 children aged 6–13 years, who

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

took lisdexamfetamine for an average of 8.8 months, reported reduced growth. Height and weight did not increase as expected.[10]

Lisdexamfetamine should not be taken during pregnancy. As amphetamines are found in breast milk, it should not be used during lactation.

Although the main trials of lisdexamfetamine were relatively short, there is a lot of clinical experience with dexamphetamine. A once-daily dose will be useful for schoolchildren with ADHD, so lisdexamfetamine should be compared with controlled-release methylphenidate. Many children with ADHD also have other mental health problems,[1] however some trials of lisdexamfetamine excluded patients with certain psychiatric comorbidities.

[T][T][T] manufacturer provided clinical evaluation

## REFERENCES *

1. Tonge B. Principles for managing attention deficit hyperactivity disorder. Aust Prescr 2013;36:162-5.
2. Biederman J, Boellner SW, Childress A, Lopez FA, Krishnan S, Zhang Y. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry 2007;62:970-6.
3. Biederman J, Krishnan S, Zhang Y, McGough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. Clin Ther 2007;29:450-63.
4. Findling RL, Childress AC, Cutler AJ, Gasior M, Hamdani M, Ferreira-Cornwell MC, et al. Efficacy and safety of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2011;50:395-405.
5. Coghill D, Banaschewski T, Lecendreux M, Soutullo C, Johnson M, Zuddas A, et al. European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder. Eur Neuropsychopharmacol 2013 Jan 14. doi: 10.1016/j.euroneuro. 2012.11.012.
6. Findling RL, Childress AC, Krishnan S, McGough JJ. Long-term effectiveness and safety of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. CNS Spectr 2008;13:614-20.
7. Adler LA, Goodman DW, Kollins SH, Weisler RH, Krishnan S, Zhang Y, et al. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry 2008;69:1364-73.
8. Ginsberg L, Katic A, Adeyi B, Dirks B, Babcock T, Lasser R, et al. Long-term treatment outcomes with lisdexamfetamine dimesylate for adults with attention-deficit/hyperactivity disorder stratified by baseline severity. Curr Med Res Opin 2011;27:1097-107.
9. Brams M, Weisler R, Findling RL, Gasior M, Hamdani M, Ferreira-Cornwell MC, et al. Maintenance of efficacy of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: randomized withdrawal design. J Clin Psychiatry 2012;73:977-83.
10. Faraone SV, Spencer TJ, Kollins SH, Glatt SJ. Effects of lisdexamfetamine dimesylate treatment for ADHD on growth. J Am Acad Child Adolesc Psychiatry 2010;49:24-32.

*First published online 1 October 2013*
*Updated version published 22 October 2013*

The Transparency score ([T]) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).