CEDAC FINAL RECOMMENDATION

LISDEXAMFETAMINE DIMESYLATE
(Vyvanse – Shire Canada Inc.)
Indication: Attention Deficit Hyperactivity Disorder

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that lisdexamfetamine not be listed.

Reason for the Recommendation:
There is insufficient evidence that lisdexamfetamine offers a therapeutic advantage compared with less expensive alternatives.

Of Note:
The Committee considered whether or not lisdexamfetamine has less abuse potential compared with other agents. Based on evidence from three abuse liability studies comparing lisdexamfetamine with placebo or short acting agents and also considering post-marketing sources that there was insufficient evidence to support that abuse potential is less with lisdexamfetamine compared with other long acting agents.

Background:
Lisdexamfetamine is approved by Health Canada for the treatment of attention deficit hyperactivity disorder (ADHD) in children aged six to 12 years. It is a prodrug of dextroamphetamine. Following oral administration, lisdexamfetamine is rapidly absorbed in the gastrointestinal tract and converted to the active form, dextroamphetamine.

The recommended starting dose of lisdexamfetamine is 30 mg daily with titration to a maximum of 50 mg daily. It is available as 30 mg and 50 mg capsules.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) of lisdexamfetamine and a critique of the manufacturer's pharmacoeconomic evaluation. The manufacturer submitted a confidential price for lisdexamfetamine. Only trials that included active comparators were

included in the CDR systematic review as the efficacy of amphetamines compared with placebo is established in the treatment of ADHD.

Clinical Trials

The CDR systematic review included one double blind randomized controlled trial of patients with ADHD, Study 201 (N=50). Study 201 was a three-week cross-over trial that compared lisdexamfetamine with placebo and included extended-release (ER) mixed amphetamine salts as a reference group. No statistical comparisons were made between lisdexamfetamine and ER mixed amphetamine salts.

- In the open-label dose titration phase, all patients received ER mixed amphetamine salts starting at 10 mg per day, titrated upward by 10 mg each week to a maximum of 30 mg per day. After three weeks, patients with adequate response entered the double-blind randomized crossover period of the study where they received one week of ER mixed amphetamine salts, one week of lisdexamfetamine, and one week of placebo. There was no washout period between each week and no assessment of the potential carryover effect. The lisdexamfetamine dose was determined by the optimized dose of ER mixed amphetamine salts during the dose titration phase of the trial. At the end of each week, outcomes were evaluated in a laboratory classroom setting over a 13-hour day.
- All included patients had the combined subtype of ADHD and moderate to severe disease. Patients with significant psychiatric co-morbidities were excluded, limiting the external validity of the trial since co-morbidities are common in children with ADHD. The results of this trial also cannot be generalized to treatment-naïve patients as patients were required to have a history of successful treatment with a stable regimen of stimulant medication.

Outcomes

The primary outcome of Study 201 was the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) Deportment Scale (DS) score across a treatment day, which is designed to assess behaviour over relatively short periods of time (e.g., 45 minutes) in a laboratory classroom setting. Items on the SKAMP-DS are rated for the degree of impairment on a seven-point scale, where higher ratings are reflective of more impaired behaviour.

In addition, the Committee discussed other outcomes included in the CDR systematic review, including the following scales that measure short term behaviour and academic performance: the SKAMP Attention Scale (AS), the Permanent Product Measure of Performance–Attempted (PERMP-A) and Correct (PERMP-C) and the clinical global impression scale (CGI).
No minimal clinically important difference has been established for any of the measured scales.

Quality of life was not measured and the trial was too short to evaluate developmental outcomes or long-term academic achievement.

Results

Efficacy or Effectiveness

- Both lisdexamfetamine and ER mixed amphetamine salts were statistically significantly better than placebo in terms of SKAMP, PERMP and CGI scores and total withdrawals. The mean (standard deviation) estimates of SKAMP-DS at the end of the study were 0.8 (0.7), 0.8 (0.8) and 1.7 (1.2) for lisdexamfetamine, ER mixed amphetamine salts and placebo,

- respectively. No statistical comparisons were made between lisdexamfetamine and ER mixed amphetamine salts.

Harms (Safety and Tolerability)

- Adverse events during the double-blind phase of the trial appeared similar between lisdexamfetamine, ER mixed amphetamine salts, and placebo (16%, 18% and 15%, respectively). The validity of these results is limited because of the one week treatment periods and the small sample size.
- While the patients in Study 201 received lisdexamfetamine doses of 30 mg to 70 mg daily (50% received 70 mg daily), the maximum recommended daily dose in Canada is 50 mg. Adverse events were not reported separately for each dose.

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison table of treatments indicated for the management of ADHD in children aged six to 12 years. At recommended doses, obtained from product monographs, the daily cost of lisdexamfetamine at the confidential submitted price [redacted] to [redacted]) is similar to atomoxetine ($3.23 to $4.07) and short- and intermediate-acting dextroamphetamine formulations ($0.55 to $6.57), but is generally more expensive compared to long-acting methylphenidate preparations (Biphentin, $0.65 to $3.00; Concerta, $2.04 to $3.30), and mixed amphetamine salts ($2.24 to 3.31).

Other Discussion Points:

- Efficacy of amphetamines compared with placebo is established. A 2006 National Health Service (NHS) health technology assessment demonstrated that amphetamines are superior to placebo based on a number of outcomes including measures of inattention, hyperactivity, impulsivity, quality of life and adverse events.
- Consistent with the premise of the CDR systematic review, two double-blind randomized placebo-controlled trials, Study 301 (N=290) and Study 311 (N=129) have demonstrated that lisdexamfetamine is statistically superior to placebo across a range of outcomes including SKAMP, PERMP, ADHD-RS-IV, Conners Parent Rating Scale (CPRS) and CGI over durations ranging from two to four weeks. While limitations of the placebo-controlled trials were similar to those of Study 201, Study 301 had a more appropriate outcome assessment and Study 311 had more appropriate dosing.
- Lisdexamfetamine is the prodrug of dextroamphetamine, therefore, the Committee considered that a trial comparing lisdexamfetamine with dextroamphetamine would have been most appropriate.
- One long-term, open-label, uncontrolled study, Study 302, evaluated the effect of lisdexamfetamine in 272 children for up to one year. Improvements in ADHD-RS and CGI were noted compared with baseline; however, the data are limited by the lack of a control group and the highly select population consisting mainly of children from previous lisdexamfetamine trials.
- The pharmacokinetics of lisdexamfetamine were discussed. The Committee considered that more pharmacokinetic data in children would have been helpful to assess differences between lisdexamfetamine and other long-acting agents as well as differences in pharmacokinetic parameters between adult and pediatric patients (e.g., Cmax and AUC between fed and fasted states differed in children but not in adults).

- The Committee discussed that long acting amphetamine preparations can help manage dosing regimens in school-aged children as they avoid school time dosing, but they have the disadvantage of insomnia.
- Based on the placebo-controlled trials, the adverse event profile of lisdexamfetamine appears similar to other stimulants. Stimulants are associated with seizures, cardiac risks and abuse potential.
- In Study 301, which evaluated fixed doses of lisdexamfetamine, adverse events were reported by dose and there appeared to be a higher incidence of adverse events with the 70 mg dose compared with the 30 mg and 50 mg doses.
- The suggestion that lisdexamfetamine may have less abuse potential, because it is a prodrug of dextroamphetamine, was discussed and issues around potential diversion of amphetamines were noted. Evidence from three abuse liability studies in adults did not support claims that the abuse potential of this drug is less than that of other long acting amphetamines when evaluated against current Health Canada standards for the evaluation of drugs with central nervous system activity. Recent evidence from post-marketing sources indicates that, consistent with other amphetamines, lisdexamfetamine abuse has been reported in adolescent and adult populations.
- The Committee emphasized the importance of having quality of life data to assess the effects of long-acting stimulants and discussed that no quality of life data are available for lisdexamfetamine.

CEDAC Members Participating:
Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:
Dr. Lindsay Nicolle.

Conflicts of Interest:
One CEDAC member reported a conflict of interest and did not participate in the vote or the discussion of the drug.

About this Document:
CEDAC provides formulary listing recommendations to publicly funded drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. An overview of these reviews as well as a plain language version of this document are posted on the CADTH website when available.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

The CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.