Canadian Agency for Drugs and Technologies in Health
COMMON DRUG REVIEW

Canadian Expert Drug Advisory Committee
Summary of Discussion

Mixed Amphetamine Salts (Adderall XR — Shire Canada Inc.)
Indication — Attention-Deficit Hyperactivity Disorder

Canadian Expert Drug Advisory Committee (CEDAC) Members Participating

Dr. Braden Manns (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Michael Evans, Dr. Malcolm Man-Son-Hing, Dr. Laurie Mallery, Ms. Nancy McColl, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Robert Peterson, Dr. Dale Quest, Dr. Kelly Zarnke.

Regrets

Dr. Michael Evans (April 16, 2008), Dr. Lindsay Nicolle (June 18, 2008).

Conflicts of Interest

One CEDAC member declared a conflict of interest and did not participate in the discussion and vote.

Description of Drug

Adderall XR is a once-daily, oral, extended-release formulation of mixed amphetamine salts (a combination of short and long-acting dexamphetamine and levoamphetamine salts in a ratio of 3:1). Adderall XR is a stimulant that is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and to increase the release of these monoamines into the extraneuronal space.

History of Submission

CEDAC had previously reviewed Adderall XR for the treatment of attention-deficit hyperactivity disorder (ADHD) in children six to 12 years of age and recommended that it not be listed (see Notice of CEDAC Final Recommendation for Adderall XR issued on November 24, 2004). Adderall XR was resubmitted for review because in 2007, Health Canada approved a new indication — treatment of ADHD in adolescents (13 to 17 years of age) and adults (older than 18 years of age) — and also because new clinical trial information in children became available.

Discussion of Clinical and Pharmacoeconomic Reviews

In making its recommendation, the CEDAC considered a systematic review of published and unpublished clinical studies prepared by CDR, and a CDR review of a pharmacoeconomic evaluation, supplied by the manufacturer. Both reviews are based on information available up to the time that CEDAC made its recommendation. An overview of these reviews and the complete CEDAC Final Recommendation and Reasons for Recommendation (technical and plain

CEDAC Meeting — April 16, 2008; CEDAC Reconsideration — June 18, 2008
Notice of CEDAC Final Recommendation — June 25, 2008

language versions) are available in the CDR Drug Database on the CADTH website (www.cadth.ca).

The following is a summary of discussions regarding this drug at the CEDAC meetings held on April 16, 2008 and June 18, 2008.

Therapeutic Rationale or Need
ADHD is a lifelong condition that persists into adolescence and adulthood in the majority of cases. Most guidelines suggest that immediate release stimulants are first-line therapy for patients with ADHD. If a response is not achieved with one stimulant, another may be tried. The use of an extended release preparation reduces drug peaks and troughs that may cause adverse effects. As well, less frequent dosing is considered generally advantageous.

Clinical Trials
Children (six to 12 years of age): One systematic review of trials in children completed subsequent to the review by CEDAC in 2004 was considered along with the systematic review of two randomized double-blind superiority trials. One trial studied 215 children, with combined subtype ADHD and a history of response to stimulants, who were given either Adderall XR (forced dose escalation to a maximum recommended 30 mg daily) or atomoxetine (1.2 mg per kg daily) in a parallel group design for 18 days. The second trial studied 52 children who received Adderall XR (10 mg to 30 mg daily, optimized dosing), or placebo, or lisdexamfetamine for three weeks in a crossover trial. As lisdexamfetamine is not available in Canada, this arm was not considered by the Committee.

Adolescents (13 to 17 years of age) and Adults: While three randomized double-blind trials, with 617 participants of mixed ADHD subtypes and varying history of stimulant use, met eligibility criteria, the review focused on two trials. A crossover trial with driving performance as its outcome measure was of uncertain quality and thus was assessed separately. The two other trials were of parallel group design: one in adolescents and one in adults. Both trials investigated Adderall XR in varying dosages compared with placebo, for four weeks. Only the treatment arms using the recommended doses, ranging from 10 mg to 30 mg daily, were evaluated.

Comparators
In the child studies, the comparators were placebo in one study and atomoxetine in the other. In the adolescent/adult studies, placebo was the comparator. No other eligible studies using active comparators were found.

Outcomes
Children: The main outcome measure was the Swanson, Kotkin, Agler, M-Flynn, Pelham (SKAMP) rating scale that is used to assess behaviour (deportment and attention) over relatively short periods of time (e.g. 45 minutes) in a laboratory classroom setting, and assesses functioning specific to ADHD. It is a surrogate marker of efficacy in a highly controlled setting rather than the child's natural environment. Other measures included the Permanent Product Measure of Performance (PERMP) – 10 minute math test, and the Clinical Global Impression (CGI) scales. Quality of life was assessed in one study by the Pediatric Quality of Life inventory. There is no widely accepted definition of a clinically relevant response to treatment for ADHD. No studies were found that assess the correlation of SKAMP or PERMP with long-term academic achievement.

Adolescents and Adults: The main outcome measure was the clinician-administered Attention-Deficit Hyperactivity Disorder Rating Scale (ADHD-RS). It has adequate reliability and validity; however, factors such as socioeconomic status, ethnicity, urban or rural residence status, and education are not adequately addressed. Other outcome measures included the Conners' Adult ADHD Rating Scale (CAARS) and CGI scores. The original sample used to develop the CAARS did not attempt to obtain a representative sample of adults with respect to socioeconomic status or ethnicity. Quality of life in adults was measured by the Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

Efficacy or Effectiveness

Children: In both trials, behaviour, academic functioning, and overall clinical improvement were significantly better with Adderall XR compared with placebo or atomoxetine as measured by SKAMP, PERMP, and CGI. Parental assessment with the Conners' Global Index Scale, Parent's version, showed no difference in one study. There was no difference in quality of life in this same study.

Adolescents and Adults: There was a significant improvement compared with placebo in behavioural symptoms, as measured by ADHD-RS for both adults and adolescents, and as measured by CAARS for adults. There was a greater proportion of observer-rated clinical improvement in both populations. There was no significant difference in quality of life for adults.

Harms (Safety and Tolerability)

In children, there was no difference between Adderall XR and placebo in adverse events; however, adverse events occurred in statistically significantly more patients on Adderall XR compared with atomoxetine (85% versus 73%). Decreased appetite/anorexia and insomnia were the most frequently reported adverse events in the Adderall XR patients.

In adults and adolescents, 63% to 85% patients receiving Adderall XR versus 59% receiving placebo experienced adverse events and the difference was statistically significant for patients receiving Adderall XR 20 mg to 30 mg daily compared with placebo. Anorexia and insomnia were the most common adverse events. Decreases in weight were significantly greater with Adderall XR compared with placebo.

Cost and Pharmacoeconomic Evaluation

As first-line treatment, the manufacturer-submitted cost per quality-adjusted life year (QALY) of Adderall XR compared with methylphenidate immediate release varies from approximately $70,000 (adolescents) to $187,000 (adults), which was deemed not cost-effective. As second-line treatment, the cost per QALY of Adderall XR was approximately $19,000 compared with no treatment, regardless of age group. The limitations of the analysis include: use of an indirect comparison of trial data; consideration of societal outcomes based largely on assumptions; extrapolation of data to the 50-year time horizon; and no comparison to alternatives such as sustained release formulations of methylphenidate.

Other Discussion Points

- The manufacturer requested listing criteria for Adderall XR as second-line treatment for children (six to 12 years of age), adolescents (13 to 17 years of age), and adults when a trial of either immediate or sustained release methylphenidate or dexamphetamine does not

permit adequate control of symptoms. No trials evaluating this population were identified. CEDAC members felt that studying this patient population is feasible.
- The enrolment of patients with a history of responsiveness to stimulants may bias the results.
- The studies are of very short duration. Longer-term studies are required.
- The surrogate outcomes, especially under artificial conditions, cannot predict long-term functional outcomes. Furthermore, it is unclear what degree of change is clinically important in the behaviour scales.
- Data related to clinically relevant outcomes, including behavioural outcomes, and social, occupational and academic performance, are needed.
- The need for more quality of life outcomes was raised.
- Concerns about the cardiovascular adverse effects of the stimulant class were raised. The incidence of insomnia with Adderall XR and the potential need for medication to treat this adverse effect were discussed.
- The abuse potential of this class of drugs was discussed.
- The risks and benefits of long-acting agents, including the avoidance of school-time dosing, was discussed. Improved compliance and an associated benefit have not been addressed in the studies.
- The cost of this agent relative to other agents used in the treatment of ADHD, as well as the Patented Medicines Prices Review Board decision that the Adderall XR price is excessive, were discussed.

CEDAC Recommendation

CEDAC recommended that Adderall XR not be listed.

CEDAC Reasons for the Recommendation

- There is insufficient evidence that Adderall XR offers a therapeutic advantage over less expensive formulations of other stimulant agents such as methylphenidate and dexamphetamine.
- While Adderall XR has been shown to improve some clinical rating scales in children, adolescents and adults when compared with placebo in short-term (<4 week) trials, no long-term randomized trials have investigated whether this translates into improvement in clinically important outcomes such as quality of life, academic performance and behavioural outcomes.
- Adderall XR has not been shown to be cost-effective when used as first-line therapy. The Committee considered whether Adderall XR should be listed for patients who had not achieved adequate control of symptoms with a trial of methylphenidate or dexamphetamine. However, there is insufficient evidence from clinical trials that Adderall XR is effective, and therefore cost-effective, in this group of patients. Given the prevalence and importance of ADHD, the Committee felt that it would be important, feasible and ethical to conduct a trial in patients who have failed to respond to methylphenidate or dexamphetamine.

The Summary of CEDAC Discussion

This document contains a summary of the relevant discussion by CEDAC members in making the formulary listing recommendation for participating public drug plans regarding this drug. This summary is not a complete record of the proceedings of the CEDAC meeting at which the drug was considered.

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The manufacturer has reviewed this document and has not requested the deletion of any confidential information.