Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Overview of CDR Clinical and Pharmacoeconomic Reports

CDR

August 2009

Mixed Amphetamine Salts
Adderall XR® – Shire Canada Inc.

Indication – Attention-Deficit Hyperactivity Disorder

Supporting Informed Decisions

À l'appui des décisions éclairées

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This overview is a synopsis of the evidence-based reviews prepared by the Common Drug Review (CDR) Directorate at the Canadian Agency for Drugs and Technologies in Health (CADTH). The evidence-based reviews are used by CDR's Canadian Expert Drug Advisory Committee (CEDAC) in making formulary listing recommendations to participating public drug plans. The information in this overview should not be used as a substitute for clinical judgment in the care of a particular patient, nor is it intended to replace professional advice. CADTH is not liable for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

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Overview of CDR Clinical and Pharmacoeconomic Reports

Mixed Amphetamine Salts Extended-Release

Adderall XR — Shire Canada Inc.

Indication — Attention-Deficit Hyperactivity Disorder

August 2009

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LIST OF ABBREVIATIONS

ADHD	attention-deficit hyperactivity disorder
ADHD-RS	Attention-Deficit Hyperactivity Disorder Rating Scale
AE	adverse event
AMX	atomoxetine
CAARS-S-S	Conners' Adult ADHD Rating Scale – Short Version – Self Report
CGI-I	Clinical Global Impression Improvement Scale
CGIS-P	Conners' Global Index Scale, Parent version
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*
MAS-XR	mixed amphetamine salts extended-release
MD	mean difference
OROS MPH	oral release osmotic system methylphenidate
PedsQL	Pediatric Quality of Life Inventory
PERMP	Permanent Product Measure of Performance
QALY	quality-adjusted life year
Q-LES-Q	Quality of Life, Enjoyment and Satisfaction Questionnaire
RCT	randomized controlled trial
SAE	serious adverse event
SKAMP	Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale
WDAE	withdrawal due to adverse event
XR	extended-release

REVIEW IN BRIEF

The resubmission for mixed amphetamine salts extended-release (Adderall XR) was filed by the manufacturer with the Common Drug Review (CDR) as the basis for a formulary listing recommendation to participating public drug plans. This Review in Brief includes the Canadian Expert Drug Advisory Committee's (CEDAC's) recommendation and reasons for recommendation, as well as a summary of the information used by CEDAC in making its recommendation. The information included a review of the best available clinical and pharmacoeconomic evidence identified by CDR, and information submitted by the manufacturer.

CEDAC Recommendation

CEDAC recommended that Adderall XR not be listed.

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.

Drug

- Adderall XR is approved by Health Canada for the treatment of attention-deficit hyperactivity disorder (ADHD) in children, adolescents, and adults.
- The capsules contain dexamphetamine and levoamphetamine salts in a 3:1 ratio with both immediate and extended-release pellets of the mixed amphetamine salts.
- Adderall XR is available in 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg capsules.

Condition

Attention-deficit hyperactivity disorder (ADHD) is a life-long condition characterized by frequent and severe inattention, hyperactivity and impulsivity that interferes with social, academic or occupational functioning.

Clinical Review

- Two systematic reviews were conducted of double-blind randomized controlled trials (RCTs) of Adderall XR in the treatment of ADHD—one in adolescents and adults and the second in children, including trials published subsequent to the review by CDR in 2004.
- Two trials met the inclusion criteria for the systematic review in children — an 18 day trial comparing Adderall XR to atomoxetine in 215 children and a three week placebo controlled crossover trial in 52 children.
- Two placebo controlled trials of four weeks duration met the inclusion criteria for the systematic review in adolescents and adults — one in each age group.

Results

Efficacy — Children

- Compared to placebo, Adderall XR improved measures of deportment and attention, and resulted in better performance on a 10-minute math test.
- A higher proportion of patients treated with Adderall XR compared to placebo were rated as being very much or much improved by clinicians.
- Compared to atomoxetine, another long acting agent for ADHD, Adderall XR resulted

in significantly greater improvement in measures of deportment and attention, 10-minute math test results, and the proportion of participants rated by clinicians as being very much or much improved.
- There was no statistically significant difference in change in quality of life between Adderall XR and atomoxetine.

Efficacy — Adolescents and Adults

- The two included trials reported a statistically significant improvement with Adderall XR compared to placebo on an ADHD symptom scale (ADHD Rating Scale)
- A higher proportion of patients treated with Adderall XR were rated by clinicians as being very much or much improved.
- There was no statistically significant difference in change in quality of life in the one trial that measured this outcome.

Adverse Events

- There were no statistically significant differences between groups in the incidence of serious adverse events in any of the trials.
- In the trial in adults, there were statistically significantly more withdrawals due to adverse events with Adderall XR compared with placebo.
- The most common adverse effects of Adderall XR are insomnia, anorexia and weight loss.

Pharmacoeconomic Review

The pharmacoeconomic analysis submitted by the manufacturer was assessed and critiqued.

Highlights

- The manufacturer submitted a cost utility analysis, evaluating Adderall XR in two treatment options: 1) as a first-line treatment compared with methylphenidate (immediate and extended-release) and dexamphetamine (immediate-release), and 2) as a second- or subsequent-line treatment compared with no therapy for patients who are intolerant to methylphenidate and dexamphetamine.
- CDR reviewers identified several limitations with the manufacturer's pharmacoeconomic evaluation, including: 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 (e.g., sustained release methylphenidate formulations).
- Adderall XR costs $2.75 per day, regardless of the dose. This is more costly than methylphenidate immediate release ($0.25 to $0.50 at 20 mg to 40 mg per day), and similar in cost compared to methylphenidate extended-release ($2.09 to $3.38 at 18 mg to 54 mg per day) and dexamphetamine ($0.52 to $6.26 at 5 mg to 60 mg per day).

What is the CDR?

CDR conducts objective, rigorous reviews of the clinical and cost-effectiveness of drugs, and provides formulary listing recommendations to the publicly funded drug plans in Canada (except Québec).

OVERVIEW

Context

This document is an overview of three Common Drug Review (CDR) reports about Mixed Amphetamine Salts (Adderall XR): the CDR Clinical Review Report, a systematic review of the clinical evidence,in adolescents and adults (63 pages in length with 67 references), the CDR Clinical Review Report, a systematic review of the clinical evidence in children (37 pages in length with 21 references), and the CDR Pharmacoeconomic Review Report, a critique of the pharmacoeconomic evaluation submitted by the manufactuer (21 pages with 27 references). These reports were prepared by CDR to support the Canadian Expert Drug Advisory Committee (CEDAC) in making a formulary listing recommendation to participating publicly funded drug plans. The reviews are an assessment of the best available evidence that CDR has identified and compiled, including that submitted by the manufacturer, up to the time that the drug was considered by CEDAC.

The manufacturer had the opportunity to provide feedback on each of the reports and also on this overview. The CDR Directorate has considered the feedback in preparing the final versions of all of these reports. The manufacturer's confidential information as defined in the CDR Confidentiality Guidelines, may have been used in the preparation of these documents and, thus, may have been considered by CEDAC in making its recommendation. The manufacturer has reviewed this document and has not requested the deletion of any confidential information.

Introduction

Adderall XR was previously considered by CEDAC in November 2004 for treatment of ADHD in children six to 12 years of age and recommended not to be listed. Adderall XR was resubmitted to CDR for review because in 2007 Health Canada approved it for 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.

Mixed amphetamine salts extended-release (Adderall XR) capsules contain dexamphetamine and levoamphetamine salts in the ratio of 3:1. The proposed mechanism of action is increased release of norepinephrine and dopamine into the presynaptic space and the blockade of re-uptake of these monamines into the presynaptic neuron. Adderall XR is approved by Health Canada for the treatment of attention-deficit hyperactivity disorder (ADHD) in children, adolescents, and adults and is available in capsules (5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg). Amphetamines are not recommended for children under 6 years of age. The usual starting dose in children 6 to 12 years is 10 mg once daily in the morning, which may be adjusted in increments of 5 mg to 10 mg at weekly intervals to a maximum of 30 mg once daily. In adolescents and adults the starting dose is 10 mg once daily, which may be adjusted in increments of 5 mg to 10 mg at weekly intervals to a usual maximum of 20 mg daily but in some cases a maximum of 30 mg daily may be required.

ADHD is defined by the American Psychiatric Association as a "persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development, present before age 7 years and in at least two settings, with clear evidence of interference with developmentally appropriate social, academic or occupational functioning".[1] ADHD is a lifelong condition that persists into adolescence and adulthood for the majority of cases.[2,3] It may also be diagnosed for the first time in adolescents

or adults, although this may be more difficult because of a lack of standardized information about function (from the school system).

The management of ADHD includes the accurate determination of diagnosis, including consideration of differential and comorbidities, the provision of information to patients or families about the diagnosis and management options, behaviour management (in school, at work, and at home), and the use of medication. Drugs such as mixed amphetamine salts, dexamphetamine, methylphenidate, atomoxetine have been approved by Health Canada for the management of ADHD.

Clinical Review

Objective

To evaluate the effects of Adderall XR on outcomes, as compared with standard therapies or placebo, in children (6 to 12 years of age), adolescents (13 to 17 years of age), and adults, diagnosed with ADHD.

Methods

For information about the methodology employed in the CDR Clinical Review of mixed amphetamine salts extended-release, refer to Appendix I. The systematic review in children was restricted to trials completed since the original CDR review of Adderall XR in 2004.

Selection Criteria

Studies were chosen for inclusion in the review based on the criteria listed in Table 1.

Table 1: Criteria for Selection of Studies

Clinical Trial Design	Patient Population	Interventions	Appropriate Comparators*	Outcomes
DB RCT	Children (6 to 12 years of age), adolescents (13 to 17 years of age), and adults, with ADHD	MAS-XR, alone or in combination with other non-drug therapies, in recommended doses	Amphetamines (immediate or sustained release) Methylphenidate (immediate or sustained release) Atomoxetine Placebo Behavioural therapy	Mortality SAE QoL Behavioural/functional/cognitive outcomes assessed via validated measures WDAE AE Total withdrawal Treatment discontinuation

ADHD=attention-deficit hyperactivity disorder; AE=adverse event; DB RCT=double-blind randomized controlled trial; MAS-XR=mixed amphetamine salts extended-release; QoL=quality of life; SAE=serious adverse event; WDAE=withdrawal due to adverse event.
*Standard therapies available in Canada (may include drug or non-drug interventions).

Results

Findings from the Literature (Figures 1 and 2)

Figure 1: QUOROM Flowchart Detailing Flow of Studies — Children

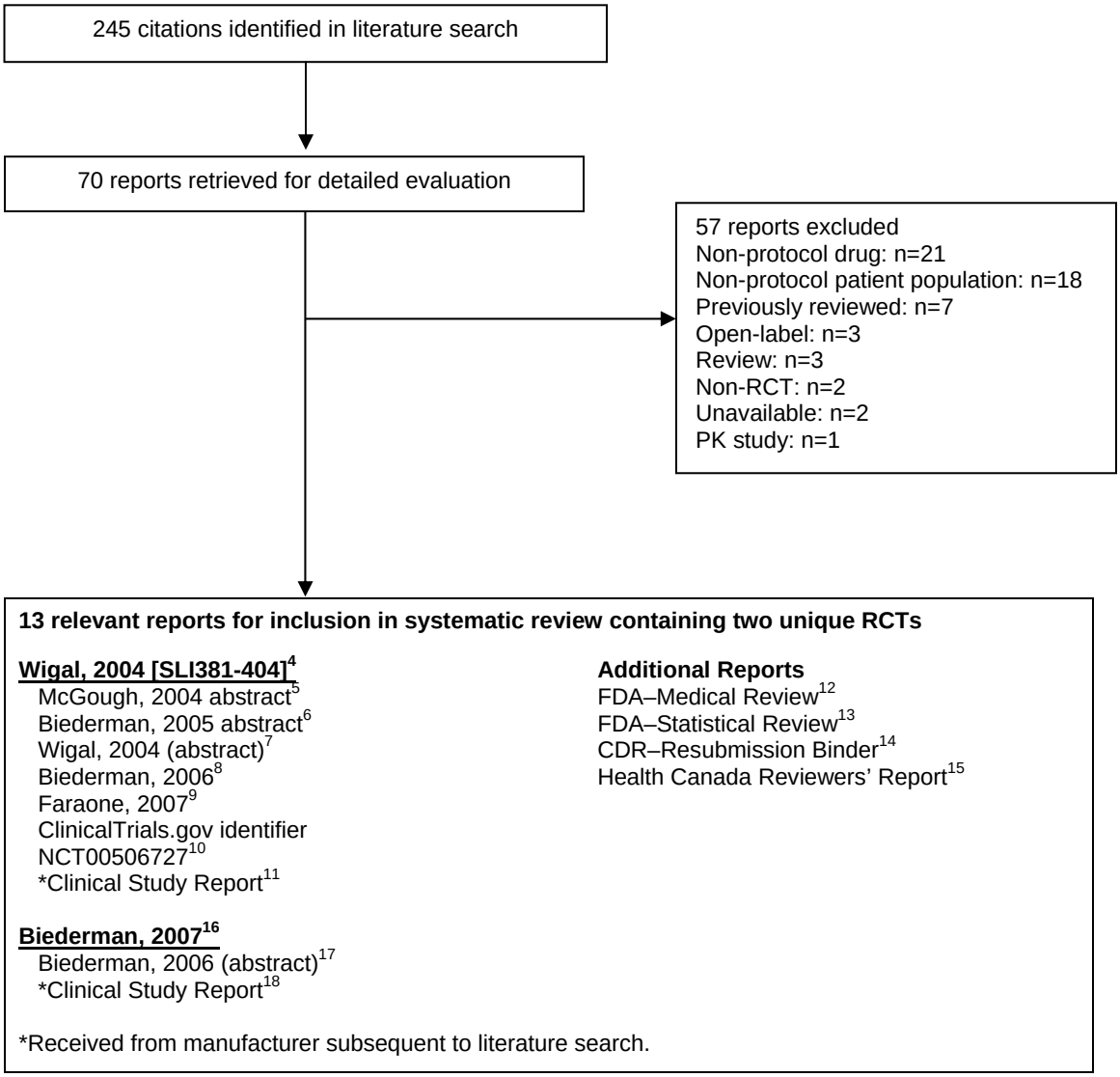
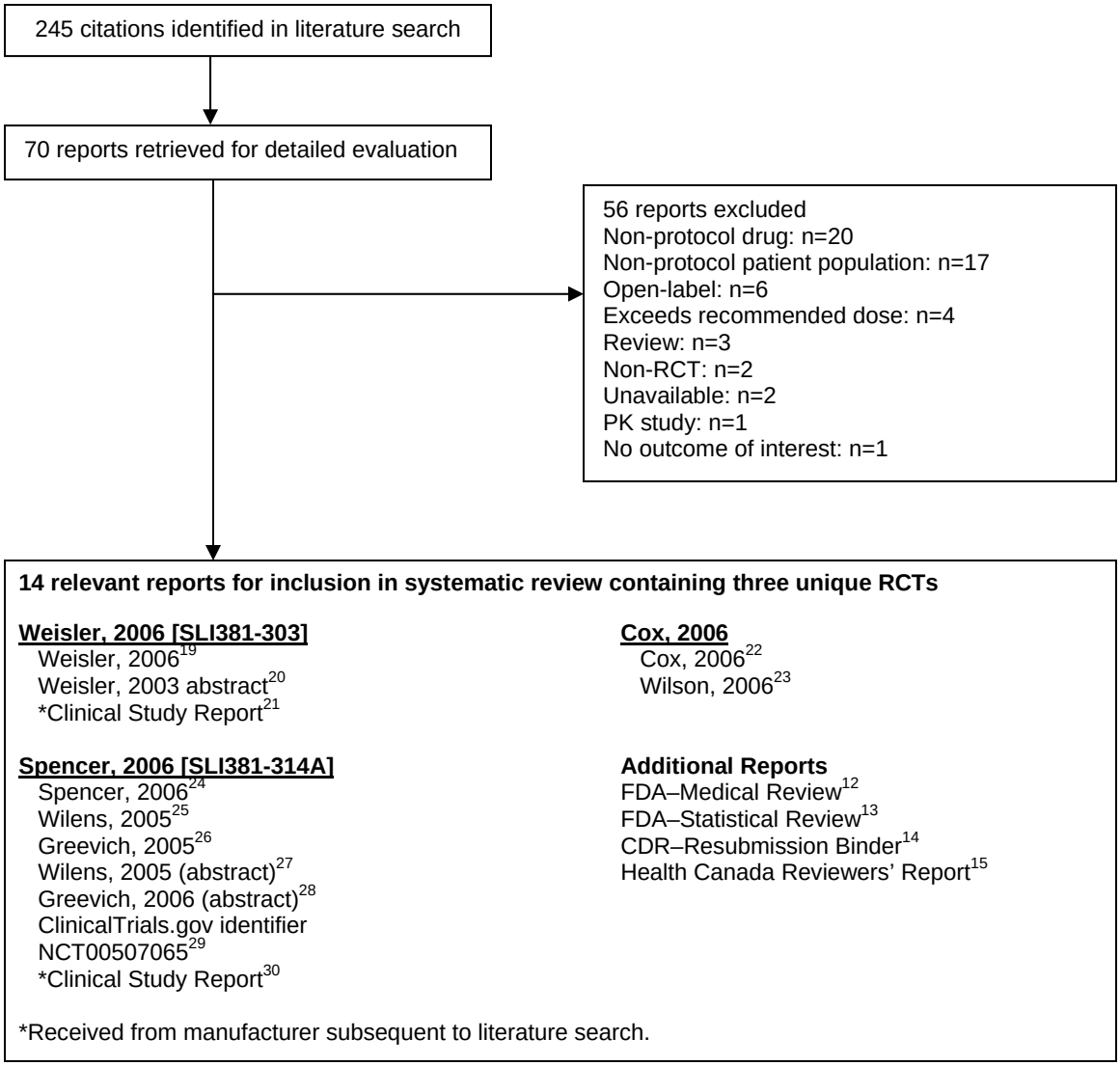


Figure 2: QUOROM Flowchart Detailing Flow of Studies — Adolescents and Adults



Summary of Evidence

Included Studies and Trial Characteristics — Children

Two double-blind randomized controlled trials (RCTs), including a total of 267 participants, were included in this review. Both trials were superiority trials. One trial[4] involving 215 subjects was an 18-day parallel-group trial comparing maximum recommended doses of Adderall XR to atomoxetine, while the remaining trial[16] involving 52 subjects was a three-week crossover trial comparing optimized doses of Adderall XR, lisdexamfetamine, and placebo. As lisdexamfetamine is not currently available in Canada, only Adderall XR and placebo results from the above trial were reported in this review. Participants in both trials included children 6 to 12 years of age, the vast majority of whom had a history of positive response to stimulants or atomoxetine.

Included Studies and Trial Characteristics — Adolescents and Adults

Three double-blind RCTs including a total of 617 participants were eligible for review. The review focused on two of the three trials, as the third (n=35) was of uncertain quality, as the sole outcome of the trial was simulated driving performance using a tool of uncertain validity. The two remaining trials were parallel group trials comparing Adderall XR (dosage ranges of 10 mg to 30 mg) to placebo, one of which[24] enrolled adolescents (13 to 17 years of age) and the other[19] enrolled adults (older than 18 years of age); both trials were of four weeks duration. Both trials included several treatment arms with doses of Adderall XR exceeding that recommended in the product monograph, results of which are not reported in detail in this review.

Summary of Results

See Table 2 for a summary of trial outcomes for children and Table 3 for trial outcomes for adolescents and adults.

Efficacy — Children

Compared with Atomoxetine:

- There was no significant difference in quality of life between children treated with Adderall XR versus atomoxetine for 18 days.
- Adderall XR reduced behavioural symptoms significantly more than atomoxetine as measured by both SKAMP (Swanson, Kotkin, Agler, M-Flynn, and Pelham) deportment and attention subscales; -0.56 versus -0.13 ($p<0.0001$) and -0.49 versus -0.08 respectively ($p<0.0001$).
- Adderall XR improved performance on the 10-minute math test significantly more than atomoxetine; 62 versus 29 additional math problems correct respectively ($p<0.0001$).
- A significantly greater proportion of participants treated with Adderall XR achieved clinical improvement [rating of very much or much improved on the Clinical Global Impression Improvement Scale (CGI-I)] compared with atomoxetine; 75% versus 36% respectively.

Compared with Placebo:

- Adderall XR resulted in improved deportment and attention (lower SKAMP scores) at endpoint compared with placebo; 0.8 versus 1.7 ($p<0.0001$) and 1.2 versus 1.8 ($p<0.0001$) respectively.
- Adderall XR resulted in better performance on the 10-minute math test at endpoint compared with placebo; 129.4 versus 84.6 math problems correct respectively ($p<0.0001$).

- A significantly greater proportion of participants treated with Adderall XR achieved clinical improvement compared with placebo: 74% versus 18%.

Harms — Children

- There were no deaths in either of the included trials, and there was one serious adverse event (SAE) (exacerbation of asthma) in a patient treated with Adderall XR.
- Withdrawal due to adverse event (WDAE) was not significantly different between Adderall XR and atomoxetine; 6% versus 4% respectively; RR=1.5 (95% CI; 0.4 to 5.2). Only one participant (receiving placebo) in the crossover trial withdrew due to an adverse event (gastroenteritis).
- Adverse events (AEs) occurred more frequently with Adderall XR than with atomoxetine; 85% versus 73% respectively [RR=1.2 (95% CI; 1.0 to 1.4)]. Decreased appetite or anorexia as well as insomnia were more common with Adderall XR than with atomoxetine. There were no significant differences in AE between Adderall XR and placebo in the crossover trial; 18% versus 15% respectively [RR=1.2 (95% CI; 0.5 to 2.8)].
- Potentially adverse cardiovascular effects (elevated blood pressure, increased pulse, prolongation of QRS and QTc intervals) occurred significantly more often with Adderall XR compared with placebo, but not with atomoxetine.

Efficacy — Adolescents and Adults

- There was no significant difference in quality of life between adults treated with Adderall XR versus placebo for four weeks:[19] mean (standard deviation) Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q) at endpoint 54.8 (0.88) versus 52.4 (0.92) respectively (p=0.29).
- Behavioural symptoms, as assessed by the Attention-Deficit Hyperactivity Disorder Rating Scale (ADHD-RS), were less pronounced with Adderall XR compared with placebo in both adolescents [Change From Baseline Mean Difference (CFB MD) (95% CI): 10 mg: -5.5 (-9.9 to -1.1); 20 mg: -11.3 (-15.5 to -7.1); 30 mg: -9.6 (-13.7 to -5.5)] and adults [endpoint MD (95% CI): -7.9 (-12.3 to -3.5)] after four weeks.
- Behavioural symptoms, as assessed by the Conners' Adult ADHD Rating Scale – Short Version – Self Report (CAARS-S-S), were less pronounced in adults treated with Adderall XR compared with placebo [endpoint MD at (95% CI): -3.4 (-6.0 to -0.8)] after four weeks.
- The proportion of participants with clinical improvement, as assessed by the Clinical Global Impression Improvement scale, after four weeks of treatment was significantly greater with Adderall XR compared with placebo for both adolescents [RR (95% CI): 10 mg: 1.9 (1.2 to 3.2); 20 mg: 2.5 (1.5 to 4.0); 30 mg: 2.6 (1.6 to 4.2)], and adults [RR (95% CI): 1.9 (1.2 to 3.1)].

Harms — Adolescents and Adults

- There were no deaths or SAEs in any of the included trials.
- Total withdrawal in adolescents and in adults was not significantly different between treatments. In the adult trial,[19] WDAE occurred significantly more often among Adderall XR participants compared with placebo: 14% versus 2% [RR (95% CI): 10 (1.2 to 81.0)].
- In the parallel group trials, AEs occurred significantly more often with Adderall XR compared with placebo in both adolescents (with the exception of those receiving 10 mg daily)

[RR (95% CI): 20 mg and 30 mg: 1.3 (1.0 to 1.7)] and adults [RR (95% CI): 1.43 (1.1 to 1.8)]. The most common AEs were similar for adolescents and adults (anorexia, insomnia) and occurred more often in the Adderall XR treatment arms compared with placebo.

- Electrocardiogram and blood pressure changes were not statistically or clinically significantly different between Adderall XR and placebo in adolescents or adults.
- Weight loss was statistically significantly greater with Adderall XR compared with placebo over four weeks in both adolescents and adults. In adolescents, the mean change from baseline (standard deviation) for Adderall XR 10 mg, 20 mg and 30 mg was: -1.1 lbs (3.4); -2.8 lbs (3.7) and -4.0 lbs (3.9) respectively compared with a weight gain of 1.5 lbs for placebo and the mean difference between Adderall XR and placebo (95% CI) was: 10 mg: -2.6 lbs (-3.8 to -1.4); 20 mg: -4.3 lbs (-5.6 to -3.0); and 30 mg: -5.5 lbs (-6.8 to -4.2). In adults the mean change from baseline (standard deviation) for Adderall XR was -1.1 kg (1.8) and for placebo was +0.1 kg (2.7) with a mean difference (95% CI) of -1.2 kg (-2.0 to -0.4).

Table 2: Summary of Trial Outcomes — Children				
	Wigal, 2004		**Biederman, 2007**	
Study Design (including publication status)	• DB RCT parallel group in children 6 to 12 years of age • Forced dose escalation to 30 mg/day of MAS-XR or 1.2 mg/kg/day of AMX • Trial duration=18 days • Full publication: Wigal[4]		• DB RCT crossover in children 6 to 12 years of age • MAS-XR titrated to optimal dose (10 to 30 mg/day) prior to randomization • Each crossover one week in duration • Full publication: Biederman[16]	
	MAS-XR	**AMX**	**MAS-XR**	**PL**
Number randomized Number in ITT population	107 102	108 101	52 50	52 50
Total withdrawals, n (%)	14 (13)	11 (10)	0	2
Mortality, n (%)	0	0	0	0
SAE, n (%)	1 (1)	0	0	0
PedsQL mean change from baseline	+7.1 **p=0.65***	+7.9	NI	NI
Mean (SD) at endpoint — SKAMP-deportment — SKAMP-attention	NR	NR	 0.8 (0.7) **p<0.0001*** 1.2 (0.7) **p<0.0001***	 1.7 (1.2) 1.8 (0.8)
Mean (SD) change from baseline — SKAMP-deportment — SKAMP-attention	 -0.56 (0.70) **p<0.0001*** -0.49 (0.55) **p<0.0001***	 -0.13 (0.65) -0.08 (0.49)	NR	NR
Mean (SD) at endpoint — PERMP-questions attempted — PERMP-questions correct	NR	NR	 133.6 (55.1) **p<0.0001*** 129.4 (51.8) **p<0.0001***	 88.7 (34.9) 84.6 (36.1)
Mean (SD) change from baseline — PERMP-questions attempted — PERMP-questions correct	 +62.6 (39.8) **p<0.0001*** +61.6 (39.9) **p<0.0001***	 +30.5 (31.8) +29.0 (29.0)	NR	NR
Mean (SD) change from baseline — CGIS-P	-8.3 (6.8) **p=0.09***	-6.6 (7.0)	NI	NI
CGI-I, n (%) very much improved or much improved	76 (75) RR=2.1 (95% CI: 1.6 to 2.8)**	36 (36)	37 (74) RR=4.1 (95% CI: 2.2 to 7.6)**	9 (18)
WDAE, n (%)	7 (7)	4 (4)	0 (0)	1 (2)
AE, n (%)	91 (85)	79 (73)	9 (18)	8 (15)
Treatment discontinuation, n (%)	NR	NR	NR	NR

AE=adverse events; AMX=atomoxetine; CGI-I=Clinical Global Impression Improvement Scale; CGIS-P=Conners' Global Index Scale, Parent version; DB RCT=double-blind randomized controlled trial; ITT=intention to treat; MAS-XR=mixed amphetamine salts extended-release; NI=outcome was not included in the trial; NR=not reported; PERMP=Permanent Product Measure of Performance (10-minute math test); PedsQL=Pediatric Quality of Life Inventory; PL=placebo; SAE=serious adverse events; SD=standard deviation; SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale; RR=relative risk; WDAE=withdrawal due to adverse event.
*p-value for the comparison of MAS-XR with comparator (AMX or PL).
** relative risk comparing MAS-XR with AMX or PL (CDR analysis)

Table 3: Summary of Trial Outcomes — Adolescents and Adults*						
	Spencer, 2006				**Weisler, 2006**	
Study design (including publication status)	• DB RCT parallel group in adolescents (13 to 17 years of age) • Initial dose of MAS-XR was 10 mg daily for all active treatment groups; for those randomized to higher doses, the dose increased by 10 mg/day weekly. • Trial duration=4 weeks • Full publication: Spencer, 2006[24] • Only data for arms containing recommended doses are presented.				• DB RCT parallel group in adults (>18 years of age) • Trial duration=4 weeks • Full publication: Weisler, 2006[19] • Only data for arms containing recommended doses are presented.	
	MAS-XR 10 mg	**MAS-XR 20 mg**	**MAS XR 30 mg**	**PL**	**MAS-XR 20 mg**	**PL**
Number randomized Number in ITT population	N=56 N=54	N=56 N=53	N=58 N=58	N=54 N=52	N=66 N=64	N=64 N=60
Total withdrawals, n (%)	7 (13)	5 (9)	3 (5)	4 (7)	19 (29)	22 (34)
Quality of life Mean (SD) Q-LES-Q at endpoint	NI	NI	NI	NI	54.8 (0.88) **p=0.29****	52.4 (0.92)
Total ADHD-RS score Mean (SD) at endpoint	20.0 (11.8)	13.3 (10.3)	16.1 (11.0)	25.7 (13.4)	18.5 (12.5) **p=0.001****	26.4 (12.2)
Total ADHD-RS score Mean (SD) change from baseline	-14.9 (12.1) **p=0.004****	-20.7 (11.2) **p<0.0001****	-19.0 (11.1) **p<0.0001****	-9.4 (10.6)	NR	NR
CAARS-S-S ADHD index score Mean (SD) at endpoint	NI	NI	NI	NI	14.9 (6.9) **p=0.002****	18.3 (7.5)
CGI-I, n (%) very much improved or much improved	28 (52) **p<0.01****	35 (66) **p<0.001****	41 (71) **p<0.001****	14 (27)	32 (50) **p=0.012****	16 (27)
WDAE, n (%)	1 (2)	1 (2)	1 (2)	0	9 (14)	1 (2)
AE, n (%)	35 (63)	43 (77)	45 (78)	32 (59)	56 (85)	38 (59)
Treatment discontinuation, n (%)	6 (11)	4 (7)	2 (4)	2 (4)	NR	NR

ADHD-RS=Attention-Deficit Hyperactivity Disorder Rating Scale; AE=adverse event; CAARS-S-S=Conners' Adult ADHD Rating Scale – Short Version – Self Report; CGI-I=Clinical Global Impression Improvement Scale; DB RCT=double-blind randomized controlled trial; ITT=intention to treat; MAS-XR=mixed amphetamine salts extended-release; NI=outcome was not included in the trial; NR=outcome results were not present in published or unpublished documents available to the CDR; PL=placebo; Q-LES-Q=Quality of Life, Enjoyment and Satisfaction Questionnaire; SAE=serious adverse events; SD=standard deviation; WDAE=withdrawal due to adverse event.

*Data from Cox 2006[22] was not included in this table as its sole objective/outcome was simulated driving performance.
** p-values represent comparisons between MAS-XR and placebo.

Note: There were no deaths or SAEs reported in either trial.

Discussion

Trials in Children

Efficacy:
This CDR review of Adderall XR addressed one of the limitations identified in the earlier CDR review by including a trial incorporating an active comparator available in Canada – atomoxetine. (Appendix II contains information on comparators.) The efficacy of Adderall XR compared to placebo in reducing behavioural symptoms (SKAMP scale) and improving academic performance (10-minute math test) is consistent with results previously reported. The Permanent Product Measure of Performance (PERMP) 10-minute math test is a measure of academic achievement, however it is unknown if this short-term outcome translates into longer-term academic performance. Adderall XR resulted in a statistically significantly reduction in behavioural symptoms and improved academic performance (SKAMP scale and 10-minute math test, as above) compared with atomoxetine.

Limitations of the newly reviewed trials should be kept in mind. Importantly, trials were of very short duration (maximum of 3 weeks) and the relationships between improvements in short-term behavioural symptoms and academic performance, and long-term outcomes, such as academic success and quality of life, have not been established in RCTs. Potential unmasking of participants due to differences in the physiological effects of medications may limit the internal validity of the results. The clinical trial environment and the select patient populations (history of stable stimulant regimen or no history of a failure to respond to study treatments, exclusion of subjects with co-morbidities) limit the ability to translate the trial results to the real world use of Adderall XR.

Harms:
The lack of mortality and limited SAEs and WDAEs observed in the trials was not unexpected given the selected patient population (children) and the short duration of the trials. AEs were commonly reported and were consistent with that reported in the original CDR review in regard to type and frequency. The proportion of participants experiencing any AEs was slightly higher with Adderall XR compared with atomoxetine, and a number of specific AE events appeared to be more likely to occur with Adderall XR (decreased appetite or anorexia and insomnia). Due to the short duration of trials, there is a lack of evidence from RCTs on long-term safety.

Due to the known pharmacological effects of Adderall XR, and rare reports of sudden death, cardiovascular effects of are of particular interest. No significant differences in vital signs (blood pressure and pulse) between Adderall XR and amoxetine were reported by Wigal. This is unsurprising given the similar pharmacology of the two agents. In contrast, significant differences were observed in blood pressure, pulse, QRS and QTc intervals between Adderall XR and placebo; however, these differences were not thought to be clinically significant. Conclusive evidence of increased incidence of rare but serious adverse events, such as sudden death, that have resulted in regulatory actions with regard to the sale of Adderall XR and other medications for ADHD, necessitate clinical trials with much larger sample sizes than have been, or are likely to be, conducted. Thus the available evidence comes from retrospective analyses reliant upon adverse event reporting systems.

Other Considerations:

- No eligible trials in the child population were relevant to the reimbursement criteria sought by the manufacturer: “when a trial of either immediate or sustained release methylphenidate or dexamphetamine does not permit adequate control of symptoms.” None of the trials targeted

this population; rather, one trial specifically included participants with a history of stable stimulant use. The remaining trial excluded participants with a history of failure to respond to Adderall XR or atomoxetine.

Trials in Adolescents and Adults

Efficacy:
The two parallel-group trials (one each in adolescents and adults) did not include an active comparator (Appendix II contains information on comparators), were of short duration (four weeks) and examined only behavioural outcomes. Both the above trials report improvement in behavioural symptoms with Adderall XR (at doses between 10 mg and 30 mg) compared with placebo, as rated by investigators (ADHD-RS) and participants (CAARS-S-S). Also a higher proportion of Adderall XR-treated participants were rated as clinically improved compared with placebo as measured by the CGI-I scale--RR range 1.9 to 2.6. The CGI-I score is not based on assessment of symptoms or behaviour which have not already been assessed but is assigned by the investigator, based on consideration of all available data (e.g., ADHD-RS and CAARS-S-S scores). Thus, the significantly higher proportion of participants assessed as clinically improved in the Adderall XR treatment arms reflects the significantly lower symptom rating scores for these participants. The validity and reliability of the CGI-I is not as firmly established as that of other rating scales for ADHD; however it does have face validity, and is more readily understood by patients and clinicians. Only one trial (Weisler) included quality of life as an outcome. However, due to the short duration of the trial, the non-significant finding is perhaps not unexpected.

One trial had a withdrawal rate of approximately 30%; however, there was no difference in the withdrawal rate between the treatment arms. Unmasking of participants due to the physiological effects of stimulants remains a threat to internal validity. A limitation of these trials is the lack of data regarding long-term functional outcomes (e.g., school and/or work performance).

Harms:
The lack of mortality and SAEs was not unexpected given the short duration of the trials. WDAEs for those treated with Adderall XR for four weeks differed between the trials (2% for adolescents and 14% for adults). This may be attributed to the higher starting dose in the adult trial or actual differences in drug sensitivity between adolescents and adults. Total AEs occurred significantly more often among those treated with Adderall XR compared with placebo; specific AEs that were more frequent included anorexia, insomnia, and weight loss. This is similar to that reported in reviews of other stimulants for ADHD.

There were few statistically significant differences between Adderall XR and placebo in terms of cardiovascular measures at recommended doses, and none were judged clinically significant; however, it was noted that two adults treated with Adderall XR withdrew due to tachycardia. Cardiovascular and psychiatric events remain a focus of interest and warnings regarding potential adverse psychiatric and cardiac events have been issued by Health Canada.

Other Considerations:

- No eligible trials in the adolescent or adult population were relevant to the reimbursement criteria sought by the manufacturer: “when a trial of either immediate or sustained release methylphenidate or dexamphetamine does not permit adequate control of symptoms.”

Pharmacoeconomic Review

Context

CDR assesses and critiques the economic evaluation, submitted by the manufacturer, with respect to its quality and validity, including the appropriateness of the methods, assumptions and inputs, and results. CDR may provide additional information on the cost-effectiveness of the submitted drug, where relevant, from other sources or by using the economic model to consider other scenarios.

Objective of the Manufacturer's Submitted Pharmacoeconomic Evaluation

- To assess the cost-effectiveness of Adderall XR for managing ADHD in children, adolescents, and adults, compared with other stimulants currently reimbursed by public drug plans in Canada.

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer conducted a cost utility analysis of Adderall XR for the management of ADHD symptoms, conducting separate analyses for children (6 to 12 years of age), adolescents (13 to 17 years of age), and adults (18 years of age and older). Adderall XR was evaluated in two treatment options: 1) as a first-line treatment compared with methylphenidate (immediate and extended-release) and dexamphetamine (immediate-release), and 2) as a second- or subsequent-line treatment compared with no therapy for patients who are intolerant to methylphenidate and dexamphetamine. This latter scenario addresses the population for which the manufacturer requested reimbursement. The pharmacoeconomic model is composed of a short-term and long-term model. The short-term model assessed patients' response to treatment based on the CGI-I, where response was defined as patients who were "very much improved" or "much improved." Patients who responded to therapy moved to a long-term Markov model (50 years) and were assumed to remain responsive for the remaining time period – outcomes in the longer term model are not dependent on the initial treatment. Quality-adjusted life years (QALYs) were calculated based on utility values that were applied to individuals who responded to treatment. Lifetime costs and outcomes were calculated in the Markov model based on potential ADHD consequences (e.g., learning disability, motor vehicle accidents, and criminal behaviour). The analysis was conducted from the perspective of society.

Data on response rates with Adderall XR were obtained from published trials,[4,19,31-34] which were pooled for the respective patient populations. Response rates for methylphenidate and dexamphetamine were obtained from a National Institute for Health and Clinical Excellence (NICE) health technology assessment (HTA) report[31] and additional published trials.[35-45] Utility values for children and adolescents were obtained from the NICE report, while values for adults were based on the QUEST study.[46] The likelihood of ADHD consequences (motor vehicle accidents, learning disabilities, and physical injuries) were obtained from the literature.[47-50] Resource use on drug treatment and physician services was obtained from the Ontario and Québec governments.

Cost Comparison

CDR produced Table 4 (Children and Adolescents) and Table 5 (Adults) to provide a comparison of the cost of treatment of the submitted drug with comparator treatments deemed appropriate by clinical experts. Comparators may reflect recommended or actual practice. Costs are manufacturer list prices, unless otherwise specified.

Table 4: Cost Comparison of Adderall XR versus Comparator Treatments — Children and Adolescents

Drug/Comparator	Strength	Dosage Form	Price ($)	Average Daily Use**	Average Daily Drug Cost ($)
Mixed amphetamine salts extended release (Adderall XR)†	5 mg 10 mg 15 mg 20 mg 25 mg 30 mg	ER capsules	2.7500 2.7500 2.7500 2.7500 2.7500 2.7500	10 mg to 30 mg daily for children 10 mg to 20 mg daily for adolescents	2.75 2.75
Methylphenidate (Ritalin and generics)	10 mg	Tablet	0.1262	20 mg to 40 mg daily in divided doses	0.25 to 0.50
Methylphenidate (Ritalin SR)	20 mg	LA tablet	0.3364	20 mg to 40 mg daily in divided doses	0.34 to 0.68
Methylphenidate OROS (Concerta)	18 mg 36 mg 54 mg	ER tablet	2.0889‡ 2.7325‡ 3.3760‡	18 mg to 54 mg once daily	2.09 to 3.38
Methylphenidate – controlled release (Biphentin)§	10 mg 15 mg 20 mg 30 mg 40 mg 50 mg 60 mg 80 mg	Capsule	0.6500 0.9300 1.2000 1.6500 2.1000 2.5500 3.0000 3.9000	10 mg to 60 mg once daily	0.65 to 3.00
Dexamphetamine (Dexedrine)	5 mg	Tablet	0.5214	5 mg to 60 mg daily in divided doses	0.52 to 6.26
Dexamphetamine (Dexedrine Spansules)	10 mg	LA capsule	0.7892‡	10 mg to 60 mg daily	0.79 to 4.74
Atomoxetine (Strattera)§	10 mg 18 mg 25 mg 40 mg 60 mg	Capsule	3.9800 3.9800 3.9800 3.9800 3.9800	40 mg†† (33 kg child receiving 1.2 mg/kg/day)	3.98

ER=extended release; LA=long-acting; OROS=oral release osmotic system; XR=extended release.

* Source: Ontario Drug Benefit Formulary (February 12, 2008) unless otherwise stated.
**Dosage information based on Compendium of Pharmaceuticals and Specialties (CPS) unless otherwise stated.
† Manufacturer's (Shire Canada Inc.) submission binder
‡ McKesson Canada Price.
§ PPS Pharma Buyers' Guide, January 2008.
††Recommended dosage: 1.2 mg/kg/day (maximum 1.4 mg/kg/day), based on mean weight of 33 kg, observed in clinical trials.

Table 5: Cost Comparison of Adderall XR versus Comparator Treatments – Adults*					
Drug/Comparator	**Strength**	**Dosage Form**	**Price ($)**	**Average Daily Use***	**Average Daily Drug Cost ($)**
Mixed amphetamine salts extended release (Adderall XR)†	5 mg 10 mg 15 mg 20 mg 25 mg 30 mg	Capsule	2.7500 2.7500 2.7500 2.7500 2.7500 2.7500	10 mg to 20 mg	2.75
Atomoxetine (Strattera)‡	10 mg 18 mg 25 mg 40 mg 60 mg	Capsule	3.9800 3.9800 3.9800 3.9800 3.9800	60 mg to 80 mg	3.98 to 7.96
Off-label medications					
Methylphenidate (Ritalin and generics)	10 mg	Tablet	0.1262	20 mg to 60 mg	0.25 to 0.76
Methylphenidate SR (Ritalin SR)	20 mg	LA tablet	0.3364	20 mg to 60 mg	0.34 to 1.01
Methylphenidate OROS (Concerta) ††	18 mg 36 mg 54 mg	Tablet	2.0889 2.7325 3.3760	18 mg to 54 mg	2.09 to 3.38
Methylphenidate – controlled release (Biphentin)†	10 mg 15 mg 20 mg 30 mg 40 mg 50 mg 60 mg 80 mg	Capsule	0.6500 0.9300 1.2000 1.6500 2.1000 2.5500 3.0000 3.9000	10 mg to 80 mg	0.65 to 3.90
Dexamphetamine (Dexedrine)	5 mg	Tablet	0.5214	10 mg to 40 mg	1.04 to 4.17

LA=long-acting; OROS=oral release osmotic system; SR=sustained release; XR=extended release.

* Source: Ontario Drug Benefit Formulary (February 12, 2008) unless otherwise stated.
**Dosage information based on Compendium of Pharmaceuticals and Specialties (CPS) unless otherwise stated.
† Manufacturer's (Shire Canada Inc.) submission binder
‡,PPS Pharma Buyers' Guide, January 2008.
††McKesson Canada Price.

Results (as submitted by the manufacturer)

The incremental costs per QALY, from the manufacturer's economic evaluation, for Adderall XR as first-line therapy compared with other treatment options are outlined in Table 6 for children, adolescents, and adults.

Table 6: Incremental Cost per QALY for Adderall XR as First-Line Therapy Compared with Other Treatments			
	Children	**Adolescents**	**Adults**
Methylphenidate (immediate-release)	$106,800	$70,700	$187,600
Methylphenidate (extended-release)	Adderall XR is more costly and results in more QALYs	Adderall XR is cost saving	$5,700
Dexamphetamine (immediate-release)	Adderall XR is more costly and results in fewer QALYs	Adderall XR is more costly and results in fewer QALYs	Adderall XR is less costly and results in fewer QALYs

QALY=quality-adjusted life year.

As a second-line or later treatment, Adderall XR reported to result in a cost per QALY of approximately $19,000 for all age groups compared with no treatment.

Pharmacoeconomic Analysis Discussion Points

In reviewing the manufacturer's submission, the CDR reviewers noted the following:

- *Lack of RCT evidence for Adderall XR in second- and subsequent-line treatment*: CDR clinical reviewers did not identify any trials of Adderall XR conducted in patients who failed or were intolerant to methylphenidate and dexamphetamine. The pharmacoeconomic model assumed that the response rate observed in the Adderall XR clinical trials for treatment as first-line therapy would apply in patients who have failed or are intolerant to methylphenidate and dexamphetamine. It is possible that patients who have failed methylphenidate or dexamphetamine would be less likely to respond to Adderall XR or as likely to be intolerant to treatment (as they fall within a similar class of treatments).

- *Limited comparative clinical data:* Given the lack of comparative RCTs for Adderall XR, indirect comparisons were required to compare across treatments, and the evaluation pooled placebo controlled trials for treatments. There were a number of limitations in the pooling of data that affect the interpretation of the results. The manufacturer included a trial for the immediate release formulation of mixed amphetamine salts in deriving the response rate for adults.[34] Also, the manufacturer considered children and adolescents as separate age groups for their analysis, but the pooled data do not necessarily reflect this distinction. Data obtained from the NICE report did not distinguish between children and adolescents, and several trials[31,38-40] reported only combined results for children and adolescent populations. Therefore, the interpretation of the results was limited given that heterogeneous placebo trials were pooled. The manufacturer did not identify any trials in the adolescent population that considered the use of dexamphetamine; thus, it is unclear what data was used for the analysis of mixed amphetamine salts versus dexamphetamine in this patient group. Finally, given the lack of longer-term trials, the manufacturer assumed that response to treatment would persist through the individual's lifetime. This is a significant assumption that does not account for changes in the management of symptoms as patients progress through various stages of life; for example, from school age through to adulthood.

- *Significance of differences in response rates between treatments*: Based on the manufacturer's indirect comparison of the clinical evidence, wide and overlapping confidence intervals for the response rates of treatments were reported.[14] Further, the

calculation of QALYs was based on response to treatment and the confidence intervals around the estimated QALYs were not provided. Given the similar response rates, similar QALYs among treatments would be expected. Consequently, rather than reporting that Adderall XR is dominant over comparators, it would be more appropriate to report that Adderall XR may be associated with lower costs and similar QALYs.

Summary of the Clinical and Pharmacoeconomic Reviews

In Children

Adderall XR:

- Significantly improved common measures of ADHD, including deportment and attention scores (SKAMP) and 10-minute math test performance, as well as increased the proportion of participants achieving clinical improvement compared with placebo or atomoxetine;
- Did not significantly improve quality of life compared with atomoxetine after 18 days of treatment.

The relationship of these short-term measures to long-term outcomes, such as academic success and quality of life, is unknown.

In Adolescents and Adults

Adderall XR:

- Resulted in less pronounced behavioural symptoms and significantly increased the proportion of participants achieving clinical improvement after four weeks compared with placebo;
- Did not significantly improve the quality of life of participants after four weeks compared with placebo.

The relationship of these short-term measures to long-term outcomes, such as academic success and quality of life, is unknown.

In General

- There were few SAEs or WDAEs, but the included trials were of short duration.
- AEs observed more frequently with Adderall XR included anorexia, insomnia, and weight loss. Cardiovascular events were not commonly reported but remain an important consideration with all medications approved for the treatment of ADHD.
- The cost of Adderall XR for children, adolescents, and adults at recommended doses is $2.75. This is significantly more expensive than some treatment options (methylphenidate), similar in price compared methylphenidate SR and dexamphetamine, and less expensive than atomoxetine.

CEDAC Final Recommendation — Issued June 25, 2008

Following careful consideration and deliberation of the information contained within the CDR Clinical and Pharmacoeconomic Review Reports, CEDAC recommended that Adderall XR not be listed.

APPENDIX I: Methodology for the CDR Clinical Review

Methods

Reviewer Information

- The systematic review of clinical trials section and the executive summary were prepared by two CDR clinical reviewers in consultation with an external clinical expert specializing in neurology who treats children, adolescents, and adults with ADHD.
- The Supplemental Issues section was prepared by one CDR reviewer.
- Background Information on the Condition section was prepared by an external clinical expert specializing in neurology.

Systematic Review Methods

Review Protocol

- The review protocol was developed jointly by the two CDR clinical reviewers and the external clinical expert in consultation with the internal and external pharmacoeconomic reviewers. Members of the Canadian Expert Drug Advisory Committee (CEDAC) also provided input and comments.

Literature Search Methods

- The literature search was performed by an internal CDR information specialist using a peer-reviewed search strategy.
- Published literature was identified by searching the following bibliographic databases: BIOSIS Previews, EMBASE, PsycINFO and MEDLINE via Ovid, and The Cochrane Library (2007, Issue 4) via Wiley InterScience.
- Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. The initial search was completed on December 19, 2007. Regular alerts have been established to update the search until CEDAC's April 17, 2008 meeting.
- Grey literature was obtained by searching the web sites of regulatory, health technology assessment, and near-technology assessment agencies as well as clinical trial registries. Google and other Internet search engines were used to search for a variety of web-based information including conference abstracts.
- In addition, the manufacturer of the drug was contacted for additional information regarding unpublished data.

Selection of Studies

- Each CDR clinical reviewer independently selected studies for inclusion according to the predetermined selection criteria. All articles considered potentially relevant by at least one reviewer were acquired from library sources. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Selection Criteria

- Studies were chosen for inclusion in the review based on the criteria listed in Table 1, located in the body of this report.

Quality Assessment

- Study bias was critically assessed independently by the two CDR clinical reviewers.

Data Analysis Methods

- The systematic review in children was restricted to trials completed since the original CDR review of Adderall XR in 2004.
- Data was extracted from published literature and unpublished literature provided by the manufacturer. For binary outcomes, clinical reviewers used Review Manager software version 4.2.10 to calculate relative risks and 95% confidence intervals. For outcomes measured on an interval scale, reviewers used Confidence Interval Analysis software version 2.1.0 to calculate mean differences and 95% confidence intervals. For the data in children, data appropriate to conduct paired analysis for the crossover trial was not available, thus unpaired analysis was conducted to calculate mean differences and 95% confidence intervals. No pooling of data was performed.

Supplemental Issues Methods

In addition to the systematic review for adolescents and adults, a number of supplemental issues were extensively considered and reported within a 17-page supplemental issue section.

Issues included:

- additional harms information
- comparator information — efficacy and harms summary
- validity of outcome measures.

Note: Supplemental issues contained in the full CDR review may or may not be included in this overview. Where they are included, supplemental issues may be represented in full or may be summaries of those contained in the full CDR review.

APPENDIX II: Comparator Information — Efficacy and Harms

The following is a summary of supporting information assessed by CDR reviewers. The information has been critically appraised, but has not been systematically reviewed.

The most common first-line therapy for ADHD is stimulant medication such as methylphenidate, dexamphetamine and mixed amphetamine salts. However, non-stimulant therapy such as atomoxetine is also available.

Methylphenidate is a central nervous system stimulant with more prominent effects on mental activities than on other activities.[31,51,52] Common AEs include insomnia; nervousness; headache; decreased appetite; abdominal pain and other gastrointestinal symptoms; and cardiovascular effects such as tachycardia, palpitations, and minor increases in blood pressure.[52] Growth can be affected, at least in the short term, so height and weight are monitored regularly.

Dextroamphetamine, a sympathomimetic amine with a central stimulant activity, is approved for the treatment of ADHD in patients greater than 6 years old.[53] Common AEs are similar to those of methylphenidate.

Atomoxetine is a selective noradrenaline reuptake inhibitor.[51] It is indicated in Canada for the treatment of ADHD in children 6 years of age and over, adolescents, and adults.[31,53] Common AEs are abdominal pain, decreased appetite, nausea and vomiting, early morning awakening, irritability, and mood swings. Increased heart rate and small increases in blood pressure were observed in clinical trials.[52] Also, there are reports of suicidal ideation in a small number of affected children.[52]

In 2008, the National Institute for Health and Clinical Excellence (NICE, UK) released a systematic review of RCTs assessing the efficacy and/or safety of pharmacological treatments for ADHD in children (primary-school age), young people (secondary-school age), and adults (draft for consultation).[52] This draft consultation indicated that for the medications studied (Adderall XR was not included in this systematic review), methylphenidate and atomoxetine were the only drugs where clear evidence exists for clinical effectiveness in reducing ADHD symptoms in school-age children, adolescents, and adults; the largest clinical effect was for methylphenidate when compared with placebo. There was no evidence from high-quality controlled trials for the efficacy of dexamphetamine in children and only one trial supported improvement in adults. A limitation of this review is that it did not include mixed amphetamine salts, which are not licensed in the UK for ADHD. Also there was a lack of quantitative pooling and quantitative statistics (due mainly to the diversity of outcomes and scales in the data) to support generalized conclusions.

In addition to pharmacological treatments for ADHD, NICE 2008 concluded that “Psychological treatment may be required at different points in time and/or stages in youth and adult development. There is little research evidence about the psychological treatment of adults with ADHD; however, strong clinical consensus exists that cognitive behavioural treatments are the most appropriate.”

In a systematic review by King *et al.* (2006),[31] dexamphetamine appeared to be effective at reducing hyperactivity and improving quality of life (in a small number of studies). For atomoxetine, studies supported that it was superior to placebo for hyperactivity and Clinical

Global Impression. The overall conclusions from this evaluation were that “drug therapy seems to be superior to no drug therapy, no significant differences between the various drugs in terms of efficacy or side effects were found, mainly owing to lack of evidence.” Limitations of this review itself are that it excluded evidence for Adderall XR and did not explicitly separate data and conclusions for children and adolescents to be able to accurately isolate findings in adolescents only.

A systematic review by McDonagh *et al.* (2006)[54] concluded that for adults, mixed amphetamine salts extended-release, dexamphetamine – immediate-release, methylphenidate – immediate-release and atomoxetine may lead to response in 50-74% of participants in placebo-controlled trials in adults. The authors highlight that “there is no evidence that any one stimulant is more effective than any other.” Also, the investigators summarize that evidence regarding treatment effects on quality of life and other ADHD-related symptoms (depressed mood, anxiety, and cognition) in adults is not compelling. The investigators note that the evidence for comparative efficacy and AEs of medications for ADHD is severely limited by small sample sizes, very short durations, and the lack of studies measuring functional or long-term outcomes. Findings in adolescents were similar to the previous summarized results from the other two reviews.

Finally, in a systematic review of long-acting medications by Banaschewski *et al.* (2006),[51] the authors reported that long-acting stimulants have similar standardized mean differences SMDs (effect sizes) to immediate-release stimulants. However SMDs for non-stimulants are somewhat smaller. Limitations of this type of analysis include the inability to control for the effects of potential confounding variables, such as “differences concerning the distribution of diagnostic subtypes, gender, and age, design of study, type of outcome score used and dosing method.”

APPENDIX III: Validity of Outcome Measures

The following is a summary of supporting information assessed by CDR reviewers. The information has been critically appraised, but it has not been systematically reviewed.

The following rating scales have been included in this review:
A. Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS)
B. Conners' Adult ADHD Rating Scale – Short Version – Self Report (CAARS-S-S)
C. Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q)

A. ADHD Rating Scale-IV (ADHD RS-IV)

The ADHD Rating Scale-IV is a norm-referenced checklist that measures the symptoms of ADHD according to the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV).[55-57] The ADHD RS-IV was developed to measure the behaviours of children with ADHD and was subsequently revised for adults.[21]

The authors conclude, based on their reliability and validity testing, that that the ADHD RS-IV has "adequate" reliability and validity when used in children and adolescents. It should be noted that limited information is presented on the socioeconomic status of the participants. Also, information is not presented on the urban/rural residence status and the parent education levels of the norm population. Furthermore, the authors highlight, the "limited cell size for ethnic groups restricts interpretation with minority populations" (data were not provided separately for ethnic groups). The authors note that, from their experience, the tool is "user-friendly and time efficient for the parent, teacher, and clinician and also may be a valuable tool as a treatment outcome measure."

ADHD RS-IV is a clinician-administered instrument for assessing ADHD symptom severity. The ADHD RS-IV has also been validated as a clinician-administered and scored instrument among American children and adolescents. Zhang *et al.* (2005) found acceptable psychometric properties for ADHD RS-IV, including inter-rater reliability, test-retest reliability, internal consistency, discriminant validity, and responsiveness. The authors conclude that the ADHD RS-IV is a useful tool, as a clinician-rated instrument, for assessing the severity of ADHD symptoms in children and adolescents in Europe.

The ADHD RS, adapted for adults, has been used in several clinical trials.[58,59] The ADHD RS for adults consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV criteria.[21] The 18 items may be grouped into two subscales: hyperactivity/impulsivity and inattentiveness.

B. Conners' Adult ADHD Rating Scales (CAARS)

The Conners' Adult ADHD Rating Scales (CAARS) were designed to assess ADHD symptoms in adults, as described in the DSM-IV.[60-64] The CAARS utilizes a short, long, and a screening self-report and observer rating scale forms.

In general, in terms of psychometric properties of CAARS, the four scales represented on the CAARS demonstrate both high internal consistency and strong test-retest reliability.[62]

Some cautions should also be highlighted in terms of the limitations of CAARS in the use of assessing treatment outcomes.[65] By their very nature, these scales allow the patient or subject to estimate the level of their own symptoms. This can be greatly affected by the demand characteristics of the treatment situation as well as their own attitudes regarding treatment.[64] Adolescents may deliberately minimize their symptoms or the extent to which the treatments affect them as part of their general opposition to adult authority. Also, adults may wish to receive a drug and therefore exaggerate the severity of their symptoms or the amount of change the drug evoked.[64]

C. Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q)

The Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q) is a self-report measure of the degree of enjoyment and satisfaction experienced in eight areas, including physical health/activities, feelings, work, household duties, school course work, leisure time activities, social relations, and general activities.[66] There is limited information on the validity of the Q-LES-Q.[67]

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