Common Drug Review
Clinical Review Report

July 2015

Drug	guanfacine hydrochloride extended release (Intuniv XR) tablets
Indication	Monotherapy for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children aged 6 to 12 years. Adjunctive therapy to psychostimulants for the treatment of ADHD in children aged 6 to 12 years with a suboptimal response to psychostimulants.
Listing request	For treatment as monotherapy in children aged 6 to 12 years suffering from ADHD in whom it has not been possible to properly control the symptoms of the disease with methylphenidate and an amphetamine or for whom these drugs are contraindicated or inadvisable and as adjunctive therapy for treatment of ADHD in children aged 6 to 12 years with a suboptimal response to psychostimulants.
Manufacturer	Shire Canada Inc.

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ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
ADHD-RS	ADHD Rating Scale-IV
AE	adverse event
ANCOVA	analysis of covariance
ATX	atomoxetine
CADDAC	Centre for ADHD Awareness, Canada
CDR	CADTH Common Drug Review
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity of Illness
CHQ	Child Health Questionnaire
CPRS	Conners' Parent Rating Scale
CTRS	Conners' Teacher Rating Scale
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition
FAS	full analysis set
GXR	guanfacine extended release
HRQoL	health-related quality of life
HUI2	Health Utilities Index Mark 2
HUI3	Health Utilities Index Mark 3
ICUR	incremental cost-utility ratio
LOCF	last observation carried forward
LS	least squares
MCID	minimal clinically important difference
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SAE	serious adverse event
WDAE	withdrawal due to adverse event
WFIRS	Weiss Functional Impairment Rating Scale

EXECUTIVE SUMMARY

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed childhood behavioural disorder. Hyperactivity, impulsivity, and inattention are core symptoms of ADHD. These symptoms affect children's cognitive, academic, behavioural, emotional, and social functioning. The reported prevalence of ADHD in children varies from 2% to 18% worldwide, while the prevalence in school-aged children is estimated to be between 8% and 10%. The prevalence of ADHD increases with increasing age, and approximately two-thirds of children with ADHD receive pharmacotherapy. It is reported that 87% of children with ADHD have at least one comorbid condition. Treatment of ADHD includes behavioural interventions, medication, school-based interventions, parent-training and education programs, and psychological interventions. Medication combined with behavioural and psychological interventions are recommended for most school-aged children and adolescents with ADHD and moderate to severe impairment. Long-acting preparations of psychostimulants are usually considered first-line drugs for uncomplicated ADHD. Long-acting preparations of psychostimulants or non-psychostimulants are recommended over short- and intermediate-acting drugs.

Guanfacine hydrochloride is a selective alpha$_{2A}$-adrenergic receptor agonist. Guanfacine extended release (GXR; brand name: Intuniv XR) is indicated as monotherapy or as adjunctive therapy to psychostimulants for the treatment of ADHD in children aged six to 12 years with a suboptimal response to psychostimulants. The maximum daily dose for GXR is 4 mg.

Indication under review
Monotherapy for the treatment of ADHD in children aged 6 to 12 years. It is also indicated as adjunctive therapy to psychostimulants for the treatment of ADHD in children aged 6 to 12 years with a suboptimal response to psychostimulants.
Listing criteria requested by sponsor
For treatment as monotherapy in children aged 6 to 12 years suffering from ADHD in whom it has not been possible to properly control the symptoms of the disease with methylphenidate and an amphetamine or for whom these drugs are contraindicated or inadvisable and as adjunctive therapy for treatment of ADHD in children aged 6 to 12 years with a suboptimal response to psychostimulants.

The objective of this review was to compare the clinical benefits and harms of GXR with those of other active treatments and placebo in children aged six to 12 years with ADHD.

Results and Interpretation

Included Studies

Seven phase 3, double-blind, parallel-group, placebo-controlled randomized controlled trials (RCTs) that enrolled children with ADHD were included in this review. One of them also randomized patients to atomoxetine (ATX). The number of enrolled patients ranged from 182 to 461. GXR was administered as monotherapy in six trials (while one of the six trials included ATX as a comparator, it was not a head-to-head trial, and GXR and ATX were not directly compared), and was co-administered with a psychostimulant in one trial. A phase 2 trial also met the inclusion criteria for the review. All studies used GXR tablets (1 mg to 4 mg) taken once daily. One study explored the effectiveness and safety of

GXR over six months, while the other studies examined the short-term (6.5 weeks to 10 weeks) effects of GXR. The primary outcome in most of the studies was mean change in ADHD Rating Scale-IV (ADHD-RS) total score from baseline.

Randomization and blinding appear to have been appropriately implemented. The populations studied were similar to some of the children with ADHD who would be seen in Canadian clinics, according to the clinical expert consulted on this review. However, the clinical expert noted that, especially in tertiary care centres, children with ADHD have many comorbidities, and these patients were not well represented in the trials. In all trials, patients with concomitant controlled or uncontrolled psychiatric disorders were excluded.

Key limitations of the evidence were the lack of direct evidence comparing GXR with other active treatments, short-term trials, high dropout rates, and exclusion of patients with comorbidities from the study populations in the trials.

Efficacy

In general, compared with placebo, GXR 1 mg to 4 mg once daily was more effective in reducing ADHD symptoms and improving functioning. In monotherapy trials, the mean differences in change of ADHD-RS total score from baseline to the end of maintenance period of study between GXR 1 mg to 4 mg once daily and placebo ranged from –5.4 to –12.3 points (Table 1). All differences were statistically significant compared with placebo. Some authors have suggested that the minimal clinically important difference (MCID) for the ADHD-RS total score is between 5.2 and 7.7 points for between-treatment comparisons. If this MCID threshold is correct, the observed differences between GXR and placebo in the included monotherapy studies appear to be clinically meaningful for most studies. In the adjunctive therapy trial, the mean difference in change of ADHD-RS total score from baseline to end of study between GXR and placebo was around –5 points.

Results for children aged six to 12 years from subgroup analyses by age groups were consistent with results observed in the overall population; however, the trials were not powered to detect a statistically significant difference in subgroups. The findings from our review are consistent with another drug class review that systematically reviewed the benefits and risks of medications for ADHD. Evidence from the short-term studies also indicated that GXR was statistically significantly superior to placebo for the outcomes of the Conners' Teacher Rating Scale-Revised (CTRS-R) scores, the Conners' Parent Rating Scale-Revised (CPRS-R) scores, and Clinical Global Impression (CGI) scores. Health-related quality of life (HRQoL) was evaluated with various instruments. Statistically significant improvements in HRQoL were observed with some instruments, but not all. Although numerous rating scales (CPRS/CTRS, CGI, Weiss Functional Impairment Rating Scale [WFIRS], and Child Health Questionnaire [CHQ]) are available, in the absence of a validated MCID for the change in these scales, the clinical relevance of these observed differences against placebo remains uncertain.

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Harms

Compared with placebo, more patients treated with GXR experienced adverse events (AEs). The rates of AEs in the GXR groups ranged from 61.5% to 88.4%, while they were 48.1% to 75.1% in the placebo group. The most commonly reported AEs in the GXR groups — in the monotherapy studies as well as the adjunctive therapy study — were somnolence, headache, sedation, and fatigue. In addition to these AEs, decreases in heart rate and blood pressure associated with the use of GXR are described in the product monograph. Serious AEs were rare in the included studies. Hypotension and cardiovascular AEs, which had been identified a priori as AEs of particular interest in the research protocol of this review, were rarely reported in the included trials. GXR-treated patients experienced higher rates of withdrawal due to AEs (2.7% to 23.3% in the GXR groups versus 0% to 7.6% in the placebo group).

In the study with an active treatment control, incidence of specific adverse events was similar in patients taking GXR compared with ATX, except for a higher incidence of somnolence.

The manufacturer performed an indirect comparison of GXR and ATX as monotherapy. There were statistically significant differences in mean change in ADHD-RS scores at end point, favouring GXR. Incomplete reporting of analyses did not allow a full analysis of methods. ███████████████████
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Pharmacoeconomic Summary

Background

GXR is being reviewed as a monotherapy or adjunctive therapy to psychostimulants for the treatment of ADHD for children aged six to 12 years. The recommended oral dose is 0.05 mg/kg to 0.012 mg/kg once daily for both monotherapy and adjunctive therapy. The daily cost of GXR is $██████ per tablet.

Summary of Economic Analysis

The manufacturer carried out two cost-effectiveness analyses (one for monotherapy and another for adjunctive therapy) based on similar Markov models.[1]

Monotherapy

The manufacturer conducted a cost-utility analysis comparing GXR with ATX over a one year time horizon from a payer perspective. In a second analysis, GXR was also compared with non-pharmacological treatment and placebo. The weekly cycle Markov model included the following health states: response (to ADHD treatment), no response, and treatment discontinuation. A matching-adjusted indirect comparison (MAIC) was used to estimate relative efficacy. (Note that data from a head-to-head trial of GXR compared with ATX [SPD503-316] have since become available.) The MAIC used patient-level data from the GXR trials (SPD503-301 and 304 trials and summary data published in the ATX trial) to adjust for differences in observed baseline characteristics among trials. Efficacy outcome was calculated as the mean change in ADHD-RS total scores from baseline to end point. A regression model was used to predict treatment response based on change in ADHD-RS total score, as the ATX trial included in the MAIC did not report response rate as an end point. Within each Markov cycle, patients can move from a health state of no response to response. The transition probability during the titration period was estimated from the regression model for GXR and ATX. At the end of the

titration period, transition was assumed to occur at a constant rate and was estimated for each treatment based on the two year rate observed in its respective long-term open-label trials.

AEs were assumed to occur at treatment initiation and persist through the entire titration period. The rates of AEs were based on those observed in the key clinical trials, although only AEs with rates of more than 5% were included in the model. Clinical parameters such as ADHD-RS score at baseline, response rate, and treatment discontinuation for non-pharmacological treatment were obtained from the placebo group. Quality of life associated with health states of response and no response was informed by a UK quality of life study in children with ADHD using the EuroQol Five-Dimension HRQoL Questionnaire filled in by parents of the patients (conference poster, further details not available). Disutilities associated with AEs were estimated from published literature. Medication costs were estimated by the manufacturer using list cost and weighted average dose. Health care resource utilization costs (primary care, mental health care, and emergency department visits) were based on a retrospective study, and it was assumed that "responders" had the same health care utilization as those with no diagnosis of ADHD.

Adjunctive Therapy
The manufacturer conducted a cost-utility analysis comparing psychostimulants and adjunctive GXR with psychostimulant monotherapy among children with ADHD who had a suboptimal response to psychostimulants. Suboptimal response was defined as treatment with a stable dose of psychostimulant for at least four weeks with no improvement in ADHD symptoms (ADHD-RS score ≥ 24 and CGI-Severity of Illness score [CGI-S] ≥ 3). The cost-utility analysis was based on a phase 3, double-blind, randomized, placebo-controlled, multi-centre, dose-optimization study, which compared GXR therapy in addition to psychostimulants with placebo plus psychostimulants. The reference case time horizon was one year, using the Canadian public payer perspective. The economic submission is based on a Markov model, which consisted of two stages: Week 0 to 8 (first stage) and Week 9 to 52 (second stage).

The weekly cycle Markov model included the following health states: severe (CGI-S score of "severely ill" or "among the most extremely ill subjects"); moderate (CGI-S score of "moderately ill" or "markedly ill"); mild (CGI-S score of "borderline ill" or "mildly ill"); and normal (CGI-S score of "normal"). All patients continued their assigned treatments during the first stage. In the second stage, patients in the moderate or severe states were considered non-responsive and thus permanently discontinued treatment. Within each Markov cycle, patients may move between health states. AEs that affected at least 5% of all treatment groups were included in the model.

Transition probabilities were calculated based on patient-level data from the phase 3 trial. In the base-case model, regression models (ordered logit model) were used to estimate the transition probabilities and were applied throughout the model period for patients remaining on treatments. A second model used a last observation carried forward (LOCF) method, in which the last observation from the trial at Week 8 was carried forward to Week 52. Quality of life was also informed by the same UK quality of life study used in the monotherapy model. Disutilities-associated AEs were taken from a US study of patients with depression. Drug costs were based on typical psychostimulant use in Canada (IMS Brogan); health care utilization costs were estimated in a similar manner as the monotherapy model (ADHD patient in the "normal" CGI-S score range = cost of patient with no ADHD diagnosis), and an assumption was made that costs would increase linearly by severity of health state (based on CGI-S score).

Results of Manufacturer's Analysis
Monotherapy
The manufacturer reported an incremental cost per quality-adjusted life-year (QALY) for GXR compared with ATX of $57,866 from the payer's perspective. The incremental cost-utility ratio (ICUR) for GXR compared with non-pharmacological treatment/placebo was $53,657 per QALY.

AdjunctiveTherapy
The manufacturer reported an incremental cost per QALY for GXR plus psychostimulants compared with psychostimulants alone of $23,720 from the payer's perspective. When the LOCF approach was used, the incremental cost per QALY was $35,669.

Interpretations and Key Limitations
- **Uncertainty in relative efficacy.** In the monotherapy model, when uncertainty in relative efficacy was explored, the ICUR changed substantially (from $57,866 to approximately $130,000 per QALY). The original manufacturer model did not provide variance estimates, nor was this uncertainty in relative efficacy (CGI-S) explored in the adjunctive model. In the manufacturer's resubmitted model, the ICUR increased to $65,528 per QALY (LOCF approach) when the lower 95% confidence interval was used for psychostimulants. The LOCF model may be more appropriate, given that it conservatively assumes that responses at 8 weeks will be seen at 52 weeks.
- **Translation of ADHD clinical trial outcomes to health states and quality of life.** The clinical relevance and true impact of ADHD-specific outcome measures are unclear (see APPENDIX 5: VALIDITY OF OUTCOME MEASURES). Furthermore, significant uncertainty exists in translating the ADHD-RS and CGI-S scales to a quality of life score. ██████████████████████████████ ██ ██
- **Resource utilization costs.** Both models used Guevara et al.'s study to estimate the health care utilization costs for patients with ADHD in the US. Since this is a US study based on Health Maintenance Organization data, it might not reflect resource utilization in Canada. More importantly, the study compared children with ADHD and children without ADHD; the latter was used to estimate the health care utilization cost for responders. It is unlikely that ADHD patients with a response would have the same primary care, mental health care, and emergency department visits as those without ADHD. This may bias in favour of GXR.
- **Assumptions on treatment discontinuation and other comparators.** Patients who discontinued treatment were assumed to remain off treatment and not to switch to new treatment in both models, as there was insufficient clinical evidence concerning how patients would be treated. However, patients may switch to other treatments, such as clonidine or antipsychotics, after failing GXR in clinical practice. In addition, other (potentially substantially less costly) comparators were not considered in the model. However, true standard of care for treatment discontinuation or use of other comparators appears to be variable, and may involve off-label use.
- **Short treatment duration.** The modelled time horizon for both models was one year. Although the one year time horizon has been commonly used in the literature on cost-effectiveness analysis of treatments for ADHD, it might not reflect clinical practice. According to the clinical experts, most children with ADHD are treated for at least two to three years, or even until adolescence or adulthood. Re-analyses on time horizon could not be conducted on provided models. However, the CADTH Common Drug Review (CDR) speculates that a time frame longer than one year would likely not alter the conclusions regarding relative cost-effectiveness.

Results of CADTH Common Drug Review Analysis
Monotherapy
Guanfacine Extended Release Versus Atomoxetine: In the CDR new base case, in which the medical costs for responders and non-responders were assumed to be equal, the ICUR was $64,449 per QALY. In one-way sensitivity analyses exploring efficacy and quality of life:

- When quality of life is assumed to be the same by treatment strategy, ATX dominates GXR.
- If the response rate from the head-to-head trial is used (instead of the rate from the MAIC), the ICUR is $93,909 per QALY.

GXR Versus Non-pharmacological Treatment: In the CDR new base case, in which the medical costs for responders and non-responders were assumed to be equal, the ICUR is $68,455 per QALY.

AdjunctiveTherapy
In the CDR analysis, in which the medical costs for responders and non-responders were assumed to be equal and the LOCF approach was used, the ICUR was $35,675 per QALY. Modification of transition probabilities to test possible variance in relative efficacy could not be performed on the original model, but was tested in manufacturer's resubmitted sensitivity analysis ($57,434 to $65,528 per QALY).

Issues for Consideration

- The proportion of patients treated using adjunctive therapy is likely to be small. As some patients and providers may prefer to avoid psychostimulants, it is possible that, if funded, GXR monotherapy may begin to supplant psychostimulant monotherapy (cost-effectiveness of GXR versus psychostimulants unknown) or increase the proportion of patients treated pharmacologically (with budget impact implications).
- It is arguable that HRQoL may not capture all relevant components of this disorder and its treatment. School performance, behaviour, and impact on family members may be relevant. While these aspects should be captured in HRQoL outcomes, it is not clear how completely these are integrated in this measure. As well, QALY may not capture all the purported benefits of treatment.

The major issue with the manufacturer's economic analysis is uncertainty in the ICUR values for both analyses. It is not clear how clinical trial outcomes translate into health state and attendant quality of life, given poor quality of data. Therefore, the true ICUR may differ from the estimates provided, but there are no data available to reduce this uncertainty. Furthermore, there is substantial uncertainty in relative efficacy, which has a major impact on cost-effectiveness estimates. When the uncertainty in relative efficacy (95% confidence interval) was explored in sensitivity analysis using the CDR reference case, the cost per QALY increased to between $92,000 and $181,000 per QALY for monotherapy. For adjunctive therapy, the ICUR increased to $57,434 to $65,528 per QALY when the 95% confidence interval was explored for the LOCF approach. The ICUR also increased to $35,181 per QALY when using the ordered logit approach.

In the CDR reference case, in which medical costs for responders and normal state were assumed to be equal, the ICUR increased to $64,449 (GXR versus ATX) and $68,455 (GXR versus non-pharmacological treatment) per QALY for monotherapy, and $35,675 per QALY for adjunctive therapy (using the LOCF approach).

Conclusions

In five well-designed RCTs, GXR monotherapy improved the symptoms of ADHD in children and adolescents compared with placebo. Measures of behavioural change and global impression also showed improvement for GXR compared with placebo, but there were no clinically meaningful differences observed in HRQoL. GXR monotherapy had a similar impact on measures of ADHD compared with atomoxetine monotherapy in one short-term RCT. GXR, used together with a psychostimulant, improved the symptoms of ADHD in children and adolescents with suboptimal response to psychostimulants as monotherapy, compared with placebo plus a psychostimulant.

AEs occurred more frequently in GXR-treated patients compared with placebo, although serious AEs were uncommon. Somnolence, headache, sedation, and fatigue were the most common complaints.

The key limitations of the evidence include lack of head-to-head comparisons between GXR and other active treatments, such as psychostimulants, which are the current standard of care for children with ADHD. The lack of long-term efficacy and safety data (i.e., beyond six months) is also a limitation, given that pharmacotherapy for ADHD is often long term. Additionally, there is a lack of data for patients who are in the lower body-weight categories.

TABLE 1: SUMMARY OF RESULTS (MONOTHERAPY, PLACEBO-CONTROLLED TRIAL)

Outcome	SPD503-301 GXR vs. PL, 8 weeks, N = 345				SPD503-304 GXR vs. PL, 9 weeks, N = 324					SPD503-307 GXR vs. PL, 9 weeks, N = 217		SPD503-314 GXR vs. PL, 9 weeks, N = 340			▮	▮
	GXR 2 mg/d N = 84	GXR 3 mg/d N = 82	GXR 4 mg/d N = 81	PL N = 78	GXR 1 mg/d N = 57	GXR 2 mg/d N = 63	GXR 3 mg/d N = 60	GXR 4 mg/d N = 63	PL N = 63	GXR 1 to 4 mg/d N = 136	PL N = 78	GXR 1 to 4 mg/d AM N = 107	GXR 1 to 4 mg/d PM N = 114	PL N = 112		
Mean change in ADHD-RS total score from baseline, (SD); *P* value vs. PL	−15.40 (12.82) *P* = 0.0006	−15.79 (13.00) *P* = 0.0005	−18.96 (13.71) *P* < 0.0001	−8.86 (12.90)	−20.4 (14.00) *P* = 0.0041	−18.0 (14.88) *P* = 0.0176	−19.4 (14.62) *P* = 0.0016	−20.9 (11.89) *P* = 0.0006	−12.2 (12.96)	−23.8 (14.43) *P* < 0.001	−11.4 (12.65)	−19.8 (12.95) *P* < 0.001	−20.1 (13.04) *P* < 0.001	−11.0 (12.93)		
Mean change in CPRS-R from baseline, (SD); *P* value vs. PL	−15.08 (14.60) *P* = 0.025	−14.70 (16.25) *P* = 0.035	−22.21 (17.02) *P* < 0.0001	−9.22 (16.12)	−20.61 (19.49) *P* = 0.001	−15.43 (19.56) *P* = 0.0468	−17.93 (19.02) *P* = 0.0056	−14.73 (16.87) *P* = 0.0237	−8.03 (17.57)	NR		−22.6 (20.48) *P* < 0.001	−21.2 (17.23) *P* < 0.001	−10.7 (17.61)		▮
Mean change in CTRS-R, (SD); *P* value vs. PL	−12.37 (14.86) *P* < 0.0001	−13.66 (19.04) *P* < 0.0001	−17.45 (16.10) *P* < 0.0001	−1.96 (13.05)	NR					NR		NR				▮
Mean change in CPRS-R:L, Oppositional Subscale, (SD)	NR				NR					−10.8 (7.23) *P* value vs. PL: <0.001	−7.0 (7.63)	NR				▮
CGI-I at end point, n (%), *P* value vs. PL	47 (55.95) *P* < 0.0001	41 (50.00) *P* = 0.0016	45 (55.56) *P* = 0.0001	20 (25.64)	31 (54.4) *P* = 0.007	27 (42.9) *P* = 0.1404	33 (55.0) *P* = 0.0055	35 (55.6) *P* = 0.0041	19 (30.2)	93 (71.5) *P* < 0.001	24 (32.0)	69 (66.3) *P* < 0.001	75 (67.0) *P* < 0.001	35 (31.8)		▮

	SPD503-301 GXR vs. PL, 8 weeks, N = 345				SPD503-304 GXR vs. PL, 9 weeks, N = 324					SPD503-307 GXR vs. PL, 9 weeks, N = 217		SPD503-314 GXR vs. PL, 9 weeks, N = 340			■	
Mean change in WFIRS-P from baseline, (SD); *P* value vs. PL	NR				NR					NR		−0.309 (0.4697) *P* = 0.004	−0.410 (0.4209) *P* = 0.001	−0.202 (0.3857)	■	■
Mean change in CHQ-PF50 Physical Summary from baseline (SD); *P* value vs. PL	0.21 (7.59) *P* = 0.97	−2.10 (7.08) *P* = 0.39	−2.70 (7.02) *P* = 0.29	0.65 (7.71)	0.42 (7.25) *P* = 0.80	0.42 (7.42) *P* = 0.78	−0.56 (8.58) *P* = 0.50	−3.38 (7.06) *P* = 0.07	0.39 (5.99)	NR		NR			■	
Mean change in CHQ-PF50 Psychosocial Summary from baseline (SD), *P* value vs. PL	8.16 (11.48) *P* = 0.14	9.80 (9.12) *P* = 0.14	10.12 (10.56) *P* = 0.02	6.24 (11.76)	11.04 (11.13) *P* = 0.04	8.09 (10.05) *P* = 0.59	9.28 (14.15) *P* = 0.21	8.54 (10.16) *P* = 0.15	5.86 (10.73)	NR		NR			■	
SAEs, n (%)	0	1 (1.2)	1 (1.2)	0	0	0	1 (1.5)	0	1 (1.5)	0	0	1 (0.9)	2 (1.8)	0	■	■
WDAEs, n (%)	9 (10.3)	13 (15.1)	20 (23.3)	1 (1.2)	2 (3.3)	2 (3.1)	6 (9.2)	9 (13.8)	5 (7.6)	12 (8.8)	0	8 (7.5)	8 (7.0)	0	■	■
TEAEs, n (%)	67 (77.0)	76 (88.4)	75 (87.2)	55 (64.0)	49 (80.3)	40 (61.5)	45 (69.2)	55 (84.6)	50 (75.8)	114 (83.8)	45 (57.7)	85 (79.4)	95 (83.3)	64 (57.1)	■	■

ADHD-RS = ADHD Rating Scale-IV; CGI-I = Clinical Global Impression–Improvement; CHQ-PF50 = Child Health Questionnaire–Parent Form; CPRS-R = Conners' Parent Rating Scale–Revised; CPRS-R:L = Conners' Parent Rating Scale–Revised long version; CTRS-R = Conners' Teacher Rating Scale–Revised; FAS = full analysis set; GXR = guanfacine extended release; LS = least squares; NR = not reported; PL = placebo; SAE = serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse event; vs. = versus; WDAE = withdrawal due to adverse event; WFIRS-P = Weiss Functional Impairment Rating Scale–Parent.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed childhood behavioural disorder. According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), ADHD is defined 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 developmental level."[2] Hyperactivity, impulsivity, and inattention are core symptoms of ADHD and may be exhibited as predominantly hyperactive/impulsive, inattentive, or a combined subtype. These symptoms affect children's cognitive, academic, behavioural, emotional, and social functioning.[3] The reported prevalence of ADHD in children varies from 2% to 18% worldwide, while the prevalence in school-aged children is estimated to be between 8% and 10%.[4] Incidence and prevalence rates of ADHD are similar among geographic locations, such as the US, Canada, and Europe.[5] The prevalence of ADHD increases with increasing age, and approximately two-thirds of children with ADHD receive pharmacotherapy.[4,6] It is reported that 87% of children with ADHD have at least one comorbid condition such as major depression, bipolar disorder, learning disorder, conduct disorder, tics, psychotic disorders, autism, and sleep-related disorders.[7]

The diagnosis and evaluation of ADHD includes comprehensive medical, developmental, educational, and psychosocial evaluation.[3] Behaviour rating scales (ADHD-specific or broadband) help to establish the presence of core symptoms of ADHD during the diagnostic evaluation. ADHD-specific rating scales are reported to have a sensitivity and specificity of greater than 90% when used in an appropriate population.[3]

The prognosis of young children with ADHD is associated with the initial clinical presentations, including severity of symptoms and comorbid conduct problems, intellect, social advantage, and the strength of ADHD response to any mode of treatment.[8]

1.2 Standards of Therapy

Treatment of ADHD includes behavioural interventions, medication, school-based interventions, parent-training and education programs, and psychological interventions. Efforts by health care professionals (treating clinician, pediatrician, dietitian, psychologist, psychiatrist, etc.), parents, and teachers are required.[7,8]

Medical management is a way to facilitate the other interventions. Medication combined with behavioural and psychological interventions are recommended for most school-aged children and adolescents with ADHD and moderate to severe impairment.[9] In the Canadian ADHD Resource Alliance clinical practice guideline, long-acting preparations of psychostimulants (amphetamine mixed salts, methylphenidate HCl, and lisdexamfetamine dimesylate) are recommended as the first-line drugs, while non-psychostimulants (atomoxetine, ATX) and short- and intermediate-acting preparations of psychostimulants are recommended as the second-line drugs.[7] ATX is preferred over stimulants for patients with a history of substance abuse or a strong family preference against stimulant medication. The long-acting preparation of selective alpha$_{2A}$-adrenergic receptor agonist (Intuniv XR) is recommended as second-line drug for treatment of ADHD in children aged six to 12 years with a suboptimal response to psychostimulants.[7] In previous trials, stimulants were reported to be more effective in reducing the core symptoms of ADHD than non-stimulants.[10] During treatment, the core symptoms and adverse effects can be monitored through parent and teacher feedback and ADHD rating

scales.[10] One study examined trends in ADHD medical treatment between 2000 and 2010 in the US, and found that psychostimulants remained the dominant treatment (96% of treatment visits in 2000 and 87% of treatment visits in 2010), while ATX use declined from 15% of treatment visits upon product launch in 2003 to 6% of treatment visits by 2010. All other therapies, such as clonidine, guanfacine, and bupropion, remained relatively constant at 5% to 9% of treatment visits.[11]

For children with ADHD with comorbid conditions, which often complicate the clinical manifestation of ADHD, the treatment should be determined by the more severe disorder.[7]

There are no recommendations from the clinical practice guidelines with respect to the treatment duration. The clinical expert consulted in this review indicated that, for children who respond well and tolerate the adverse effects from the drugs, pharmacotherapy is expected to continue until adulthood. Annual evaluations are needed in these children.

1.3   Drug

Guanfacine hydrochloride is a selective alpha$_{2A}$-adrenergic receptor agonist, and it has an affinity 15 to 20 times higher for this receptor subtype than for the alpha$_{2B}$ or alpha$_{2C}$ subtypes.[12] Guanfacine extended release (GXR; brand name: Intuniv XR) is indicated as monotherapy for the treatment of ADHD in children aged six to 12 years. It is also indicated as adjunctive therapy to psychostimulants for the treatment of ADHD in children aged six to 12 years with a suboptimal response to psychostimulants. GXR is supplied as oral tablets and should be swallowed without crushing, chewing, or breaking. The recommended starting dose for both monotherapy and adjunctive therapy to psychostimulants is 1 mg, taken orally once daily (morning or evening). The dose should be adjusted in increments of no more than 1 mg per week up to a maximum daily dose of 4 mg, for both monotherapy and adjunctive therapy to psychostimulants, according to the clinical response and tolerability.[12]

Indication under review
Monotherapy for the treatment of ADHD in children aged 6 to 12 years. It is also indicated as adjunctive therapy to psychostimulants for the treatment of ADHD in children aged 6 to 12 years with a suboptimal response to psychostimulants.
Listing criteria requested by sponsor
For treatment as monotherapy in children aged 6 to 12 years suffering from ADHD in whom it has not been possible to properly control the symptoms of the disease with methylphenidate and an amphetamine or for whom these drugs are contraindicated or inadvisable and as adjunctive therapy for treatment of ADHD in children aged 6 to 12 years with a suboptimal response to psychostimulants.

TABLE 2: KEY CHARACTERISTICS OF DRUGS USED TO TREAT ADHD

	Amphetamine formulations	Methylphenidate formulations	Non-stimulants	Alpha$_{2A}$-adrenergic receptor agonists
Drugs available in Canada	Lisdexamfetamine; amphetamine mixed salts; dextroamphetamine (short and intermediate-acting)	Methylphenidate (short, intermediate and long-acting)	Atomoxetine	Guanfacine extended release
Mechanism of action	Stimulate dopamine release; mechanism for alleviating ADHD symptoms not well understood	Inhibits dopamine and norepinephrine reuptake and stimulates their release	Norepinephrine reuptake inhibitor	Alpha$_{2A}$-adrenergic receptor agonist
Health Canada indication		ADHD (children ≥ 6 years), adolescents and adults		ADHD (children aged 6 to 12 years) as monotherapy or as adjunctive therapy to psychostimulants
Route of administration	Oral			
Recommended dose	Lisdexamfetamine: 30 mg/d to 60 mg/d; amphetamine mixed salts: 5 mg/d to 30 mg/d; dextroamphetamine: 5 mg/d to 40 mg/d	5 mg/d to 60 mg/d	10 mg/d to 100 mg/d	1 mg/d to 4 mg/d
Serious adverse effects/safety issues	Abuse potential, sudden death, increase in blood pressure, growth suppression, weight loss, psychosis, bipolar illness, seizure, blurred vision, aggression, exacerbation of motor tics		Suicide, induction of mania, psychosis, severe liver injury, effects on growth, decreased appetite, increased heart rate and blood pressure, orthostatic hypotension, sudden death	Somnolence, sedation, hypotension, bradycardia, syncope, elevation in blood pressure and heart rate, QTc interval increase (approximately 5 ms from baseline)

ADHA = attention-deficit/hyperactivity disorder; ms = milliseconds; QTc = corrected QT interval.
Source: product monographs of Adderall XR,[13] Vyvanse,[14] atomoxetine,[15] Dexedrine,[16] Concerta,[17] Biphentin.[18]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of Intuniv XR (GXR) as monotherapy for the treatment of ADHD in children aged six to 12 years, and as adjunctive therapy for treatment of ADHD in children aged six to 12 years with a suboptimal response to psychostimulants such as methylphenidate or amphetamine.

2.2 Method

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Children aged 6 to 12 years Subgroup: children in whom it has not been possible to properly control the symptoms of the disease with psychostimulants or for whom these drugs are contraindicated or inadvisable
Intervention	Guanfacine hydrochloride extended release tablets 1 mg to 4 mg daily
Comparators	• Amphetamines (immediate or sustained release) o lisdexamfetamine dimesylate o amphetamine mixed salts o dextroamphetamine • Methylphenidate (immediate or sustained release) • Atomoxetine • Clonidine • Placebo or no treatment • Behavioural therapy
Outcomes	**Key efficacy outcomes:** Behavioural, functional, developmental, or cognitive outcomes assessed by validated scales Health-related quality of life **Harms outcomes:** SAEs, WDAEs, mortality, AEs, and AEs of particular interest (hypotension, cardiovascular AEs, etc.)
Study Design	Published and unpublished DB RCTs

AE = adverse event; DB = double-blind; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Supplemental issues:
• Validity of outcome measures reported in the included clinical trials.
• Long-term efficacy and safety of GXR in open-label extension phases of short-term double-blind randomized controlled trials (RCTs).
• Critical appraisal of the manufacture-submitted indirect comparison between GXR (as monotherapy) and psychostimulants and other non-psychostimulants.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Intuniv XR (guanfacine).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on January 8, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on May 21, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search, and Open Access Journals. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3.   RESULTS

3.1   Findings from the Literature

A total of eight double-blind RCTs were identified from the literature for inclusion in the systematic review (Figure 1). Trial characteristics of six phase 3 trials in which GXR was used as monotherapy are summarized in Table 4 and described in Section 3.2. One trial assessed the effectiveness and safety of combination of GXR plus a psychostimulant in patients with suboptimal response to psychostimulant. This trial is described in Table 5. One phase 2 non-inferiority study relevant to this review is described in Section 3.2 as well. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES
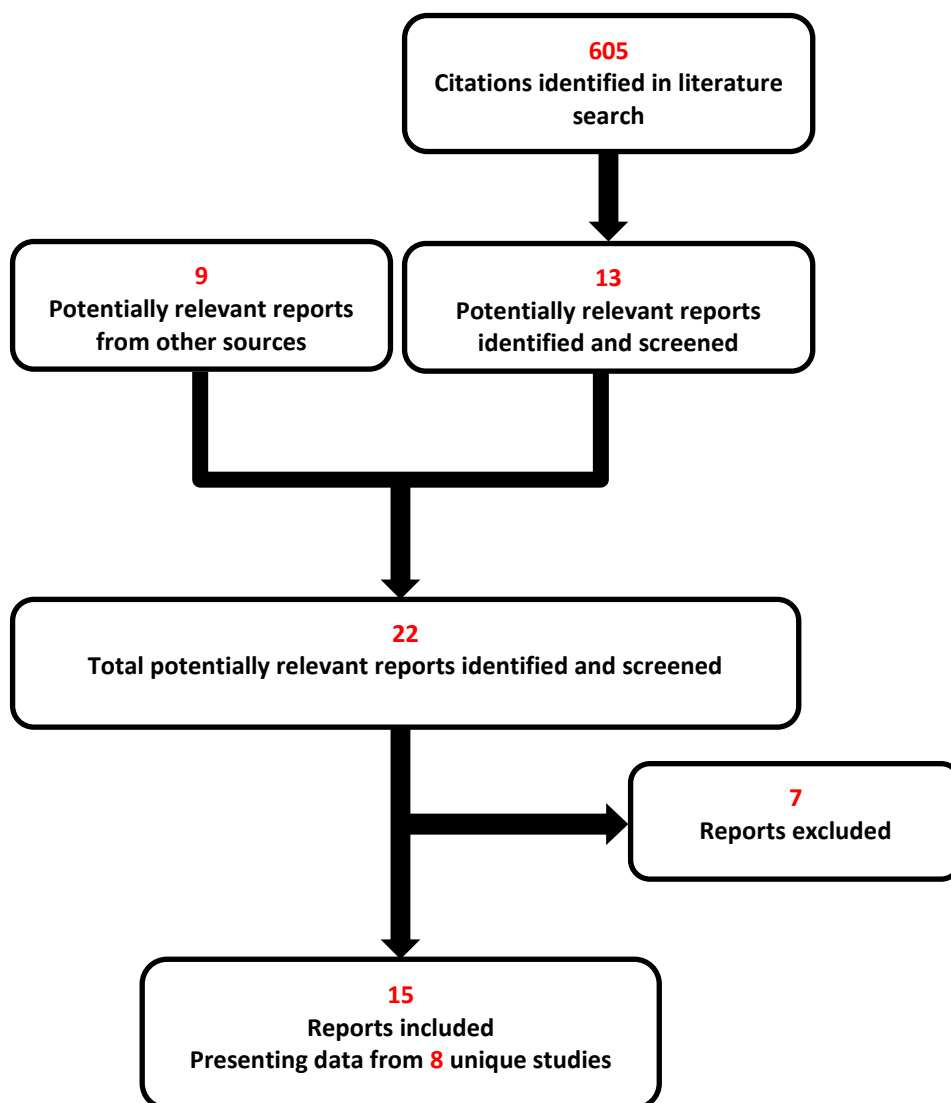
QUOROM = Quality of Reporting of Meta-analyses

TABLE 4: DETAILS OF INCLUDED STUDIES – GXR AS MONOTHERAPY (PLACEBO-CONTROLLED AND ACTIVE-CONTROLLED TRIALS)

		SPD503-301	SPD503-304	SPD503-307	SPD503-314	SPD503-315	SPD503-316
DESIGNS AND POPULATIONS	**Study design**	DB RCT					
	Locations	48 centres in the US	51 centres in the US	33 centres in the US	47 centres in Canada and the US	67 centres in Canada, the US, and Europe	58 centres in Canada, the US, and Europe
	Randomized (N)	345	324	217	340	316 involved in the DB phase	338
	Inclusion criteria	Aged **6 to 17** years, (ADHD-RS total score not specified)	Aged **6 to 17** years, an ADHD-RS total score ≥ **24**	Aged **6 to 12** years, with oppositional symptoms, an ADHD-RS total score ≥ **24**	Aged **6 to 12** years, diagnosis of ADHD with combined subtype or impulsive/ hyperactive subtype, ADHD-RS total score of ≥ **28** and CGI-S score ≥ 4 at baseline	Aged **6 to 17** years, ADHD-RS total score ≥ **32** and CGI-S score of ≥ 4	Aged **6 to 17** years, ADHD-RS total score ≥ **32** and CGI-S score of ≥ 4
		Diagnosis of ADHD using DSM-IV-TR criteria and normal/non-significant ECG findings, intellectually functioning at age-appropriate levels, BP within the 95th percentile for age, gender, and height					
	Exclusion criteria	Current uncontrolled comorbid psychiatric diagnosis (except ODD) with significant symptoms; weight < 55 lb or morbidly overweight; hypertensive; any cardiac condition; current use of medications that affect the CNS, blood pressure, or heart rate; pregnant or lactating					
		Seizure during the last 2 years, tic disorder, Tourette syndrome, taking an investigational drug < 28 days before baseline	Seizure during the last 2 years, tic disorder, Tourette syndrome, taking an investigational drug < 30 days before baseline, or medications that have CNS effects or affect performance	Use of another investigational product in a clinical study < 30 days before screening, history of alcohol/other substance abuse or dependence	At risk for suicide, primary sleep disorder, history of seizure, tic disorder Tourette syndrome, use of another investigational product in a clinical study < 30 days before baseline, history of alcohol/other substance abuse or dependence	Children aged 6 to 12 years with a body weight of < 25 kg or adolescents with a body weight of < 34 kg or > 91 kg, seizure disorder, serious tic disorder, Tourette syndrome, use of another investigational product in a clinical study < 30 days before screening	Children aged 6 to 12 years with a body weight of < 25 kg or adolescents with a body weight of < 34 kg or > 91 kg, seizure disorder, serious tic disorder, Tourette syndrome, use of another investigational product in a clinical study < 30 days before screening

		SPD503-301	SPD503-304	SPD503-307	SPD503-314	SPD503-315	SPD503-316
DRUGS	**Intervention**	GXR 2 mg, 3 mg, or 4 mg q.d. P.O.	GXR 1 mg, 2 mg, 3 mg, or 4 mg q.d. P.O.	GXR 1 mg to 4 mg q.d. P.O.	GXR 1 mg to 4 mg q.d. P.O.in the morning (GXR AM) GXR 1 to 4 mg q.d. P.O.in the evening (GXR PM)	GXR 1 mg to 4 mg q.d. P.O. for children 6 to 12 years, maximum of 4 mg to 7 mg for adolescents 13 to 17 years	GXR 1 mg to 4 mg q.d. P.O. for children 6 to 12 years, maximum of 4 to 7 mg for adolescents 13 to 17 years
	Comparator(s)	PL	PL	PL	PL	PL	ATX (up to 1.4 mg/kg/d for children 6 to 12 years or adolescents < 70 kg; or up to 100 mg/d for children or adolescents ≥ 70 kg); P.O.
DURATION	**Phase**						
	Washout	1 week, or minimum of 5 times the established half-life of the prior medications	1 week, or minimum of 5 times the established half-life of the prior medications	3 days, or minimum of 5 times the established half-life of the prior medications	Minimum of 5 times the half-life of the prior medications	3 to 35 days or 5 times the established half-life of the prior medications	3 to 35 days
	Double-blind	8 weeks (titration: 5 weeks; tapering: 3 weeks; no maintenance)	9 weeks (titration: 3 weeks; maintenance: 3 weeks; tapering: 3 weeks)	9 weeks (titration: 5 weeks; maintenance: 3 weeks; tapering: 1 week)	65 days (titration: 5 weeks; maintenance: 3 weeks; tapering: 1 week)	26 weeks following a 13 week open-label optimization/ maintenance period (titration: 7 weeks; maintenance: 6 weeks) Tapering: 2 weeks after the 26-week DB period	10 weeks for children 6 to 12 years (titration: 4 weeks; maintenance: 6 weeks; tapering: 2 weeks after DB period) 13 weeks for adolescents 13 to 17 years
	Follow-up	30 ± 2 days following the patient's last dose of study drug	Up to 30 ± 2 days following the patient's last dose of study drug	30 ± 2 days following the patient's last dose of study drug	7 days following the patient's last dose of study drug	1 week after the last dose of study drug	7 to 9 days after the last dose of study drug

		SPD503-301	SPD503-304	SPD503-307	SPD503-314	SPD503-315	SPD503-316
OUTCOMES	**Primary end point**	ADHD-RS total scores at the last treatment week before dose tapering (week 5)	ADHD-RS total scores at the last treatment week before dose tapering (week 6)	Oppositional Subscale of CPRS-R:L, measured after baseline and before first dose taper medication (week 8)	ADHD-RS total scores at the last on-treatment visit of the dose titration or dose maintenance period (week 8)	Treatment failure (defined as patients who had a ≥ 50% increase in ADHD-RS total score and a ≥ 2-point increase in CGI-S score compared with the respective scores at the DB baseline visit, at 2 consecutive visits; and those discontinued the study for any reason)	ADHD-RS total score at the last treatment week before dose tapering (week 10)
	Other end points	CPRS-R CTRS-R CGI-S CGI-I HRQoL measured by CHQ (completed by parent/caregiver or children ≥ 10 years) Safety	CPRS-R CGI-S CGI-I HRQoL measured by CHQ Safety	ADHD-RS scores CGI-S CGI-I Safety	CGI-S CGI-I CPRS-R HRQoL measured by WFIRS-P and HUI2/3 (completed by parent/caregiver) Safety	ADHD-RS total scores CGI-S CGI-I HRQoL measured by WFIRS-P and HUI2/3 Safety	CGI-S CGI-I HRQoL measured by WFIRS-P and HUI2/3 Safety
NOTES	**Publications**	Biederman et al., 2008[19]	Sallee et al., 2009[20]	Connor et al., 2010[21]	Newcorn et al., 2013[22]	NA	NA

ADHD = attention-deficit/hyperactivity disorder; ADHD-RS = ADHD Rating Scale-IV; ATX = atomoxetine; BP = blood pressure; CDR = CADTH Common Drug Review; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity of Illness; CHQ = Child Health Questionnaire; CNS = central nervous system; CPRS-R = Conners' Parent Rating Scale–Revised: Short Form; CTRS-R = Conners' Teacher Rating Scale–Revised: Short Form; DB = double-blind; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; ECG = electrocardiogram; GXR = guanfacine extended release; HRQoL = health-related quality of life; HUI2/3 = Health Utilities Index Mark 2 and Mark 3; NA = not available; ODD = oppositional defiant disorder; PL = placebo; P.O. = oral administration; q.d. = once daily; RCT = randomized controlled trial; WFIRS-P = Weiss Functional Impairment Rating Scale–Parent.
Note: Three additional reports were included (CDR submission binder,[23] Health Canada reviewer's report,[24] US Food Drug Administraton statistical review[25]).
Source: Clinical study reports for SPD503-301,[26] SPD503-304,[27] SPD503-307,[28] SPD503-314,[29] SPD503-315,[30] and SPD503-316.[31]

TABLE 5: DETAILS OF INCLUDED STUDIES — GXR AS ADJUNCTIVE THERAPY (PLACEBO-CONTROLLED)

		SPD503-313
DESIGNS & POPULATIONS	**Study design**	DB RCT
	Locations	59 centres in the US
	Randomized (N)	461
	Inclusion criteria	Aged 6 to 17 years, diagnosis of ADHD, had a suboptimal response (defined as treatment with a stable dose of psychostimulant for at least 4 weeks with improvement; however, mild to moderate ADHD symptoms remain present, ADHD-RS ≥ 24 and CGI-S ≥3) to their current, long-acting psychostimulant
	Exclusion criteria	Current, controlled/uncontrolled comorbid psychiatric diagnosis (except ODD), including any severe comorbid DSM-IV-TR Axis II disorders or severe Axis I disorders; body weight of < 55 lbs or > 176 lbs; presence of cardiac abnormalities; or risk of suicide
DRUGS	**Intervention**	GXR (1 mg/d to 4 mg/d) in the morning + psychostimulant, P.O. GXR (1 mg/d to 4 mg/d) at bedtime + psychostimulant, P.O.
	Comparator(s)	PL + psychostimulant
DURATION	**Phase**	
	Washout	5 times the established half-life of the prohibited medications
	Double-blind	9 weeks (titration: 5 weeks; maintenance: 3 weeks; tapering: ≤ 9 days)
	Follow-up	1 week after the final dose of study drug
OUTCOMES	**Primary end point**	ADHD-RS total scores at the last treatment week before dose tapering (Week 8)
	Other end points	CGI-S CGI-I Safety
NOTES	**Publications**	Wilens et al., 2012[32] Wilens et al., 2013[33]

ADHD = attention-deficit/hyperactivity disorder; ADHD-RS = ADHD Rating Scale-IV; CDR = CADTH Common Drug Review; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity of Illness; DB = double-blind; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; GXR = guanfacine extended release; ODD = oppositional defiant disorder; PL = placebo; P.O. = oral administration; RCT = randomized controlled trial.
Note: Three additional reports were included (CDR submission binder,[23] Health Canada reviewer's report,[24] US Food and Drug Administration statistical review[25]).
Source: Clinical study report for SPD503-313.[34]

3.2 Included Studies

3.2.1 Description of Studies

In total, eight trials were included in this systematic review. Six randomized, double-blind, phase 3 placebo- or active-controlled trials (SPD503-301,[26] 304,[27] 307,[28] 314,[29] 315,[30] and 316[31]) evaluating the clinical efficacy and safety of GXR as monotherapy in school-age children with ADHD are summarized in Table 4. One double-blind RCT[34] assessing the effectiveness and safety of a combination of GXR and a psychostimulant in children with ADHD with suboptimal response to psychostimulant is presented in Table 5. Findings from a phase 2 study[35] are also summarized briefly in Section 3.8.

All patients were followed for 1 week to 30 days after the last dose of study drug for safety assessment.

3.2.2   Populations
a)   Inclusion and Exclusion Criteria

The included studies enrolled school-aged children with a diagnosis of ADHD and an ADHD-RS total score of at least 24 to 32 at screening. Study participants were required to have age-appropriate intellectual functioning, normal results of electrocardiography, and normal blood pressure. In Study 313, in which GXR was given as adjunctive therapy, patients were required to have a suboptimal response to previous psychostimulant, defined as treatment with a stable dose of psychostimulant for at least four weeks with improvement; however, mild to moderate ADHD symptoms remained present, and the ADHD-RS total score was ≥ 24 and the Clinical Global Impression–Severity of Illness (CGI-S) score was ≥ 3. In Study 315, patients who met the protocol-defined response criteria at the end of the open-label dose titration and dose maintenance phases entered a 26 week double-blind treatment period. The response criteria were defined as a reduction of at least 30% in the ADHD-RS total score and a CGI-S score of 1 or 2 with tolerable adverse effects.

Children were excluded from all studies if they had co-existing controlled or uncontrolled psychiatric conditions or any cardiac conditions, were underweight or overweight, were taking an investigational drug within one month before the screening, or were taking medications that might have central nervous system effects or affect performance.

b)   Baseline Characteristics

The included studies were primarily conducted in North America and enrolled patients from Canada and the US. Two studies also included patients from European countries.[30,31]

There were no notable differences observed in patient characteristics of any of the included trials between GXR and placebo groups, or between GXR and active-control groups. Children in Studies 307[28] and 314[29] were six to 12 years of age, while in other studies patients were six to 17 years of age. In studies enrolling older children, 68% to 89% of them were younger than 12 years old. In general, more boys than girls participated in the studies. The majority of the children (61% to 98%) were diagnosed with the combined subtype of ADHD. The mean ADHD-RS total score ranged from 36 to 44 across all trials at baseline, indicating moderate to severe ADHD symptoms. In Study 313,[34] in which GXR was used as adjunctive therapy to a psychostimulant, the commonly used concomitant psychostimulants were Concerta (methylphenidate HCl), Vyvanse (lisdexamfetamine dimesylate), and Adderall XR (amphetamine mixed salts). Proportions of the use of such psychostimulants were similar between treatment arms.

A summary of the characteristics for the included studies are presented Table 6, Table 7 and Table 8.

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS — GXR AS MONOTHERAPY (PLACEBO-CONTROLLED TRIALS)

Title	SPD503-301				SPD503-304					SPD503-307		SPD503-314			SPD503-315	
	GXR 2 mg/d (N = 87)	GXR 3 mg/d (N = 86)	GXR 4 mg/d (N = 86)	PL (N = 86)	GXR 1 mg/d (N = 61)	GXR 2 mg/d (N = 65)	GXR 3 mg/d (N = 65)	GXR 4 mg/d (N = 65)	PL (N = 66)	GXR 1 mg, 2 mg, 3 mg, and 4 mg/d (N = 136)	PL (N = 86)	GXR AM (N = 107)	GXR PM (N = 114)	PL (N = 112)		
Age (years)																
Mean (SD)	10.6 (2.35)	10.8 (2.76)	10.1 (2.86)	10.6 (2.70)	9.3 (2.14)	10.6 (2.81)	11.1 (2.96)	10.5 (2.53)	10.8 (2.89)	9.4 (1.73)	9.3 (2.04)	9.1 (1.77)	9.3 (1.76)	8.9 (1.78)	■	■
Range	6 to 16	6 to 17	6 to 17	6 to 17	6 to 13	5 to 17	6 to 17	6 to 16	6 to 17	6 to 12	6 to 13	6 to 12	6 to 12	6 to 12	■	■
6 to 12 years, n (%)	69 (79.3)	60 (69.8)	70 (81.4)	66 (76.7)	54 (88.5)	47 (72.3)	44 (67.7)	50 (76.9)	46 (69.7)	136 (100)	78 (100)	107 (100)	114 (100)	112 (100)	■	■
13 to 17 years, n (%)	18 (20.7)	26 (30.2)	16 (18.6)	20 (23.3)	7 (11.5)	17 (26.2)	21 (32.3)	15 (23.1)	20 (30.3)	NA		NA			■	■
Gender, n (%)																
Male	67 (77.0)	69 (80.2)	57 (66.3)	64 (74.4)	41 (67.2)	46 (70.8)	48 (73.8)	53 (81.5)	45 (68.2)	87 (64.0)	60 (76.9)	72 (67.3)	78 (68.4)	85 (75.9)	■	■
Female	20 (23.0)	17 (19.8)	29 (33.7)	22 (25.6)	20 (32.8)	19 (29.2)	17 (26.2)	12 (18.5)	21 (31.8)	49 (36.0)	18 (23.1)	35 (32.7)	36 (31.6)	27 (24.1)	■	■
Weight (lb)																
Mean (SD)	98.9 (38.45)	97.9 (36.47)	93.2 (35.64)	93.8 (31.08)	77.2 (16.7)	99.1 (32.1)	102.6 (39.7)	100.7 (37.4)	98.8 (37.2)	79.9 (20.48)	77.6 (21.77)	77.95 (19.44)	80.38 (20.91)	75.79 (17.57)	■	■
Range	55 to 271	55 to 197	54 to 207	55 to 175	55 to 109	55 to 183	56 to 220	55 to 185	55 to 237	55 to 138	55 to 140	55 to 141	55 to 151	55 to 140	■	■
Height (in)																
Mean (SD)	58.0 (6.15)	57.8 (7.06)	56.2 (6.08)	57.1 (6.58)	54.23 (4.50)	57.67 (6.28)	58.12 (6.66)	57.59 (6.00)	57.7 (6.29)	55.2 (4.75)	55.0 (5.05)	54.93 (4.31)	55.20 (4.41)	54.16 (3.88)	■	■
Range	47 to 73	44 to 71	46 to 71	46 to 73	47 to 64	47 to 71	46 to 72	48 to 68	41 to 71	47 to 66	47 to 66	45.5 to 67	47 to 67.5	46 to 62.5	■	■
ADHD subtype, n (%)																
Inattentive	28 (32.2)	20 (23.3)	23 (26.7)	19 (22.1)	12 (19.7)	14 (21.5)	15 (23.1)	18 (27.7)	23 (34.8)	16 (11.8)	11 (14.1)	3 (2.8)[a]	3 (2.6)[a]	1 (0.9)[a]	■	■
Hyperactive-impulsive	4 (4.6)	1 (1.2)	2 (2.3)	0	1 (1.6)	1 (1.5)	1 (1.5)	0	3 (4.5)	3 (2.2)	4 (5.1)	3 (2.8)	2 (1.8)	1 (0.9)	■	■
Combined	55 (63.2)	65 (75.6)	61 (70.9)	67 (77.9)	48 (78.7)	50 (76.9)	49 (75.4)	47 (72.3)	40 (60.6)	117 (86.0)	63 (80.8)	101 (94.4)	109 (95.6)	110 (98.2)	■	■

Title	SPD503-301				SPD503-304					SPD503-307		SPD503-314			SPD503-315	
	GXR 2 mg/d (N = 87)	GXR 3 mg/d (N = 86)	GXR 4 mg/d (N = 86)	PL (N = 86)	GXR 1 mg/d (N = 61)	GXR 2 mg/d (N = 65)	GXR 3 mg/d (N = 65)	GXR 4 mg/d (N = 65)	PL (N = 66)	GXR 1 mg, 2 mg, 3 mg, and 4 mg/d (N = 136)	PL (N = 86)	GXR AM (N = 107)	GXR PM (N = 114)	PL (N = 112)		
Years since ADHD diagnosis																
Mean (SD)	2.31 (2.86)	3.03 (3.01)	2.39 (3.14)	2.71 (3.56)	1.2 (2.01)	2.0 (2.80)	2.3 (2.90)	2.1 (2.99)	2.3 (3.01)	2.65 (2.36)	2.68 (2.48)	1.5 (2.12)	2.0 (2.24)	1.6 (2.13)		
Range	0 to 13	0 to 10	0 to 13	0 to 12	0 to 8	0 to 12	0 to 14	0 to 11	0 to 11	0 to 7.9	0 to 8.5	0 to 8	0 to 9	0 to 8		
ADHD-RS total score at baseline (ITT/FAS population)																
Mean (SD)	36.10 (9.99)	36.77 (8.72)	38.40 (9.21)	38.14 (9.34)	41.7 (7.81)	39.9 (8.74)	39.1 (9.22)	40.6 (8.57)	39.3 (8.85)	42.3 (7.70)	42.3 (8.08)	41.7 (6.39)	41.6 (6.66)	42.9 (6.21)		
Range	11 to 54	17 to 54	15 to 54	13 to 54	24 to 54	21 to 54	18 to 52	25 to 54	24 to 54	25 to 54	26 to 54	28 to 54	29 to 53	28 to 54		
CPRS-R at baseline (ITT population)																
Mean (SD)	42.92 (18.48)	42.32 (18.29)	43.71 (16.41)	44.98 (17.77)	46.55 (17.02)	44.25 (19.71)	45.33 (18.70)	40.31 (20.40)	43.38 (16.83)	NR		47.0 (18.88)	48.0 (15.63)	49.6 (17.51)		
CTRS-R at baseline (ITT population)																
Mean (SD)	34.23 (20.11)	33.19 (17.34)	38.11 (17.10)	33.86 (19.40)	NR					NR		NR				
CGI-S at baseline (ITT population)																
Mean (SD)	4.61 (0.74)	4.61 (0.66)	4.68 (0.67)	4.65 (0.79)	4.8 (0.79)	4.6 (0.75)	4.6 (0.77)	4.8 (0.78)	4.7 (0.68)	NR		All patients' score > 2				
CHQ-PF50 scores at baseline (ITT population)																
Physical Summary, mean (SD)	56.60 (7.68)	56.12 (6.34)	57.62 (6.10)	54.85 (8.10)	56.76 (6.73)	56.67 (8.35)	56.74 (6.79)	57.85 (6.39)	56.19 (8.44)	NR		NR				
Psychosocial Summary, mean (SD)	34.96 (12.86)	31.80 (9.72)	33.78 (10.00)	32.50 (10.98)	33.75 (10.28)	32.55 (10.84)	33.85 (12.45)	36.09 (10.71)	35.31 (9.43)	NR		NR				

ADHD = attention-deficit/hyperactivity disorder; CGI-S = Clinical Global Impression–Severity of Illness; CPRS-R = Conners' Parent Rating Scales–Revised: Short Form; CTRS-R = Conners' Teacher Rating Scales–Revised: Short Form; FAS = full analysis set;
GXR = guanfacine extended release; GXR AM = GXR administered in the morning; GXR PM = GXR administered in the evening; ITT = intention to treat; NA = not applicable; NR = not reported; PL = placebo; SD = standard deviation.
[a]Only the combined subtype and impulsive-hyperactive subtype were included in this study.
Source: Clinical study reports for SPD503-301,[26] 304,[27] 307,[28] 314,[29] and 315.[30]

TABLE 7: SUMMARY OF BASELINE CHARACTERISTICS — GXR AS MONOTHERAPY (ACTIVE-CONTROLLED TRIAL)

Title	SPD503-316		
	███████	████████	█ █
Age (years)			
████████	██████	██████	██████
██████	██	██	██
████████████	██████	██████	██████
██████████	██████	██████	██████
Gender, n (%)			
██████	██████	██████	██████
██████	██████	██████	██████
ADHD subtype, n (%)			
██████████	██████	██████	██████
██████████████	███	███	███
██████	██████	██████	██████
Years since ADHD diagnosis			
████████	██████	██████	██████
██████	██	██	██
ADHD-RS total score at baseline (FAS population)			
████████	██████	██████	██████
██████	██	██	██
CGI-S at baseline			
████████████	█	█	█
██████████████	██	██	██

██
████████████████████

Source: Clinical study report of SPD503-316.[31]

TABLE 8: SUMMARY OF BASELINE CHARACTERISTICS – GXR AS ADJUNCTIVE THERAPY (PLACEBO-CONTROLLED TRIALS)

Title	SPD503-313		
	GXR AM + psychostimulant N = 150	GXR PM + psychostimulant N = 152	PL + psychostimulant N = 153
Age (years)			
Mean (SD)	11.0 (2.6)	10.6 (2.3)	10.8 (2.3)
Range	6 to 17	6 to 17	6 to 17
6 to 12 years, n (%)	114 (76.0)	124 (81.6)	123 (80.4)
13 to 17 years, n (%)	36 (24.0)	28 (18.4)	30 (19.6)
Gender, n (%)			
Male	108 (72.0)	106 (69.7)	112 (73.2)
Female	42 (28.0)	46 (30.3)	41 (26.8)
Height (in)			
Mean (SD)	58.10 (6.0)	57.05 (5.4)	57.65 (5.5)
Range	46.0 to 73.7	46.4 to 71.0	47.6 to 70.0
Weight (lb)			
Mean (SD)	90.76 (29.7)	85.40 (26.5)	89.14 (27.9)
Range	55.0 to 175.0	55.0 to 164.0	55.0 to 164.0
ADHD subtype, n (%)			
Inattentive	31 (20.7)	24 (15.8)	26 (17.0)
Hyperactive-impulsive	3 (2.0)	2 (1.3)	1 (0.7)
Combined	116 (77.3)	126 (82.9)	126 (82.4)
Years since ADHD diagnosis			
Mean (SD)	3.9 (2.8)	3.8 (2.87)	3.9 (2.99)
Range	0 to 11	0 to 13	0 to 15
Concomitant psychostimulant, %			
amphetamine mixed salts (Adderall XR)	17.3	18.4	17.6
methylphenidate HCl (Concerta)	46.0	44.7	45.1
Dexmethylphenidate HCl (Focalin XR)	6.0	5.9	5.9
methylphenidate HCl (Metadate CD)	1.3	0.7	1.3
methylphenidate HCl (Ritalin LA)	0.7	0.0	0.7
lisdexamfetamine dimesylate (Vyvanse)	28.7	30.3	29.4
ADHD-RS total score at baseline (FAS population)			
Mean (SD)	37.6 (8.13)	37.0 (7.65)	37.7 (7.75)
Range	16 to 54	16 to 54	16 to 54

ADHD = attention-deficit/hyperactivity disorder; CGI-S = Clinical Global Impression–Severity of Illness; GXR AM = guanfacine extended release administered in the morning; GXR PM = guanfacine extended release administered in the evening; SD = standard deviation.
Source: Clinical study report (CSR) for Study 313.[34]

3.2.3   Interventions and Comparators

After screening, eligible patients were randomized to GXR 1 mg to 4 mg once daily or a matching placebo in double-blind manner. Treatment comprised dose optimization, dose maintenance, and dose tapering periods. Patients' doses were usually escalated in 1 mg weekly, beginning at 1 mg once daily at Week 1, and were reduced in 1 mg weekly in the dose tapering period until the GXR doses returned to 1 mg once daily. After the double-blind treatment phase, patients discontinued the treatment or had the option of entering the open-label extension phase (APPENDIX 6: SUMMARY OF OTHER STUDIES) in some studies (Studies 301 and 304). The maximum daily dose for GXR for children six to 12 years was 4 mg once daily. Adolescents aged 13 to 17 years in the 58.5 kg to 91.0 kg weight group may have had the opportunity to be titrated to 7 mg once daily, which is higher than the recommended maximum dose of 4 mg once daily.[12] In Study 313, concomitant psychostimulant was allowed in both GXR and placebo groups.

All but one study evaluated the short-term effects of the study drug, with treatment durations ranging from 8 to 10 weeks. The efficacy outcomes in the included studies were assessed before dose tapering; therefore, the treatment effects of GXR were in fact evaluated in an even shorter (5 to 10 week) period. In Study 315,[30] all patients received 13 weeks' open-label GXR therapy after screening. After the open-label phase, patients who met the pre-defined response criteria (defined as a reduction of at least 30% from the open-label baseline visit in the ADHD-RS total score and a CGI-S score of 1 or 2 with tolerable adverse events [AEs]) entered a 26-week double-blind treatment period during which GXR was compared with placebo.

In Study 316,[31] patients were randomized to GXR, ATX, or placebo in a double-blind, double-dummy manner. The doses of ATX were based on patients' baseline body weight. For children aged six to 12 years and adolescents aged 13 to 17 years with body weight < 70 kg, dosing was initiated with approximately 0.5 mg/kg once daily, and may have been increased to the target of approximately 1.2 mg/kg once daily. The total daily dose did not exceed 1.4 mg/kg once daily. For children and adolescents with body weight ≥ 70 kg, the maximal daily dose was not permitted to exceed 100 mg.

3.2.4   Outcomes

Detailed descriptions of the outcome measures adopted in the included studies are presented in APPENDIX 5: VALIDITY OF OUTCOME MEASURES.

a)   ADHD Rating Scale-IV Total Score

This outcome measures the behaviours of children with ADHD. It consists of 18 items designed to reflect current symptoms of ADHD based on DSM-IV criteria. Each item is scored from a range of 0 (no symptoms) to 3 (severe symptoms), with total scores ranging from 0 to 54. The 18 items may be grouped into two subscales: hyperactivity/impulsivity and inattentiveness. The ADHD-RS was administered by the clinician in the included studies at each visit, except for the dose tapering visit, to capture the ADHD symptoms within each study week. This was a primary outcome in most of the included studies, and a secondary outcome in Study 315. While there is no consensus on a minimal clinically important difference (MCID), some publications have suggested a range of 5.2 to 7.7 for the ADHD-RS total score difference between treatment and placebo.

b)   Conners' Parent Rating Scale and Conners' Teacher Rating Scale

These scales measure a cross-section of ADHD-related symptoms and problem behaviours, and are completed by parent/caregiver or teacher. The Conners' Parent Rating Scale–Revised: Short Form (CPRS-R) contains 27 questions in 4 subscales (oppositional, cognitive problems, hyperactivity, and

ADHD Index) relating to the child's behaviours. The Conners' Teacher Rating Scale (CTRS) has 28 questions in the same subscales. Each item is scored from a range of 0 (reflecting no symptoms) to 3 (reflecting severe symptoms). A clear definition of MCID for these scales has not been established.

The long form version of the parents' scale (CPRS-R:L) is a comprehensive, multi-dimensional 80-item rating scale designed to evaluate problem behaviours, ADHD, and comorbid disorders based on current DSM-IV symptoms. Its oppositional subscale contains 10 items designed to reflect DSM-IV criteria for oppositional defiant disorder. Each item is scored from a range of 0 (not true at all) to 3 (very much true) with total scores ranging from 0 to 30 for this subscale. This outcome was the primary outcome in Study 307.

b)   Clinical Global Impression
CGI-S is a seven-point scale ranging from 1 (normal, no symptoms) to 7 (among the most extremely ill patients, very severe symptoms), and it permits a global evaluation of the patient's severity of illness. At baseline and each visit of all included studies, except for the dose tapering visit, the investigator used CGI-S to rate the severity of the patient's condition.

During the treatment, the investigator assessed the patient's improvement relative to his or her symptoms at baseline using Clinical Global Impression–Improvement (CGI-I), a seven-point scale ranging from 1 (very much improved) to 7 (very much worse). Some suggest an MCID for the CGI-I of 1 (very much improved) or 2 (much improved), see APPENDIX 5: VALIDITY OF OUTCOME MEASURES.

c)   Treatment Failure
This was the primary outcome measure in the six month double-blind randomized-withdrawal phase of Study 315. It was defined as:
- patients who had an increase (worsening) of 50% or more in ADHD-RS total score and an increase of two points or more in CGI-S score compared with the respective scores at the double-blind baseline visit, at two consecutive visits
- those who discontinued the study for any reason.

Weiss Functional Impairment Rating Scale–Parent Report
This scale is designed to evaluate how a child is able to function. It is completed by a parent and is regarded as a useful instrument for evaluating the functional impairment associated with ADHD. It has 50 questions in six domains: family, learning and school, life skills, self-concept, social activities, and risky activities. Each question is scored on a four-point scale ranging from 0 (never or not at all) to 3 (very often or very much). This is a secondary outcome in Studies 314, 315, and 316. An MCID of the Weiss Functional Impairment Rating Scale (WFIRS) is not available.

d)   Health Utilities Index Mark 2 and Mark 3
This instrument was developed in response to the need for a standardized system to measure health status and generic health-related quality of life (HRQoL) to describe:
- the experience of patients undergoing therapy
- long-term outcomes associated with disease or therapy
- the efficacy, effectiveness, and efficiency of health care interventions
- the health status of general populations.

The combined Health Utilities Index Mark 2 and Mark 3 (HUI2/3) consists of 15 questions designed to classify a patient's health status. The HUI2 is an HRQoL instrument specifically developed for use with children and consists of seven dimensions of health status (sensation, mobility, emotion, cognition, self-care, pain, and fertility), with three to five levels per dimension. The levels range from "normal functioning for age" to "extreme disability." The HUI3 has eight dimensions (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain) with five to six levels per dimension.

e)   Child Health Questionnaire

This is a validated scale that measures the physical and psychosocial well-being of children aged five years and older. The CHQ-P50 has 50 items assessing 14 core health concepts and is completed by the parent/caregiver, and the CHQ-CF87 has 87 items assessing 12 concepts and is completed by patients aged 10 years or older. CHQ comprises a hierarchy of items, scales, and summary measures. The categorical responses to individual items are transformed into continuous numeric variables with possible values ranging from 0 to 100, with higher scores indicating better health. The scores contribute to two summary scores for physical and psychosocial functioning/well-being. An MCID for CHQ is unknown.

f)   Before-School Functional Questionnaire

This new scale assesses commonly reported areas of dysfunction in early-morning activities associated with ADHD. It contains two parts: parent-rated items (on early-morning before-school activities), and patient-rated items (on patient's feeling about his or her relationship with family, success with morning activities/problems; this was divided into a Feelings and Behaviors subscales). An MCID for the Before-School Functional Questionnaire is unknown.

g)   Safety

An adverse event (AE) was defined as any untoward medical occurrence in a patient of a clinical investigation who was administered a pharmaceutical product; an AE did not necessarily have a causal relationship with this treatment. An AE was considered treatment-emergent if the start date occurred on or after the first dispensing day. Results for treatment-emergent AEs are presented in this report. A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity.

3.2.5   Statistical Analysis

Power calculations or sample size calculations were provided in the included studies. Mean differences and relative least squares (LS) mean, difference in LS mean between active treatment and placebo, and 95% confidence intervals for the difference were reported for symptom scale scores and HRQoL scores where applicable. When mean ADHD-RS change from baseline score at study end point was a primary outcome, primary efficacy analysis was performed for the intention-to-treat population or full-analysis set (FAS), using an analysis of covariance (ANCOVA) model. Study end point for a given parameter was defined as the last non-missing post-baseline observation for that parameter before dose tapering. The corresponding baseline score was used as a covariate. The type I error rate for rejecting the null hypothesis was set at 0.05. Statistical adjustment for multiple pairwise comparisons was employed in the model to control the inflated type I error rate when individual dose levels of GXR were considered separately. A hierarchical testing procedure was employed to compare the ADHD-RS mean change scores between the active drug and placebo groups. Starting from the active drug group receiving the highest dose (4 mg once daily), a contrast within the ANCOVA model was used to assess each pairwise difference in ADHD-RS mean change score compared with placebo. If the difference was significant, then the next active drug group in descending order of dose was assessed and compared with placebo. If the

difference was not significant, then no further comparisons of the remaining active drug groups against placebo were assessed. The last observation carried forward (LOCF) technique was used to replace missing data. In Study 315, a Cochran-Mantel-Haenszel test was used in primary efficacy analysis to evaluate "treatment failure," the primary outcome. For Study 316, both GXR and ATX were compared with placebo; this study was not designed to directly compare GXR with ATX.

a)   Analysis Populations

The primary population for efficacy analyses in the included studies was the intention to treat population, which included all randomized patients for whom the baseline and at least one post-randomization primary efficacy measurement were recorded, to maintain the advantages of randomization. In Study 315, the primary population for efficacy analyses was the randomized FAS population, consisting of all patients who were randomized and took at least one dose of investigational product during the double-blind randomized-withdrawal phase. In Study 316, the primary efficacy analysis was performed in the FAS population, consisting of all patients who had taken at least one dose of investigational product during the study.

Safety analysis was performed in the safety population, which was defined as all patients who participated or enrolled in the study (Study 301) or all patients who received at least one dose of the study drug (Studies 304, 307, 313, 314, 315, and 316).

3.3   Patient Disposition

The proportions of patients who withdrew from the included studies were 21% to 39% in the short-term studies, ███████████████████████████ (Table 9 and Table 10). Compared with placebo, discontinuation was less frequent in the GXR groups in most of the included studies. However, discontinuation was higher in the GXR groups than in the placebo group in Study 313 (GXR as adjunctive therapy) and in Study 316. AEs (rates ranged from 1.9% to 16.2% for GXR, and from 0.9% to 7.6 for placebo) and lack of efficacy (rates ranged from 2.2% to 8.3% for GXR, and from 12.6% to 17.7% for placebo) were the most common reasons for study discontinuation. More patients treated with GXR than those given placebo discontinued the study because of AEs, except in Study 304.

TABLE 9: PATIENT DISPOSITION — GXR AS MONOTHERAPY (PLACEBO-CONTROLLED AND ACTIVE-CONTROLLED TRIALS)

	SPD503-301		SPD503-304		SPD503-307		SPD503-314		SPD503-315		SPD503-316		
	GXR 2 mg, 3 mg, and 4 mg/d	PL	GXR 1 mg, 2 mg, 3 mg, and 4 mg/d	PL	GXR 1 mg, 2 mg, 3 mg, and 4 mg/d	PL	GXR AM and GXR PM	PL	▮	▮	▮	▮	▮
Screened, N	259	86	258	66	138	79	440			▮		▮	
Randomized, N (%)	259 (100)	86 (100)	258 (100)	66 (100)	138 (100)	79 (100)	227 (100)	113 (100)	▮	▮	▮	▮	▮
Discontinued, N (%)	97 (37.4)	33 (38.4)	88 (34.1)	25 (37.9)	29 (21.0)	31 (39.2)	60 (26.4)	37 (32.7)	▮	▮	▮	▮	▮
Adverse event	42 (16.2)	1 (1.2)	19 (7.4)	5 (7.6)	14 (10.1)	1 (1.3)	16 (7.0)	1 (0.9)	▮	▮	▮	▮	▮
Protocol violation	3 (1.2)	1 (1.2)	1 (0.4)	1 (1.5)	1 (0.7)	7 (8.9)	3 (1.3)	1 (0.9)	▮		▮	▮	▮
Patient choice	9 (3.5)	9 (10.5)	NR		NR		NR			▮		▮	
Consent withdrawn	NR	NR	26 (10.1)	5 (7.6)	7 (5.1)	6 (7.6)	14 (6.2)	6 (5.3)	▮	▮	▮	▮	▮
Lost to follow-up	9 (3.5)	3 (3.5)	18 (7.0)	4 (6.1)	1 (0.7)	4 (5.1)	9 (4.0)	8 (7.1)	▮	▮	▮	▮	▮
Lack of efficacy	21 (8.1)	15 (17.4)	NR	NR	3 (2.2)	12 (15.2)	9 (4.0)	20 (17.7)	▮	▮	▮	▮	▮
Treatment failure criteria met	NR		NR		NR		NR		▮	▮		▮	
Other	13 (5.0)	4 (4.7)	24 (9.3)	10 (15.2)	3 (2.2)	1 (1.3)	9 (4.0)	1 (0.9)	▮		▮	▮	▮
ITT/FAS, N	247 (95.4)	78 (90.7)	243 (94.2)	63 (95.5)	136 (98.6)	78 (98.7)	221 (97.4)	112 (99.1)	▮	▮	▮	▮	▮
PP, N	179 (69.1)	61 (70.9)	171 (66.3)	41 (62.1)	123 (89.1)[a]	77 (97.5)[a]	NR			▮		▮	
Safety, N	259 (100)	86 (100)	256 (99.2)	66 (100)	136 (98.6)	78 (98.7)	221 (97.4)	112 (99.1)	▮	▮	▮	▮	▮

FAS = full analysis set; GXR AM = guanfacine extended release administered in the morning; GXR PM = guanfacine extended release administered in the evening; ITT = intention-to-treat; NR = not reported; PL = placebo; PP = per-protocol.

[a] Modified FAS

Source: Clinical Study Reports for SPD503-301,[26] SPD503-304,[27] SPD503-307,[28] SPD503-314,[29] SPD503-315,[30] and SPD503-316.[31]

TABLE 10: PATIENT DISPOSITION — GXR AS ADJUNCTIVE THERAPY (PLACEBO-CONTROLLED TRIAL)

	SPD503-313		
	GXR AM + psychostimulant	**GXR PM + psychostimulant**	**PL + psychostimulant**
Screened, N	154	153	154
Randomized, N (%)	154 (100)	153 (100)	154 (100)
Discontinued, N (%)	33 (21.4)	25 (16.3)	25 (16.2)
Adverse event	4 (2.6)	6 (3.9)	1 (0.6)
Protocol violation	8 (5.2)	6 (3.9)	3 (1.9)
Refused further participation	7 (4.5)	8 (5.2)	11 (7.1)
Lost to follow-up	9 (5.8)	3 (2.0)	5 (3.2)
Lack of efficacy	3 (1.9)	2 (1.3)	5 (3.2)
Other	2 (1.3)	0	0
FAS, N	150 (97.4)	152 (99.3)	153 (99.4)
PP, N	NR	NR	NR
Safety, N	150 (97.4)	152 (99.3)	153 (99.4)

GXR AM = guanfacine extended release administered in the morning; GXR PM = guanfacine extended release administered in the evening; FAS = full analysis set; NR = not reported; PL = placebo; PP = per-protocol.
Source: Clinical study report of SPD503-313.[34]

3.4   Exposure to Study Treatments

Treatment compliance was assessed by tablet counts. Compliance rates were calculated by dividing the number of tablets taken by the number of tablets that should have been taken during the double-blind treatment period and multiplying by 100%. Patients who had taken 80% to 120% of the study drug during the study were considered compliant. Compliance was similar in the included trials, ranging from 96% to approximately 100% in the GXR and placebo groups. The mean (standard deviation) daily doses of GXR received in the included trials ranged from 2.9 (1.0) mg to 3.6 (1.3) mg.

3.5   Critical Appraisal
3.5.1   Internal Validity

Trial procedures for randomization, allocation concealment, and blinding were adequate. Within trials, patient baseline characteristics and demographics were balanced.

Methods of sample size calculation were described in all studies.

A number of scales, such as ADHD-RS, CGI-S, CGI-I, CTRS-R, CPRS-P, CHQ, WFIRS, and HUI2/3, were employed in the included studies to assess improvement in symptoms, change in function, or patient's general health status. Although some of these scales are generally accepted in ADHD clinical trials, it is uncertain whether they have been validated, and whether an MCID is available to determine the clinical importance of an observed difference.

In Study 315, LOCF imputation (assuming no change in data) was used to handle missing data; however, the ADHD symptom scores may not remain at the same level over time.[36] The validity of this technique for missing data is unclear.

3.5.2 External Validity

All studies were conducted in North America; some enrolled Canadian patients. Treatment regimens were consistent with those seen in clinical practice. The patient characteristics in the studies were somewhat different from clinical practice, as a result of the selection criteria. The exclusion criteria in the included studies were extensive. Patients with concurrent controlled or uncontrolled psychiatric disorders or with any cardiovascular abnormalities were not eligible. The generalizability of the results, especially the safety results, is limited by the narrowly defined patient populations, who had few comorbidities and used few or no concomitant medications. In addition, one of the exclusion criteria was body weight < 55 lbs. In the included studies, the mean age of the participating children with ADHD was approximately 10 years old, with an average body weight of 95 lbs (Table 6, Table 7 and Table 8).

According to a growth chart developed for children aged 2 to 20 years in the US by the Centers for Disease Control and Prevention,[37] for a child aged 10 years old, the weight of 95 lbs is around the 90th weight percentile; at the age of 8 years, about half of the children will weigh < 55 lbs; at the age of 6 years, around 90% of the children will weigh < 55 lbs. This could mean that only a small proportion of the population was included in the study. The study population may not reflect the general population, and the generalizability of the study results may be limited.

All included studies were short-term. Most of them had treatment durations ranging between 6.5 and 10 weeks. The efficacy outcomes were examined at the last treatment week before dose tapering, implying an even shorter observation period (5 to 10 weeks in the included studies) for the treatment effects of GXR. One study had a six month double-blind treatment period. Evidence from longer-term RCTs is needed to determine the long-term benefits and risk of GXR therapy. According to the clinical expert consulted in this review, ADHD medications would be used for months to years in practice, depending on patients' response and tolerability. ████████████████████████████████ ██ However, it is challenging to generalize these results to patients in real-world practice, who may receive longer-term pharmacotherapy.

There are no studies to help us understand the sequencing of GXR, except Study 313, in which participants were previously treated with psychostimulants but optimal response was not observed.

There is a lack of evidence from head-to-head trials. One study (316) included an active control group (ATX), yet the study was not designed to directly compare GXR with ATX. Therefore, there were insufficient statistical comparisons between these two groups to estimate the comparative clinical effectiveness of GXR and ATX.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in this section (Section 2.2, Table 3). Results for key efficacy outcomes are presented in Table 11, Table 12 and Table 13. Results for the subgroup of children aged six to 12 years are presented when they are available, because this subgroup was specified in the listing request by the manufacturer. None of the included trials were powered to detect a difference in the age subgroups; however, almost all trials showed statistically significant improvements in changes in ADHD-RS total score from baseline for the subgroup of children aged six to 12 years for which the drug is indicated. See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Behavioural, Functional, Developmental, and Cognitive Outcomes
a) ADHD Rating Scale-IV Total Score
Monotherapy, GXR Versus Placebo

Change in ADHD-RS total score from baseline was assessed in all placebo-controlled trials in which GXR was used as monotherapy (Table 11, Table 12). In general, the reduction in this score (indicating symptom improvement) was approximately six to nine points greater in the GXR-treated groups than in the placebo groups. The between-group differences were statistically significant for all trials. The changes in ADHD-RS scores in each GXR group were similar; however, statistical comparisons were not performed between them. A dose-dependent relationship was not observed in all GXR dosage groups.

In Study 301, findings from a subgroup analysis based on age groups showed that children aged six to eight years demonstrated significant improvement from baseline to end point compared with placebo: placebo-adjusted LS mean changes from baseline of −14.57 in the GXR 2 mg group ($P = 0.0005$), −16.06 in the GXR 3 mg group ($P < 0.0001$), and −21.11 in the GXR 4 mg group ($P < 0.0001$) (Table 11). Most children aged 9 to 12 years demonstrated statistically significant improvement from baseline to end point compared with placebo: placebo-adjusted LS mean changes from baseline of −7.26 in the GXR 2 mg group ($P = 0.0225$), −7.20 in the GXR 3 mg group ($P = 0.0393$), and −6.00 in the GXR 4 mg group ($P = 0.0979$). There were no statistically significant placebo-adjusted changes from baseline in any GXR groups in the 13 to 17 years subgroup compared with placebo (APPENDIX 4: DETAILED OUTCOME DATA).

In Study 304, placebo-adjusted LS mean end point changes from baseline were statistically significant in all GXR groups (Table 11). In the subgroup analysis by age groups, younger patients (aged six to 12 years) who received GXR demonstrated statistically significant improvement from baseline to end point when compared with placebo for all GXR dose groups. The placebo-adjusted LS mean end point changes from baseline for the 1 mg, 2 mg, 3 mg, and 4 mg GXR groups were −9.08 ($P = 0.0007$), −5.44 ($P = 0.0448$), −10.29 ($P = 0.0003$), and −10.77 ($P < 0.0001$), respectively.

Studies 307 and 314 reported similar results on ADHD-RS total score, showing a statistically significant difference in change from baseline to study end point between GXR and placebo ($P < 0.001$). In Study 314, GXR was administered either in the morning or in the evening, but the treatment effects on symptom improvement were similar between these two dosing schedules (Table 11).

In Study 315, patients received open-label GXR therapy for 13 weeks after screening (for the purpose of dose optimization), and patients who were eligible to enter the double-blind treatment phase received GXR or placebo during the following 26 weeks (Table 11). ██████████████████████████████

Monotherapy, GXR Versus ATX and Placebo

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Adjunctive Therapy, GXR Versus Placebo
In Study 313 (Table 13), compared with placebo plus psychostimulant, patients in both GXR plus psychostimulant groups (morning or evening) had statistically significant reductions in ADHD-RS total score. Findings from the subgroup analysis by age group were similar to those in the overall population: for children (six to 12 years), between-group differences in change in ADHD-RS total score from baseline were –3.6 (P = 0.023) for the GXR plus psychostimulant (morning) group, and –5.1 (P = 0.001) for the GXR plus psychostimulant (evening) group.

Although a between-group MCID has not been fully established, based on previous studies that have used a difference (MCID) of 5.2 to 7.7 in the ADHD-RS, most of these reported differences would be considered clinically important.

b)   Conners' Parent Rating Scale–Revised Total Score
Three placebo-controlled studies reported this outcome (Table 11).[26,27,29] In general, patients treated with GXR had improved (i.e., lower) CPRS-R scores from baseline than those given placebo. The between-group differences ranged from –7 to –13, and were statistically significant for all dose groups of GXR. The differences between various GXR dose groups and placebo were not dose-related. There was no statistical comparison between the various GXR dosage groups.

In Study 301, the LS mean changes in CPRS-R total score from baseline were statistically significant in all the GXR groups compared with placebo: –6.94 in the 2 mg group (P = 0.025), –6.78 in the 3 mg group (P = 0.035), and –12.83 in the 4 mg group (P < 0.0001).

In Study 304, the LS mean changes in CPRS-R total score from baseline were statistically significant for all GXR treatment groups, when compared with placebo. When examined by age group, the younger GXR patients (six to 12 years) demonstrated improvement in CPRS-R scores from baseline to end point when compared with placebo, and the results were statistically significant for the 1 mg, 3 mg, and 4 mg GXR groups. The placebo-adjusted LS mean end point changes from baseline for the 1 mg, 2 mg, 3 mg, and 4 mg GXR groups were –13.90 (P = 0.0005), –7.91 (P = 0.0506), –13.28 (P = 0.0023), and –10.07 (P = 0.0134), respectively. There was no significant improvement from baseline to end point in any treatment group for patients 13 to 17 years of age when compared with the placebo group (APPENDIX 4: DETAILED OUTCOME DATA).

Similarly, in Study 314, both morning- and evening-administered GXR showed statistically significant improvement in CPRS-R total score compared with placebo.

c)   Conners' Teacher Rating Scale–Revised Total Score
This was reported in one study.[26] Results in Study 301 indicated that statistically significant improvements (i.e., reductions) were observed in all GXR groups when compared with placebo; the between-group LS mean differences were –10.84, –12.71, and –13.01 for 2 mg, 3 mg, and 4 mg GXR groups, respectively. All P values were < 0.0001.

d) **Oppositional Subscale of Conners' Parent Rating Scale–Revised Long-Form Version**
This was the primary outcome measure in Study 307. At study end point, a statistically significantly greater mean reduction from baseline (indicating improvement) in oppositional subscale of CPRS-R:L was observed in the GXR groups compared with the placebo (difference versus placebo –4.1, *P* < 0.001).

e) **Clinical Global Impression – Improvement**
In Studies 301, 304, 307, and 314, statistically significant differences in CGI-I were observed at study end point between GXR and placebo (except for the 2 mg/day GXR group in Study 304, where *P* = 0.14), with more patients in the GXR groups demonstrating improvement.

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3.6.2 **Health-Related Quality of Life**
a) **Weiss Functional Impairment Rating Scale – Parent Report**
Three studies[29-31] reported results on the functional impairment in the study population (Table 11, Table 12). In the short-term placebo-controlled trial, Study 314, patients in both GXR groups showed statistically significant improvement from baseline in functional impairment, compared with placebo (differences versus placebo –0.15 for GXR [morning dose] and –0.18 for GXR [evening dose], both *P* values < 0.01). In the six month Study 315, the between-group difference was not statistically significant (difference between GXR and placebo –0.06, *P* = 0.118). In Study 316, both GXR and ATX were statistically significantly superior to placebo in the Learning/School Domain (differences versus placebo –0.22, *P* = 0.003 for GXR; –0.16, *P* = 0.026 for ATX) and the Global score (differences versus placebo – 0.17, *P* = 0.001 for GXR; –0.10, *P* = 0.048 for ATX) of this questionnaire, but only GXR was statistically significantly better than placebo in the Family Domain of WFIRS (differences versus placebo –0.21, *P* = 0.006 for GXR; –0.09, *P* = 0.242 for ATX).

Health Utilities Index Mark 2 and Mark 3
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Child Health Questionnaire-PF50
Studies 301 and 304 reported data on this HRQoL instrument (Table 11). Overall, after five and six weeks' treatment, respectively, scores in the GXR groups did not differ statistically significantly from those in the placebo group, except for the GXR 4 mg/day group in Study 301 (*P* = 0.02 for the Psychosocial summary score) and 1 mg/day GXR group in Study 304 (*P* = 0.04 for the Psychosocial summary score).

Before-School Functional Questionnaire
One study (Study 313, in which GXR was used as adjunctive therapy) reported this outcome. For the parent-rated items, statistically significant differences were found in "change from baseline" for GXR (morning dose) and GXR (evening dose) compared with placebo; the differences in mean change from baseline were –5.1 (*P* < 0.001) and –4.7 (*P* = 0.002) versus placebo, respectively. For the patient-rated items, no statistically significant differences were found between treatment groups, for either Feelings or Behaviors subscales.

3.6.3   Treatment Failure

TABLE 11: KEY EFFICACY OUTCOMES — GXR AS MONOTHERAPY (PLACEBO-CONTROLLED TRIALS)

	SPD503-301 (ITT Population)				SPD503-304 (ITT Population)					SPD503-307 (FAS)		SPD503-314 (FAS)		
Outcome	GXR 2 mg/d N = 84	GXR 3 mg/d N = 82	GXR 4 mg/d N = 81	PL N = 78	GXR 1 mg/d N = 57	GXR 2 mg/d N = 63	GXR 3 mg/d N = 60	GXR 4 mg/d N = 63	PL N = 63	GXR 1 mg to 4 mg/d N = 136	PL N = 78	GXR 1 mg to 4 mg/d AM N = 107	GXR 1 mg to 4 mg/d PM N = 114	PL N = 112
ADHD-RS total score, mean (SD)														
Baseline	36.10 (9.99)	36.77 (8.72)	38.40 (9.21)	38.14 (9.34)	41.7 (7.81)	39.9 (8.74)	39.1 (9.22)	40.6 (8.57)	39.3 (8.85)	42.3 (7.70)	42.3 (8.08)	41.7 (6.39)	41.6 (6.66)	42.9 (6.21)
End point	20.69 (13.45)	20.98 (13.87)	19.43 (11.91)	29.28 (14.94)	21.3 (12.78)	21.9 (14.08)	19.7 (12.46)	19.7 (11.01)	27.1 (15.02)	18.5 (14.62)	30.8 (13.28)	22.0 (12.42)	21.7 (12.59)	32.0 (13.67)
Change from baseline	−15.40 (12.82)	−15.79 (13.00)	−18.96 (13.71)	−8.86 (12.90)	−20.4 (14.00)	−18.0 (14.88)	−19.4 (14.62)	−20.9 (11.89)	−12.2 (12.96)	−23.8 (14.43)	−11.4 (12.65)	−19.8 (12.95)	−20.1 (13.04)	−11.0 (12.93)
Difference compared with placebo, LS mean (95% CI, P value)	−7.42 (−12.07, −2.77) P = 0.0006	−7.52 (−12.19, −2.85) P = 0.0005	−9.99 (−14.67, −5.32) P < 0.0001	–	−6.75 (−11.3, −2.2) P = 0.0041	−5.41 (−9.9, −0.9) P = 0.0176	−7.31 (−11.8, −2.8) P = 0.0016	−7.88 (−12.3, −3.4) P = 0.0006	–	−12.3 (−16.2, −8.5) P < 0.001	–	−9.4 (−12.8, −6.0) P < 0.001	−9.8 (−13.1, −6.4) P < 0.001	–
CPRS-R, mean (SD)														
Baseline	42.92 (18.48)	42.32 (18.29)	43.71 (16.41)	44.98 (17.77)	46.55 (17.02)	44.25 (19.71)	45.33 (18.70)	40.31 (20.40)	43.38 (16.83)	NR		47.0 (18.88)	48.0 (15.63)	49.6 (17.51)
End point	25.68 (19.09)	25.13 (19.95)	22.65 (16.01)	35.01 (21.10)	26.07 (19.66)	29.63 (22.12)	25.88 (19.60)	26.02 (19.50)	34.84 (21.75)			25.2 (19.58)	27.5 (18.88)	38.9 (23.61)
Change from baseline	−15.08 (14.60)	−14.70 (16.25)	−22.21 (17.02)	−9.22 (16.12)	−20.61 (19.49)	−15.43 (19.56)	−17.93 (19.02)	−14.73 (16.87)	−8.03 (17.57)			−22.6 (20.48)	−21.2 (17.23)	−10.7 (17.61)
Difference compared with placebo, LS mean (95% CI, P value)	−6.94 (−13.18, −0.69) P = 0.025	−6.78 (−13.18, −0.37) P = 0.035	−12.83 (−19.30, −6.37) P < 0.0001	–	−11.1 (−17.6, −4.5) P = 0.001	−6.55 (−13.0, −0.1) P = 0.0468	−9.53 (−16.2, −2.8) P = 0.0056	−7.52 (−14.0, −1.0) P = 0.0237	–	–		−12.5 (−17.8, −7.3) P < 0.001	−10.8 (−16.0, −5.6) P < 0.001	–
CTRS-R, mean (SD)														
Baseline	34.23 (20.11)	33.19 (17.34)	38.11 (17.10)	33.86 (19.40)	NR					NR		NR		
End point	20.81 (15.27)	18.28 (16.24)	21.85 (14.28)	32.15 (19.83)										

Outcome	SPD503-301 (ITT Population)				SPD503-304 (ITT Population)					SPD503-307 (FAS)		SPD503-314 (FAS)			
	GXR 2 mg/d N = 84	GXR 3 mg/d N = 82	GXR 4 mg/d N = 81	PL N = 78	GXR 1 mg/d N = 57	GXR 2 mg/d N = 63	GXR 3 mg/d N = 60	GXR 4 mg/d N = 63	PL N = 63	GXR 1 mg to 4 mg/d N = 136	PL N = 78	GXR 1 mg to 4 mg/d AM N = 107	GXR 1 mg to 4 mg/d PM N = 114	PL N = 112	
Change from baseline	−12.37 (14.86)	−13.66 (19.04)	−17.45 (16.10)	−1.96 (13.05)											
Difference compared with placebo, LS mean (95% CI, *P* value)	−10.84 (−16.51, −5.18) *P* < 0.0001	−12.71 (−18.55, −6.86) *P* < 0.0001	−13.09 (−18.95, −7.22) *P* < 0.0001	−											
CPRS-R:L, Oppositional Subscale, mean (SD)															
Baseline	NR				NR					19.3 (4.74)	19.9 (4.29)	NR			
End point										8.4 (7.24)	12.8 (7.08)				
Change from baseline										−10.8 (7.23)	−7.0 (7.63)				
Difference compared with placebo, LS mean (95% CI, *P* value)										−4.1 (−6.1, −2.1) *P* <0.001	−				
CGI-S and CGI-I															
CGI-S at baseline	4.61 (0.74)	4.61 (0.66)	4.68 (0.67)	4.65 (0.79)	4.8 (0.79)	4.6 (0.75)	4.6 (0.77)	4.8 (0.78)	4.7 (0.68)	4.8 (0.67)	4.8 (0.70)	Mean score was not reported. All patients' score > 2			
CGI-S at end point	NR				NR					2.9 (1.38)	3.9 (1.21)	≤ 2: 33 (31.7%) > 2: 71 (68.3%)	≤ 2: 41 (36.6%) > 2: 71 (63.4%)	≤ 2: 14 (12.7%) > 2: 96 (87.3%)	
CGI-I at end point, n (%)	47 (55.95)	41 (50.00)	45 (55.56)	20 (25.64)	31 (54.4)	27 (42.9)	33 (55.0)	35 (55.6)	19 (30.2)	93 (71.5)	24 (32.0)	69 (66.3)	75 (67.0)	35 (31.8)	
Difference in % of patients rated "improved" at end point (GXR vs. PL), *P* value	30.31 *P* <0.0001	24.36 *P* = 0.0016	29.92 *P* = 0.0001	−	24.2 *P* = 0.0074	12.7 *P* = 0.1404	24.8 *P* = 0.0055	25.4 *P* = 0.0041	−	39.5[a] *P* <0.001	−	NR *P* < 0.001	NR *P* < 0.001	NR	
Treatment failure															
N (%), 95% CI for % of treatment failure	NR				NR					NR		NR			

Outcome	SPD503-301 (ITT Population)				SPD503-304 (ITT Population)					SPD503-307 (FAS)		SPD503-314 (FAS)		
	GXR 2 mg/d N = 84	GXR 3 mg/d N = 82	GXR 4 mg/d N = 81	PL N = 78	GXR 1 mg/d N = 57	GXR 2 mg/d N = 63	GXR 3 mg/d N = 60	GXR 4 mg/d N = 63	PL N = 63	GXR 1 mg to 4 mg/d N = 136	PL N = 78	GXR 1 mg to 4 mg/d AM N = 107	GXR 1 mg to 4 mg/d PM N = 114	PL N = 112
Difference compared with PL (95% CI), *P* value														
WFIRS-P														
Baseline	NR				NR					NR		0.88 (0.43)	1.02 (0.49)	1.00 (0.43)
End point												0.58 (0.40)	0.64 (0.40)	0.78 (0.48)
Change from the DB baseline, mean (SD)												−0.309 (0.47)	−0.410 (0.42)	−0.202 (0.39)
Difference compared with PL (95% CI), *P* value												−0.15 (−0.26, −0.05) *P* = 0.004	−0.18 (−0.28, −0.07) *P* = 0.001	−
HUI2/3, mean (SD)[b]														
Baseline	NR				NR					NR		0.875 (0.1135)	0.865 (0.1151)	0.867 (0.1140)
End point												0.929 (0.1022)	0.923 (0.0805)	0.906 (0.0895)
CHQ-PF50 Physical Summary														
Baseline	56.60 (7.68)	56.12 (6.34)	57.62 (6.10)	54.85 (8.10)	56.76 (6.73)	56.67 (8.35)	56.74 (6.79)	57.85 (6.39)	56.19 (8.44)	NR		NR		
End point	56.65 (7.44)	54.75 (8.30)	54.68 (5.94)	55.24 (7.54)	57.07 (6.18)	57.03 (5.90)	55.48 (6.20)	55.08 (8.12)	56.40 (7.74)					
Change from baseline (SD)	0.21 (7.59)	−2.10 (7.08)	−2.70 (7.02)	0.65 (7.71)	0.42 (7.25)	0.42 (7.42)	−0.56 (8.58)	−3.38 (7.06)	0.39 (5.99)					

Outcome	SPD503-301 (ITT Population)				SPD503-304 (ITT Population)					SPD503-307 (FAS)		SPD503-314 (FAS)		
	GXR 2 mg/d N = 84	GXR 3 mg/d N = 82	GXR 4 mg/d N = 81	PL N = 78	GXR 1 mg/d N = 57	GXR 2 mg/d N = 63	GXR 3 mg/d N = 60	GXR 4 mg/d N = 63	PL N = 63	GXR 1 mg to 4 mg/d N = 136	PL N = 78	GXR 1 mg to 4 mg/d AM N = 107	GXR 1 mg to 4 mg/d PM N = 114	PL N = 112
Difference compared with placebo, LS mean (95% CI, *P* value)	0.42 (−2.44, 3.28) *P* = 0.97	−1.64 (−4.50, 1.21) *P* = 0.39	−1.95 (−4.94, 1.05) *P* = 0.29	–	0.32 (−2.2, 2.8) *P* = 0.80	0.36 (−2.2, 2.9) *P* = 0.78	−0.90 (−3.6, 1.8) *P* = 0.50	−2.43 (−5.0, 0.2) *P* = 0.07	–					
CHQ-PF50 Psychosocial Summary														
Baseline	34.96 (12.86)	31.80 (9.72)	33.78 (10.00)	32.50 (10.98)	33.75 (10.28)	32.55 (10.84)	33.85 (12.45)	36.09 (10.71)	35.31 (9.43)	NR		NR		
End point	43.41 (11.37)	42.12 (10.51)	44.95 (8.55)	39.11 (12.11)	44.71 (9.13)	41.39 (11.75)	43.67 (12.21)	44.66 (10.83)	41.21 (10.38)					
Change from baseline (SD)	8.16 (11.48)	9.80 (9.12)	10.12 (10.56)	6.24 (11.76)	11.04 (11.13)	8.09 (10.05)	9.28 (14.15)	8.54 (10.16)	5.86 (10.73)					
Difference compared with placebo, LS mean (95% CI, *P* value)	3.31 (−0.80, 7.41) *P* = 0.14	3.29 (−0.79, 7.36) *P* = 0.14	4.92 (0.65, 9.19) *P* = 0.02	–	4.27 (0.2, 8.3) *P* = 0.04	1.13 (−3.0, 5.2) *P* = 0.59	2.73 (−1.6, 7.1) *P* = 0.21	3.09 (−1.1, 7.3) *P* = 0.15	–					

ADHD-RS = ADHD Rating Scale-IV; CDR = CADTH Common Drug Review; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity of Illness; CHQ-PF50 = Child Health Questionnaire–Parent Form; CI = confidence interval; CPRS-R = Conners' Parent Rating Scales–Revised: Short Form; CTRS-R = Conners' Teacher Rating Scales–Revised: Short Form; CPRS-R:L = Conners' Teacher Rating Scales–Revised long version; FAS = full analysis set; GXR = guanfacine extended release; HUI2/3 = Health Utilities Index Mark 2 and Mark 3; ITT = intention to treat; LS = least squares; NR = not reported; PL = placebo; SD = standard deviation; vs. = versus; WFIRS-P = Weiss Functional Impairment Rating Scale–Parent.
[a] Calculated by CDR; [b] *P* values not reported.
Source: Clinical study reports for Studies 301,[26] 304,[27] 307,[28] 314,[29] and 315.[30]

TABLE 12: KEY EFFICACY OUTCOMES — GXR AS MONOTHERAPY (ACTIVE-CONTROLLED TRIAL)

Outcome	SPD503-316 (FAS)		
	█	█	█
ADHD-RS total score, mean (SD)			
Baseline	█	█	█
End point	█	█	█
Change from baseline	█	█	█
Difference from placebo, LS mean (95% CI, *P* value)	█	█	█
CGI-I			
Improvement at end point, n (%)	█	█	█
Improved difference vs. placebo, % (95% CI)	█	█	█
P value	█	█	
WFIRS-P (Learning and School Domain)			
Baseline	█	█	█
End point	█	█	█
Change from baseline, mean (SD)	█	█	█
Difference vs. PL (95% CI), *P* value	█	█	█
WFIRS-P (Family Domain)			
Baseline	█	█	█
End point	█	█	█
Change from baseline, mean (SD)	█	█	█
Difference vs. PL (95% CI), *P* value	█	█	█
WFIRS-P (Global score)			
Baseline	█	█	█
End point	█	█	█
Change from baseline, mean (SD)	█	█	█
Difference vs. PL (95% CI), *P* value	█	█	█
HUI2/3, mean (SD)			
Baseline	█	█	█
End point	█	█	█

ADHD-RS = ADHD Rating Scale-IV; CGI-I = Clinical Global Impression –Improvement; CI = confidence interval; GXR = guanafacine extended release; HUI2/3 = Health Utilities Index Mark 2 and Mark 3; LS = least squares; PL = placebo; SD = standard deviation; WFIRS-P = Weiss Functional Impairment Rating Scale–Parent; vs. = versus.

Source: Clinical study report for Study 316.[31]

TABLE 13: KEY EFFICACY OUTCOMES — GXR AS ADJUNCTIVE THERAPY (PLACEBO-CONTROLLED TRIALS)

Outcome	SPD503-313 (FAS)		
	GXR AM + psychostimulant N = 150	GXR PM + psychostimulant N = 152	PL + psychostimulant N = 153
ADHD-RS total score, mean (SD)			
Baseline	37.6 (8.13)	37.0 (7.65)	37.7 (7.75)
End point	17.3 (12.86)	16.1 (11.84)	21.7 (12.98)
Change from baseline	−20.4 (12.77)	−21.0 (12.39)	−16.0 (11.77)
Difference from placebo, LS mean (95% CI, *P* value)	−4.5 (−7.5 to −1.4) *P* = 0.002	−5.3 (−8.3 to −2.3) *P* < 0.001	–
CGI-I			
Improvement at end point, n (%)	105 (70.5)	110 (74.3)	88 (57.9)
P value	0.024	0.003	–

ADHD-RS = ADHD Rating Scale-IV; CGI-I = Clinical Global Impression –Improvement; CI = confidence interval; FAS = full analysis set; GXR AM = guanfacine extended release administered in the morning; GXR PM = guanfacine extended release administered in the evening; LS = least squares; SD = standard deviation.
Source: Clinical study report for Study 313.[34]

3.7 Harms

Only those harms identified in the review protocol are reported below (Section 2.2.1, Protocol).

3.7.1 Adverse Events

The proportions of patients experiencing at least one treatment-emergent AE ranged from 48% to 88%. More patients receiving active treatment reported AEs than those in the placebo group. The most common AEs reported in the GXR groups were somnolence, upper abdominal pain, fatigue, headache, and sedation (Table 14, Table 15, and Table 16). ███████████████████████████████████

Consistent dose-dependent trends in AEs were not observed.

3.7.2 Serious Adverse Events

The overall incidence of SAEs in the included studies was relatively low (less than 5%). Most of the SAEs were reported in the active treatment groups (Table 14, Table 15, and Table 16). ███

3.7.3 Withdrawals Due to Adverse Events

The rates of withdrawal due to adverse events (WDAEs) ranged from 2.7% to 23.3% in the GXR groups, and from 0% to 7.6% in the placebo group. More GXR-treated patients withdrew due to AEs in Studies 301, 307, 313, 314, and 316. In Study 304, rates of WDAE were lower in low-dose GXR groups (3.3% for 1 mg once daily and 3.1% for 2 mg once daily), but higher in high-dose GXR groups (9.2% for 3 mg once daily and 13.8% for 4 mg once daily), compared with placebo (7.6%). ██████████████████████████████████████

3.7.4 Mortality

No deaths were reported during the treatment period of any of the included trials.

TABLE 14: HARMS — GXR AS MONOTHERAPY (PLACEBO-CONTROLLED TRIALS)

	SPD503-301				SPD503-304					SPD503-307		SPD503-314			SPD503-315	
	GXR 2 mg/d N = 87	GXR 3 mg/d N = 86	GXR 4 mg/d N = 86	PL N = 86	GXR 1 mg/d N = 61	GXR 2 mg/d N = 65	GXR 3 mg/d N = 65	GXR 4 mg/d N = 65	PL N = 66	GXR 1 to 4 mg/d N = 136	PL N = 78	GXR 1 mg to 4 mg/d AM N = 107	GXR 1 mg to 4 mg/d PM N = 114	PL N = 112	▬	▬
TEAEs																
Patients with > 0 TEAEs, N (%)	67 (77.0)	76 (88.4)	75 (87.2)	55 (64.0)	49 (80.3)	40 (61.5)	45 (69.2)	55 (84.6)	50 (75.8)	114 (83.8)	45 (57.7)	85 (79.4)	95 (83.3)	64 (57.1)	▬	▬
Most common AEs (> 10%)																
Upper abdominal pain	9 (10.3)	14 (16.3)	14 (16.3)	5 (5.8)	5 (8.2)	2 (3.1)	1 (1.5)	8 (12.3)	6 (9.1)	16 (11.8)	2 (2.6)	7 (6.5)	20 (17.5)	8 (7.1)	▬	▬
Fatigue	16 (18.4)	18 (20.9)	13 (15.1)	3 (3.5)	6 (9.8)	3 (4.6)	7 (10.8)	8 (12.3)	2 (3.0)	15 (11.0)	4 (5.1)	11 (10.3)	13 (11.4)	3 (2.7)	▬	▬
Dizziness	4 (4.6)	5 (5.8)	9 (10.5)	2 (2.3)	3 (4.9)	0	6 (9.2)	6 (9.2)	4 (6.1)	7 (5.1)	3 (3.8)	6 (5.6)	5 (4.4)	3 (2.7)		
Headache	23 (26.4)	19 (22.1)	26 (30.2)	21 (24.4)	16 (26.2)	16 (24.6)	5 (7.7)	16 (24.6)	7 (10.6)	30 (22.1)	14 (17.9)	19 (17.8)	18 (15.8)	12 (10.7)	▬	▬
Sedation	8 (9.2)	11 (12.8)	14 (16.3)	3 (3.5)	1 (1.6)	6 (9.2)	3 (4.6)	5 (7.7)	3 (4.5)	18 (13.2)	1 (1.3)	15 (14.0)	17 (14.9)	3 (2.7)		
Somnolence	21 (24.1)	29 (33.7)	33 (38.4)	3 (3.5)	16 (26.2)	11 (16.9)	15 (23.1)	27 (41.5)	8 (12.1)	69 (50.7)	5 (6.4)	50 (46.7)	48 (42.1)	14 (12.5)	▬	▮
Irritability	9 (10.3)	2 (2.3)	5 (5.8)	3 (3.5)	4 (6.6)	4 (6.2)	2 (3.1)	4 (6.2)	3 (4.5)	11 (8.1)	2 (2.6)	8 (7.5)	8 (7.0)	3 (2.7)		
SAEs																
Patients with > 0 SAEs, N (%)	0	1 (1.2)	1 (1.2)	0	0	0	1 (1.5)	0	1 (1.5)	0	0	1 (0.9)	2 (1.8)	0	▬	▬
Most common SAEs		Severe pneumo-thorax	Severe asthma aggravated				Concussion and convulsions		Lower limb fracture			Syncope	1 for syncope, self-injurious ideation, suicidal ideation		▮	▮
WDAEs																
WDAEs, N (%)	9 (10.3)	13 (15.1)	20 (23.3)	1 (1.2)	2 (3.3)	2 (3.1)	6 (9.2)	9 (13.8)	5 (7.6)	12 (8.8)	0	8 (7.5)	8 (7.0)	0	▬	▬
Reasons for early discontinuation																
Headache	3 (3.4)	0	1 (1.2)	0	0	0	0	1 (1.5)	1 (1.5)	1 (0.7)	0	0	0	0	▮	▮
Sedation	2 (2.3)	0	7 (8.1)	0	0	0	1 (1.5)	1 (1.5)	1 (1.5)	4 (2.9)	0	2 (1.9)	3 (2.6)	0	▬	▮

	SPD503-301				SPD503-304					SPD503-307		SPD503-314			SPD503-315	
Somnolence	2 (2.3)	4 (4.7)	5 (5.8)	0	2 (3.3)	1 (1.5)	1 (1.5)	4 (6.2)	0	4 (2.9)	0	2 (1.9)	0	0	■	▮
Others					Dizziness,	Fatigue, affect lability, depres-sion, enuresis	Fatigue, affect lability, anxiety aggravated, depression, nightmare, hypotension	Upper abdominal pain, fatigue, anorexia, dizziness, tremor	Eye swelling, abdominal pain, constipa-tion, dyspepsia, dizziness, irritability	1 for anxiety, crying, psycho-motor retardation, bradycardia, arrhythmia, dysphagia, varicella, dyspnea, hypotension, tremor		Fatigue, weight increased, syncope	lethargy, syncope, suicidal ideation, rash generalized, hypo-tension		■	■
Deaths																
N (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	▮	▮

AE = adverse event; GXR = guanfacine extended release; PL = placebo; SAE = serious adverse event; TEAE = treatment-emergent adverse event (occurred on or after the start date of treatment and within 3 days of the last dose); WDAE = withdrawal due to adverse event.

Source: Clinical study reports for Studies 301,[26] 304,[29] 307,[28] 314,[29] and 315.[30]

TABLE 15: HARMS — GXR AS MONOTHERAPY (ACTIVE-CONTROLLED TRIALS)

	SPD503-316		
	▮	▮	▮
AEs			
Patients with > 0 TEAEs, N (%)	▮	▮	▮
Most common AEs (> 10%)			
Abdominal pain	▮	▮	▮
Fatigue			
Dizziness			
Headache			
Somnolence			
Nausea			
Vomiting			
SAEs			
Patients with > 0 SAEs, N (%)	▮	▮	▮
Most common SAEs	▮		▮
WDAEs			
WDAEs, N (%)	▮	▮	▮
Deaths			
N (%)	▮	▮	▮

AE = adverse event; GXR = guanfacine extended release; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical study report of Study 316.[31]

TABLE 16: HARMS — GXR AS ADJUNCTIVE THERAPY (PLACEBO-CONTROLLED TRIALS)

	SPD503-313		
	GXR AM + psychostimulant N = 150	GXR PM + psychostimulant N = 152	PL + psychostimulant N = 153
AEs			
Patients with > 0 TEAEs, N (%)	116 (77.3)	116 (76.3)	97 (63.4)
Most common AEs (> 10%)			
Insomnia	8 (5.3)	18 (11.8)	6 (3.9)
Fatigue	18 (12.0)	11 (7.2)	4 (2.6)
Dizziness	15 (10.0)	8 (5.3)	9 (8.1)
Headache	32 (21.3)	32 (21.1)	20 (13.1)
Somnolence	21 (14.0)	20 (13.2)	7 (4.6)
SAEs			
Patients with > 0 SAEs, N (%)	1 (0.7)	2 (1.3)	0
Most common SAEs	Self-injurious behaviour/ worsening aggression/ adjustment disorder	Syncope, contact with poison ivy	
WDAEs			
WDAEs, N (%)	4 (2.7)	6 (3.9)	1 (0.7)
	Pharyngitis, weight decreased, aggression, hypotension	Cardiac disorder, fatigue, pharyngitis, exposure to toxic agent, weight decrease, dizziness, somnolence, aggression, hypotension	Aggression
Deaths			
N (%)	0	0	0

AE = adverse event; GXR AM = guanfacine extended release administered in the morning; GXR PM = guanfacine extended release administered in the evening; PL = placebo; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical study report of study 313.[34]

3.8 Study SPD503-206

A phase 2, double-blind, placebo-controlled RCT (Study 206[35,38]) with a non-inferiority design, involving 182 patients (121 in the GXR group and 57 in the placebo group), was included in our review as well. Findings from this study are briefly summarized below.

This study had inclusion criteria similar to those of the phase 3 studies: children aged six to 17 years with a diagnosis of ADHD and baseline ADHD-RS total score ≥ 24 were eligible; patients were excluded if they had any current comorbid psychiatric diagnosis, body weight < 25 kg, cardiac conditions that might have increased the safety risk to the patient, or if they had taken an investigational drug within 30 days before screening. The treatment duration of this study was 6.5 weeks. The maximum dose for GXR was 3 mg once daily. Patients were followed for four weeks following the last dose of study drug. The primary objective of this non-inferiority trial was to evaluate whether GXR had no greater effect on alertness or psychomotor functioning than placebo. A non-inferiority margin for the primary outcome was preset. Change in ADHD-RS total score from baseline was assessed in this study in FAS using an ANCOVA model, in which the baseline score was the covariate.

The dropout rates were 5.8% in the GXR group and 5.3% in the placebo group. Baseline patient characteristics were comparable between the two treatment groups, and 44.9% of the population was aged six to 12 years. The mean ADHD-RS total scores improved significantly from baseline in the GXR group compared with placebo group at end point, –18.0 versus –11.9, respectively. LS mean difference between GXR and placebo was –6.3, $P = 0.001$. Subgroup analysis by age group indicated greater efficacy of GXR in children (ADHD-RS total scores were improved by a mean of –21.6 in the GXR group versus –10.6 in the placebo group, $P < 0.001$) than in adolescents (ADHD-RS total scores were improved by a mean of –15.0 in the GXR group versus –13.0 in the placebo group, $P = 0.33$). In Study 206, a significantly greater percentage of patients in the GXR group was deemed "improved" compared with the placebo group using CGI-I scores, 56.8% versus 35.1%, respectively, $P = 0.007$.

The overall incidence of AEs was higher in the GXR group (79.3%) than in the placebo group (70.2%). The most common AEs observed in the GXR group included upper abdominal pain, headache, sedation, and somnolence. Rates of WDAEs were 3.3% in the GXR group and 1.8% in the placebo group. One SAE occurred in the GXR group.

4.   DISCUSSION

4.1   Summary of Available Evidence

Among the seven phase 3 double-blind, parallel, placebo-controlled studies included in this review, GXR was administered as monotherapy in six studies (one of them including atomoxetine as a comparator), and was co-administered with a psychostimulant in one study. The numbers of enrolled patients ranged from 182 to 461. All enrolled school-aged children (aged six to 17 years in six studies, aged six to 12 years in two studies) had ADHD. All studies investigated GXR tablets (1 mg to 4 mg) taken once daily. One study explored the effectiveness and safety of GXR over six months, while the other studies examined the short-term effects of GXR. The primary outcome was mean change in ADHD-RS total score from baseline in most of the studies. The study population may not be reflective of Canadian practice, because of restricted patient-selection criteria. (In all the trials, patients with concomitant controlled or uncontrolled psychiatric disorders were excluded, while in practice, the majority of children with ADHD have comorbidities.) In addition, baseline characteristics of the study population were not consistent with the general population, in that the weight distribution seems to be much higher than the general population in Canada. (As a result, many younger children with lower body weight may not have been included.) Therefore, the generalizability of the results to such patients is limited.

A key limitation of the evidence was the lack of direct evidence comparing GXR with other active treatments. Another limitation was the lack of long-term data to assess the sustained treatment effect of GXR.

4.2   Interpretation of Results
4.2.1   Efficacy

The observed differences in ADHD-RS between GXR and placebo in the included studies were modest, but appeared to be clinically meaningful based on estimates of MCID in the literature.[39] Results from subgroup analysis by age groups were consistent with those observed in the overall population: compared with placebo, GXR significantly reduced ADHD symptoms, as measured by ADHD-RS, in younger patients (six to 12 years old). The results of other scales used in the trials were generally congruent with the ADHD-RS results, although validated MCIDs for some of these scales (e.g., CPRS-R, CTRS-R, and WFIRS) have not been conclusively established.

Most of the included studies had short treatment durations, ranging from 6.5 weeks to 10 weeks, but the treatment effect of GXR was assessed at earlier time points in some studies. Therefore, the available evidence supports the benefits of short-term treatment with GXR only. In clinical practice, the medical treatment of many children with ADHD, especially those with more severe symptoms or comorbid disorders, needs to continue for several years.[40] █████████████████████████████████████ ██ ██ ██ ██ This had an impact on the reliability of the outcomes. Previous research demonstrated the correlation between patient's adherence to treatment and improvement in symptoms. It has also been shown that the clinical effectiveness of some ADHD medications (including popularly prescribed psychostimulants, atomoxetine, and GXR) could be maintained over a treatment period of up to 24 months.[40]

GXR is indicated as both monotherapy and adjunctive therapy to a psychostimulant. According to the clinical expert for this review, some patients prefer not to take psychostimulants, and guanfacine offers an alternative. Input from the ADHD patient group also indicated that patients were very supportive of more treatment options that may provide better symptom control and may reduce adverse effects compared with the conventional ADHD drugs. In patients with suboptimal response to previous ADHD pharmacotherapy, GXR is more likely to be used along with a psychostimulant, according to the clinical expert. The evidence regarding the clinical effectiveness of GXR as adjunctive therapy is limited. Only one study evaluated the effect of GXR when combined with a psychostimulant. Compared with the monotherapy trials, the difference (approximately 5 points) in ADHD-RS total score change between GXR plus stimulant and placebo plus stimulant was smaller. This could be related to the effect of using concurrent psychostimulants.

Symptoms of ADHD negatively impact children's quality of life and functional status. This is also reflected in the Patient Input (APPENDIX 1: PATIENT INPUT SUMMARY). According to the clinical expert consulted in this review, functional and quality of life impairment are important outcomes in ADHD research. Generic and ADHD-specific questionnaires were used in the included trials. The limited data suggested that short-term treatment with GXR was associated with improved functioning and HRQoL. However, validated MCIDs were not available for these instruments to determine the importance of these findings in clinical practice. ████████████████████████████████████ ██ ██ ███████████████████████████

One trial included atomoxetine (ATX), but the trial was not powered to detect a difference between GXR and ATX. ██ ██ ██

Psychostimulants are the current standard of treatment in ADHD pharmacotherapy and generally have a larger effect size than non-stimulants such as ATX and GXR,10 but there are no head-to-head trials

directly comparing them with GXR. The manufacturer submitted an indirect comparison analysis between GXR and ATX, in which both drugs were used as monotherapy. There were statistically significant differences in mean difference of change in ADHD-RS scores at study end point, favouring GXR. However, the indirect comparison analysis was not transparently reported, making it difficult to assess validity of its results (APPENDIX 7: SUMMARY AND APPRAISAL OF MANUFACTURER-SUBMITTED MATCHING-ADJUSTED INDIRECT COMPARISON).

4.2.2   Harms

Compared with placebo, more patients treated with GXR experienced AEs. In general, commonly reported AEs such as somnolence, headache, sedation, and fatigue were more likely to be reported in patients treated with GXR in the monotherapy trials as well as the adjunctive therapy trial. Hypotension and cardiovascular AEs, which were identified as AEs of particular interest in the research protocol development phase of this review, were rarely reported in the included trials. This can be partially explained by the restricted selection criteria in such studies, which excluded patients with a history of cardiac abnormality or cardiac dysfunction. A systematic review published in 2013 evaluated the risk of serious cardiovascular AEs associated with the medications for ADHD. The authors indicated that there were no reports of serious cardiovascular AEs, sudden cardiac death, or proarrhythmia associated with clonidine and guanfacine, alone or in combination with psychostimulants in recent large RCTs.[41] Mania is another important AE that may be associated with guanfacine therapy. Although they were not reported in the studies included in this CDR review, manic episodes were observed immediately following the administration of guanfacine in a case series.[42] Mania has also been reported in children receiving clonidine, another alpha$_{2A}$-adrenergic receptor agonist.[43] In addition to these AEs, decreases in heart rate and blood pressure associated with the use of GXR were indicated in the product monograph,[12] although the rates of such AEs were low in the included trials.

SAEs were uncommon in the placebo-controlled trials. Given the relatively low rates of SAEs, any differences between treatment groups could be due to chance; hence, the data are largely inconclusive. GXR-treated patients experienced higher rates of WDAEs.

Safety data from two open-label extension studies (of 24 months' duration) of GXR are summarized in APPENDIX 6: SUMMARY OF OTHER STUDIES. Most of the patients who enrolled in these trials had previously been enrolled in the SPD503-301 and SPD503-304 studies. The rates of SAEs in these two year open-label studies were higher than those in the double-blind RCTs. The common AEs included somnolence, sedation, fatigue, and headache. Design limitations (open label, no control group, and high patient dropout rate) limit their usefulness for providing any further information on the risk of harm for GXR.

5. CONCLUSIONS

In five well-designed RCTs, GXR monotherapy improved the symptoms of ADHD in children and adolescents compared with placebo. Measures of behavioural change and global impression also showed improvement for GXR compared with placebo, but there were no clinically meaningful differences observed in HRQoL. GXR monotherapy had a similar impact on measures of ADHD as atomoxetine monotherapy in one short-term RCT. GXR used together with a psychostimulant improved the symptoms of ADHD in children and adolescents with suboptimal response to psychostimulants as monotherapy, compared with placebo plus a psychostimulant.

AEs occurred more frequently in GXR-treated patients than in those given placebo, although SAEs were uncommon. Somnolence, headache, sedation, and fatigue were the most common complaints.

The key limitations of the evidence include lack of head-to-head comparisons between GXR and other active treatments, such as psychostimulants, which are the current standard of care for children with ADHD. The lack of long-term efficacy and safety data (i.e., beyond six months) is also a limitation given that pharmacotherapy for ADHD is often given long term. Additionally, there is a lack of data for patients in the lower body-weight categories.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient group.

1. Brief Description of Patient Group(s) Supplying Input

The Centre for ADHD Awareness, Canada (CADDAC) is a national, non-profit, umbrella organization that is committed to providing up-to-date scientific information on ADHD that aims to increase ADHD understanding and decrease the stigma associated with it. This organization was founded in 2005 and advocates for both Canadian ADHD organizations and affected individuals through the use of education, awareness, and advocacy.

In the past three years, CADDAC has received educational grants from the following pharmaceutical companies: Janssen, Purdue Pharma, Eli Lilly, and Shire Canada. CADDAC declared no conflicts of interest with regard to this submission.

2. Condition and Current Therapy-Related Information

Collective patient perspectives from 288 individuals were obtained through a national bilingual online survey conducted between May 21 and July 19, 2013. The main participants were parents and caregivers of children with ADHD seeking better symptom control. Another 2012 survey of 595 parents of children diagnosed with ADHD was also referenced in order to provide more in depth information on the impact of ADHD and subsequent experiences. In addition, numerous one-to-one conversations were also used to inform this submission.

Daily activities and quality of life are affected in children with ADHD. Children often experience significant impairments in academic, emotional regulation, and psychosocial aspects of life. They can exhibit a few or many behavioural issues such as impulsivity, risky behaviour, frustration, anger, outbursts, meltdowns, restlessness, oppositional behaviour, hopelessness, and moodiness. This, in turn, can lead to difficulties making and maintaining friendships and difficulties participating in group and sporting activities, which can ultimately lead to ostracization. They are often bullied or get into trouble because of their overly aggressive behaviour and can have low self-esteem. This low self-esteem can also lead to poor self-care and lack of hygiene, which can further exclude children.

Children with ADHD have trouble focusing and completing school work. They experience difficulties with executive functioning, including organizational skills, problem solving, and time management. Many are unable to follow instructions unless they are broken down into one or two steps, and they are forgetful of routines. Additionally, children with ADHD have difficulties in stopping activities that are highly stimulating, such as playing computer games, texting, participating in chat rooms, and watching television. One set of parents had noted that, before their son's diagnosis, "their son was treated like a 'bad' kid and the parents incompetent."

Co-existing disorders, occurring with or caused by ADHD, such as anxiety, learning disabilities, and depression, often compound the degree of impairment. Increases in sibling conflict along with sleeping difficulties are additionally hard on families.

Most parents and caregivers surveyed experience an increase in stress or other related issues. These include increased conflict with their child; increased conflict with their spouse or partner; increased financial burden due to therapy, tutoring, and medications; and an increase in stress with extended family members, friends, or the general public over the stigma and misunderstanding surrounding ADHD. In addition, parents and caregivers note that interactions with teachers and coaches are often difficult and stressful and that their child's return to school in September is particularly problematic.

Parents and caregivers often decrease their social interactions and free time in order to limit the number of embarrassing situations and to help manage their child. They note their inability to "truly relax" or "take a break" as their children are in constant need of "monitoring." In addition, many are unable to relax as they are always waiting for the "phone to ring from school, another child's parent, or the police." Embarrassing situations and meltdowns are frequently highlighted for both the child with ADHD and family members, particularly siblings, as another cause of increased stress. In addition, parents and siblings are often required to "clean up" after the impulsive behaviour displayed by the child with ADHD.

Surveyed parents have administered the following ADHD medications to their children: Strattera, Biphentin, Concerta, Adderall, Vyvanse, Ritalin, and Dexedrine. Children are also often placed on concomitant clonidine or risperidone for significant oppositional defiant disorder or emotional dysregulation or both. The survey found that more than 50% of children with ADHD do not have their symptoms satisfactorily controlled, the most problematic symptoms being moodiness, irritability, inattention, and impulsivity, with additional concerns expressed about symptoms of aggression, hyperactivity, and anxiety not being sufficiently managed. In addition, some medications also increase the level of aggression, which subsequently negatively affects the child's ability to be in any structured environment. AEs such as headaches, depression, loss of appetite, and difficulty sleeping are concerns raised by parents and caregivers. Some parents cease or are reluctant to administer medications because of these AEs, while the majority of parents remain concerned with the potential for long-term effects. Parents also note that children experience rebound issues when the medications have left their system.

3. Related Information About the Drug Being Reviewed
Parents of children with ADHD are very supportive of more treatment options that may provide better symptom control and may reduce AEs. There are current gaps and unmet needs for children, who continue to have difficulties due to minimal or no symptom control of attention regulation, impulsivity, or hyperactivity; significant AEs of the current medications (including psychotic incidents and suicidal ideation and attempts); as well as the daily struggles with mood regulation, anger outbursts, and aggression.

Of the parents who have heard of Intuniv XR, many are hopeful that sleep issues and symptoms of Tourette syndrome (a common comorbidity associated with ADHD) will be resolved and that second doses of stimulant medications may be skipped, allowing sleep and reducing tics. Parents are aware of the potential harms of Intuniv XR, including the potential to cause low blood pressure.

To date, the experience with the use of Intuniv XR in children with ADHD is limited. Parents who completed the survey and whose children have used Intuniv XR reported that it helps to manage the emotional components of ADHD. Two children were reported to be better able to deal with anxiety and social issues (which has subsequently led to an increase in self-esteem). In one child, the stimulant

dosage was reduced without losing therapeutic benefit. Two parents were unsure of specific benefits in using Intuniv XR or did not see improvement.

Many parents who were interviewed by telephone expressed that their child experienced symptom control with this medication whereas no other medication tried to date had had any effect on their child's symptoms, or could be tolerated due to AEs, leaving the child untreated for many years. This medication was reported by parents as changing the quality of their child's life.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present
	MEDLINE Daily and MEDLINE 1946 to present
	MEDLINE In-Process & Other Non-Indexed Citations
	Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	January 8, 2014
Alerts:	Weekly search updates until May 21, 2014
Study Types:	No search filters were applied
Limits:	No date or language limits were used
	Human filter was applied
	Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic;
	or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

#	Strategy
1	(Intuniv* or GXR).ti,ab,ot,sh,hw,rn,nm.
2	exp Guanfacine/
3	(Tenex or Akfen or Dipresan or Estulic or Hipertensal or guanfacin* or bs 100 141 or bs 100141 or bs100141 or Lon798).ti,ab,ot,sh,hw,rn,nm.
4	(UNII-30OMY4G3MK or UNII30OMY4G3MK or 30OMY4G3MK or 29110-47-2 or "29110472" or 29110-48-3 or "29110483").rn,nm.
5	1 or 2 or 3 or 4
6	5 use pmez
7	(Intuniv* or GXR).ti,ab.
8	exp *guanfacine/
9	(Tenex or Akfen or Dipresan or Estulic or Hipertensal or guanfacin* or bs 100 141 or bs 100141 or bs100141 or Lon798).ti,ab.
10	7 or 8 or 9
11	10 use oemezd
12	11 not conference abstract.pt.
13	6 or 12
14	exp animals/
15	exp animal experimentation/ or exp animal experiment/
16	exp models animal/
17	nonhuman/
18	exp vertebrate/ or exp vertebrates/
19	animal.po.
20	or/14-19
21	exp humans/
22	exp human experimentation/ or exp human experiment/
23	human.po.
24	or/21-23
25	20 not 24
26	13 not 25
27	remove duplicates from 26

OTHER DATABASES

PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	To December 19, 2013
Keywords:	Intuniv, Intuniv XR, GXR, guanfacine, Tenex, Akfen, Dipresan, Estulic, Hipertensal, ADD, ADHD, attention deficit
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:
- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Outcome not of interest

Center for Drug Evaluation and Research. Medical review(s) [Internet]. In: Title: Intuniv (guanfacine) extended-release 1 mg, 2 mg, 3 mg, and 4 mg tablets. Company: Shire, Inc. Application no: 22-037. [FDA approval package]. Rockville (MD): Center for Evaluation and Research; 2009. Available from: www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022037s000medr.pdf.

Inappropriate study design — retrospective analysis

Sikirica V, Xie J, He TL, Erder MH, Hodgkins P, Yang H, et al. Immediate-release versus extended-release guanfacine for treatment of attention-deficit/hyperactivity disorder. Am J Pharm Benefits. 2013;5(4):e85-e94.

Inappropriate study design — post-hoc analysis

Sallee FR, Kollins SH, Wigal TL. Efficacy of guanfacine extended release in the treatment of combined and inattentive only subtypes of attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol [Internet]. 2012 Jun [cited 2014 Jan 14];22(3):206-14. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3373219/pdf/cap.2010.0135.pdf

Inappropriate study design — open-label

Spencer TJ, Greenbaum M, Ginsberg LD, Murphy WR. Safety and effectiveness of coadministration of guanfacine extended release and psychostimulants in children and adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol [Internet]. 2009 Oct [cited 2014 Jan 14];19(5):501-10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2861960/pdf/cap.2008.0152.pdf

Sallee FR, Lyne A, Wigal T, McGough JJ. Long-term safety and efficacy of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2009 Jun;19(3):215-26.

Inappropriate intervention — not extended release formula

Scahill L, Chappell PB, Kim YS, Schultz RT, Katsovich L, Shepherd E, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. Am J Psychiatry [Internet]. 2001 Jul [cited 2014 Jan 14];158(7):1067-74. Available from: http://ajp.psychiatryonline.org/data/Journals/AJP/3726/1067.pdf

Inappropriate population — adults

Taylor FB, Russo J. Comparing guanfacine and dextroamphetamine for the treatment of adult attention-deficit/hyperactivity disorder. J Clin Psychopharmacol. 2001 Apr;21(2):223-8.

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 17: CHANGE FROM BASELINE IN MEAN ADHD RATING SCALE-IV TOTAL SCORE (ITT/FAS POPULATION) — SUBGROUP ANALYSIS BY AGE GROUPS

	GXR				PL
Study 301	**GXR 2 mg/d**		**GXR 3 mg/d**	**GXR 4 mg/d**	**PL**
6 to 8 years	16		20	27	22
Placebo-adjusted difference, LS mean, *P* value	−14.57 0.0005		−16.06 < 0.0001	−21.11 < 0.0001	−
9 to 12 years	51		37	39	37
Placebo-adjusted difference, LS mean, *P* value	−7.26 0.0225		−7.20 0.0393	−6.00 0.0979	−
13 to 17 years	17		25	15	19
Placebo-adjusted difference, LS mean, *P* value	0.63 0.9978		−0.24 0.9998	−3.07 0.8273	−
Study 304	**GXR 1 mg/d**	**GXR 2 mg/d**	**GXR 3 mg/d**	**GXR 4 mg/d**	**PL**
6 to 12 years	50	46	41	48	45
Placebo-adjusted difference, LS mean, *P* value	−9.08 0.0007	−5.44 0.0448	−10.29 0.0003	−10.77 < 0.0001	−
13 to 17 years	7	17	19	15	18
Placebo-adjusted difference, LS mean, *P* value	1.06 0.8426	−5.43 0.1867	−0.24 0.9503	0.26 0.9516	−
Study 313	**GXR AM + psychostimulant**		**GXR PM + psychostimulant**		**PL**
6 to 12 years	114		124		123
Placebo-adjusted difference, LS mean, *P* value	−3.6 0.023		−5.1 0.001		−
13 to 17 years	36		28		30
Placebo-adjusted difference, LS mean, *P* value	−8.2 0.003		−6.3 0.033		−
Study 315	**GXR 1 mg to 4 mg/d**				**PL**
6 to 12 years	113				113
Placebo-adjusted difference, LS mean, *P* value	−7.13 < 0.001				−
13 to 17 years	37				38
Placebo-adjusted difference, LS mean, *P* value	−3.57 0.207				−
Study 316	**GXR 1 mg to 4 mg/d**		**ATX up to 1.4 mg/kg/d**		**PL**
6 to 12 years	81		82		79
Placebo-adjusted difference	−11[a] *P* value NR		−3[a] *P* value NR		−
13 to 17 years	33		30		32
Placebo-adjusted difference	−4.3[a] *P* value NR		−3.2[a] *P* value NR		

ATX = atomoxetine; FAS = full-analysis set; GXR AM = guanfacine extended release administered in the morning; GXR PM = guanfacine extended release administered in the evening; ITT = intention to treat; LS = least squares; NR = not reported; PL = placebo.
[a] Calculated by the CADTH Common Drug Review.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Objective

To describe the scales used in the guanfacine extended release studies and report minimal clinically important difference (MCID) estimates, where available.

Findings

TABLE 18: SUMMARY OF SCALES USED IN THE INCLUDED STUDIES

Scale	Rater	Description	Minimum Important Difference	Comments
ADHD-RS	Investigator	18 items (range 0 to 3 points each) Total range: 0 to 54 (lower score represents fewer symptoms) 18 items are grouped into two subscales: hyperactivity-impulsivity and inattentiveness	Various views exist: • 30% mean total score change difference between treatment groups[44] • Between-treatment difference of 5.2 to 7.7 points[39]	Parent and teacher versions exist, but in the included studies, the investigator version was used.
CPRS-R	Parent	48 items (range 0 to 3 points each) Lower score represents fewer symptoms Measures: conduct problems, learning problems, psychometric problems, impulsivity and hyperactivity, and anxiety	Not defined	Abbreviated versions of the Conners' scales were used in some studies (e.g., Study 301) The primary outcome of Study 307 was the Oppositional Subscale of CPRS-R (long version)
CTRS-R	Teacher	38 items (range 0 to 3 points each) Lower score represents fewer symptoms Measures: hyperactivity, conduct problems, emotional overindulgence, anxious-passiveness, asocial behaviour and daydreaming-attendance problems	Not defined	
CGI-S and CGI-I	Investigator	At baseline, the CGI-S is used on a scale of 1 (no symptoms) to 7 (very severe symptoms). Subsequently, the CGI-I is used on a scale of 1 to 7 where 1 to 3 means improvement, 4 means no change, and 5 to 7 means worse	Various opinions exist: • CGI-I of 1(very much improved) or 2(much improved)[44] • 1 point difference on CGI-S correlates with 8 to 10 points on ADHD-RS[45] • 2 level improvement on CGI-I correlates with 50 to 60% improvement on ADHD-RS[45]	

Scale	Rater	Description	Minimum Important Difference	Comments
WFIRS	Parent	Measure of functioning. Six domains: family, learning and school, life skills, child's self-concept, social activities, and risky activities 50 questions (score 0 to 3 for each, total score up to 150)	Not defined	
HUI2/3	Parent	HUI2 range (−0.03 to 1.0) HUI3 range (−0.36 to 1.0)	Various opinions exist. The developers of the scales cite the following range: 0.03 to 0.05[46,47]	These scales not previously used in clinical studies of ADHD, according to the manufacturer.
CHQ	CHQ-P50: patient or caregiver CHQ-CF87: children 10 or older	CHQ-P50 (50 items) CHQ-CF87 (87 items) Domains include: physical functioning, role/social limitations, bodily pain, general health perception, role/social limitations, self-esteem, mental health, general behaviour, emotional impact on the parent and time impact on the parent, family activities, and family cohesion. Scores range from 0 to 100, the higher scores indicating better HRQoL.	Not defined	

ADHR-RS = ADHD Rating Scale-IV; HRQoL = health related quality of life; HUI2/3 = Health Utilities Index Mark 2 and 3; CHQ = Child Health Questionnaire; WFIRS = Weiss Functional Impairment Rating Scale; CGI-S/I = Clinical Global Impression – Severity of Illness/Improvement; CPRS-R = Conners' Parent Rating Scale–Revised; CTRS-R = Conners' Teacher Rating Scale–Revised.

ADHD Rating Scale-IV

The ADHD Rating Scale-IV (ADHD-RS) rates the 18 symptoms of ADHD as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) on a four-point (0 to 3) scale from "never" to "always" and on a number of related scales.[44] (Total score range is 0 to 54.) It can be completed by the parent (P-home form) or the teacher (school form) or the investigator on the basis of information provided by the teacher or parent (PI). The scale has high utility for multiple applications due to its quick completion, ease of scoring, and sensitivity to treatment. There is a large, ethnically and geographically representative normative base, consisting of parents and teachers' ratings of approximately 2,000 children and youths 5 to 18 years old. Test-retest reliability is good, but there is low agreement between teachers' and parent's assessments. Differences between scores on the parent and the investigator versions are small.[48] There is considerable evidence of discriminant validity between children and youths with ADHD and clinical controls and between subtypes. Sensitivity and specificity appear to be suboptimal and can lead to misclassification of patients on screening. Utility in children under 5 years of age and adults has not been established.[49]

Some publications have suggested that a 30% mean total score change, or 5.2 to 7.7 points' difference between treatment groups represents a MCID.[39,44] Some studies have defined a responder as a patient

who has achieved a mean score of 2 from all items on this scale. This reflects a reduced frequency of symptoms, occurring on average "sometimes."[44]

Conners' Rating Scales

The Conners' Rating Scales were initially developed to assess a wide variety of children's behaviour problems. The Conners' Rating Scale–Revised (R) contains items that are specific to DSM-IV defined ADHD. Normative data are available from parent and teacher ratings of children in the US and Canada, with values presented separately by gender for different age groups from three to 17 years. There is also an Adolescent Self-Report available, which includes 12 items regarding adolescent behaviour.[49]

Conners' Teacher Rating Scale–Revised

This scale is used by clinicians and researchers to assess teachers' perception of children's behaviour in the classroom. This scale has 38 items rated using a four-point Likert scale (ranging from 0 for not at all true to 3 for very much true). It contains six scales and assesses behaviour along the dimensions of hyperactivity, conduct problems, emotional overindulgence, anxious-passiveness, asocial behaviour, and daydreaming-attendance problems.[50] There is a large, ethnically and geographically representative normative base, consisting of teachers' ratings of 1,702 youths, in separate cohorts of three to seven, eight to 12, and 13 to 17 years of age. It has moderate test-retest reliability but high sensitivity and specificity. The CTRS–R has excellent clinical utility and provides reliable, valid, and convenient means of measuring teachers' perceptions but should constitute only one component of the evaluation process and should not be solely relied upon for making clinical decisions.[51]

Conners' Parent Rating Scale–Revised

This scale is used by clinicians and researchers to assess parents' perception of children's behaviour in the classroom. This scale has 48 items rated using a four-point Likert scale (ranging from 0 for "not at all true" to 3 for "very much true"). The Conners' Parent Rating Scale–R contains five scales and assesses the behaviour of children along dimensions of conduct problems, learning problems, psychometric problems, impulsivity and hyperactivity, and anxiety. It has low to adequate one year test-retest reliability, adequate one year test-retest reliability for the impulsivity/hyperactivity factor, and low inter-parent inter-rater reliability.[50]

Clinical Global Impression–Severity of Illness/Improvement

At baseline, the investigator rates the severity of symptoms on a seven-point scale at baseline from 0 to 6 (0 = no symptoms and 6 = "very severe" symptoms). In subsequent assessments, the patient's improvement is measured relative to baseline using a seven-point scale from 1 to 7 (1 = "very much improved" and 7 = "very much worse"). This can then be converted to a dichotomous measure, grouping those who improved ("very much improved" and "much improved") and those who did not (all other categories).

There is no widely accepted definition of a clinically relevant response for ADHD. A reduction of 30% in a severity scale score (e.g., ADHD-RS) is likely to equate to a CGI of 1 ("very much improved") or 2 ("much improved") and has been used as a clinically relevant measure of response in some studies.[44]

Child Health Questionnaire

The Child Health Questionnaire (CHQ) is a multi-dimensional generic measure of health-related quality of life (HRQoL) that can be used with children as young as five years of age. It measures 11 domains of health. Physical domains include physical functioning, role/social limitations as a result of physical health, bodily pain and discomfort, and general health perception. Psychosocial domains include

role/social limitations as a result of emotional-behavioural problems, self-esteem, mental health, general behaviour, emotional impact on the parent, and time impact on the parent. Separate domains measure impact on family activities and family cohesion. Scores for the domains and items range from 0 to 100, the higher scores indicating better HRQoL. Summary scores have a mean of 50 and standard deviation of 10. The CHQ has undergone extensive validation and normative data testing.[52]

Weiss Functional Impairment Rating Scale–Parent Report
The Weiss Functional Impairment Rating Scale–Parent Report is a 50-item parent-rated measure of functioning across six domains: family, learning and school, life skills, child's self-concept, social activities, and risky activities. Each item is rated using a four-point Likert scale ranging from 0 (never or not at all) to 3 (very often or very much) and then summed to provide domain and total scale scores.[53]

Health Utility Index Mark 2 and Mark 3[30,47]
The Health Utility Index Mark 2 (HUI2) and Mark 3 (HUI3) are generic health profiles and preference-based systems for measuring health status and HRQoL, and for producing utility scores. They describe the experience of patients undergoing therapy; long-term outcomes associated with disease or therapy; the efficacy, effectiveness, and efficiency of health care interventions; and the health status of general populations.

The self-administered, parent-assessed version of the HUI2 and HUI3 that was used in several guanfacine trials consists of 15 questions required to classify a patient's health status. Three additional questions were included to capture additional information of use for health status measurement surveys.

APPENDIX 6: SUMMARY OF OTHER STUDIES

Objective

To summarize the results of two open-label extension studies of guanfacine extended release.

Findings

Data from two Shire-sponsored, open-label trials are summarized below. The main purpose of these two studies was to document risks of guanfacine over a 24-month period. Patients from three other trials were eligible to enroll in these open-label studies. Most of the patients who enrolled in these trials had previously been enrolled in the SPD503-301 and SPD503-304 trials summarized in this CADTH Common Drug Review (CDR) Clinical Report.

The inclusion criteria were broad, but less than half of the patients from the SPD503-301 and SPD503-304 trials enrolled in these open-label extension studies. The baseline ADHD Rating Scale-IV scores are similar to the baseline values observed at the beginning of the SPD503-303 and SPD503-305 trials.

Approximately 20% of the patients who enrolled in the open-label extension studies completed 24 months' treatment. Patients who were receiving concomitant psychostimulants appeared to remain in the study longer than patients on guanfacine monotherapy. High dropout rates are common in long-term open-label trials, but this significantly limits the generalizability of the results of these studies. The lack of a comparator also limits the utility of these data for providing reliable estimates of efficacy.

TABLE 19: OPEN-LABEL STUDIES

	SPD503-303	SPD503-305
Antecedent studies	SPD503-301	SPD503-304 and an open-label study that co-administered GXR with psychostimulants
Main objective	Safety assessment	Safety and tolerability assessment
Secondary objectives	ADHD-RS, PGA, CHQ	Effects of co-administration of amphetamine or methylphenidate ADHD-RS, CGI-S/I, CHQ, PK
Doses used	1 to 4 mg/d	1 to 4 mg/d
Combined subtype, n (%)	174 (72.5%)	189 (73.0%)
Age of patients	6 to 12 years (78.3%), > 12 years (21.7%)	6 to 12 years (73.7%), > 12 years (26.3%)
% male	76.7%	72.6%
Duration	Up to 24 months	Up to 24 months
Median drug exposure	5.95 months	15.8 months using psychostimulants 10.6 months not using psychostimulants
Analysis populations		
Enrolled, N	240	262
Safety, n (%)	240 (100%)	206 (monotherapy), 53 (coadministration of stimulants)
Completed 24 months, n (%)	42 (18%)	60 (22.9%) overall: 42.6% using psychostimulants, 17.8% not using psychostimulants

	SPD503-303	**SPD503-305**
SAE, n (%)	11(5%), including convulsions, syncope, orthostatic hypotension, intermittent explosive disorder, empyema, pneumonia, accidental overdose, lymphoma, gastrointestinal injury, stoma complication	16 (6.2%), including appendicitis, peritonitis, accidental overdose, concussion, head injury, extradural hematoma, spinal compression fracture, slipped femoral epiphysis, loss of consciousness, simple partial seizure, syncope, aggression, mood disorder, suicidal ideation
WDAE, n (%); most common, n	50 (20.8%); Weight increase (n = 7), somnolence (n = 9), ECG abnormality (n = 3)	31 (12%); Somnolence (n = 6), syncope (n = 3), depression (n = 3), ECG abnormality (n = 1)
Most common AEs	Sedation (13%), fatigue (14%), headache (26%), somnolence (30%)	Somnolence (30%), headache (24%), fatigue (14%), upper abdominal pain (13%), mean increase SBP/DBP: +1.2 mm Hg/+0.9 mm Hg
ADHD-RS	Baseline: 38.1 MCFB: −17.5 (6 to 12 years of age)	Baseline: 38.3 MCFB: −20.4 (6 to 12 years of age)
Other efficacy results	PGA "much improved" or "very much improved" in 59% of patients. CHQ overall score MCFB: NR	CGI-I mean at end point: 2.5 CPRS MCFB: −18.2 CHQ overall score MCFB: NSS

ADHD-RS = ADHD Rating Scale-IV; AE = adverse events; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity of Illness; CHQ = Child Health Questionnaire Parent; CPRS = Conners' Parent Rating Scale; ECG = electrocardiographic; MCFB = mean change from baseline; NSS = not statistically significant; PGA = parent global impression; PK = pharmacokinetics; SAE = serious adverse event; SBP/DBP = systolic/diastolic blood pressure; WDAE = withdrawal due to adverse events.

Summary

The trials were primarily designed to investigate the safety of guanfacine. Design limitations (open label, no control group, and high patient dropout rate) limit their usefulness for providing any further information on the risk of harm or efficacy for guanfacine.

APPENDIX 7: SUMMARY AND APPRAISAL OF MANUFACTURER-SUBMITTED MATCHING-ADJUSTED INDIRECT COMPARISON

Objective
The objective of this review is to summarize the methods and results, and to conduct a critical appraisal of the matching-adjusted indirect comparison (MAIC) between guanfacine extended release (GXR) and atomoxetine (ATX) conducted by the manufacturer. This indirect comparison was provided as part of the economic submission to the CADTH Common Drug Review (CDR) for this Clinical Report (guanfacine monotherapy).

Summary of Matching-Adjusted Indirect Comparison
Rationale
The manufacturer did not specifically indicate the reason for performing the indirect comparison of GXR and ATX.

Several recent publications report indirect comparisons of these two drugs.[54-57] Since the file for GXR was submitted to the CDR in September 2013, one GXR trial with an active control group (ATX) was completed by Shire in unpublished format (Study 316, October 2013).[31]

Methods
a)   Eligibility Criteria
In order to be eligible for inclusion, trials had to be double-blind and randomized, and include patients six to 18 years of age with attention-deficit/hyperactivity disorder (ADHD). Trials also had to have commonly reported efficacy outcomes (ADHD Rating Scale-IV [ADHD-RS]).

b)   Intervention and Comparators
GXR and ATX must have been used as monotherapy with a dose of 0.09 to 0.12 mg/kg once daily for GXR and 1.2 mg/kg once daily for ATX. All trials were placebo-controlled.

These target doses formed the base case for the indirect comparison, and the sensitivity analysis included comparisons between lower doses of GXR (0.046 to 0.075 mg/kg once daily and 0.075 to 0.090 mg/kg once daily) and the dose of ATX recommended in the Canadian product monograph (1.2 mg/kg once daily).

c)   Outcomes
The main outcome of interest for the indirect comparison was the mean change in ADHD-RS total score from baseline to end point.

d)   Analysis
Patient-level data from two trials comparing GXR with placebo (Studies 301 and 304) and summary data from one published trial comparing ATX with placebo[58] met the inclusion criteria for the report. The quality of the included studies was not reported.

Patients from the guanfacine trials were selected based on the same inclusion/exclusion criteria as the atomoxetine trial. Trial populations were matched by assigning weights to individual patients in the

guanfacine trials such that their weighted mean and standard deviations for baseline characteristics (age, gender, baseline ADHD-RS inattentive and hyperactivity/impulsivity subscale scores, and ADHD subtypes), and mean placebo group efficacy (change in ADHD-RS total score from baseline) matched those reported for the ATX trial.

Results
a)   Study and Patient Characteristics
A total of three relevant placebo-controlled randomized controlled trials (RCTs) were identified and included in the indirect comparison. The age of the patients in the trials ranged from 8 to 18 years because patients six to seven years of age were absent from the atomoxetine trial. Between 71% and 75% of the patients were male across the trials. Trial duration was either eight or nine weeks. In the guanfacine trials, patients were randomized to fixed doses of either 2 mg once daily to 4 mg once daily (study 301) or 1 mg once daily to 4 mg once daily (study 304). In the atomoxetine trial, patients were randomized to 0.5, 1.2, or 1.8 mg/kg once daily. All three trials had ADHD-RS total score as a primary outcome.

b)   Results of the Matching-Adjusted Indirect Comparison
Statistically significant differences favouring GXR mid- or high dose compared with ATX were shown in the ADHD-RS score changes from baseline (Table 20). The absolute differences in scores between GXR and ATX were between six and seven points. No statistically significant differences were observed between the GXR low-dose group and the ATX group. Statistically significant differences were reported between GXR mid- and high doses, compared with ATX, favouring GXR. No statistical analyses were provided for the response rate data.

TABLE 20: MATCHING-ADJUSTED INDIRECT COMPARISON RESULTS

	GXR LOW 0.046 mg/kg to 0.075 mg/kg/d	GXR MID 0.075 mg/kg to 0.090 mg/kg/d	GXR HIGH 0.09 mg/kg to 1.2 mg/kg/d	ATX 1.2 mg/kg/d
Sample size before matching	**n = 147**	**n = 46**	**n = 82**	**n = 84**
Effective sample size after matching	**n = 49**	**n = 16**	**n = 38**	**n = 84**
Change in ADHD Rating Scale from baseline	−17.3 (95%CI, −19.9 to −14.7), P = 0.07 vs. ATX	−19.6 (95%CI, −23.9 to −15.3), P = 0.02 vs. ATX	−20.6 (95%CI, −16.6 to −10.6), P < 0.01 vs. ATX	−13.6 (95%CI,−16.6 to −10.6)
Predicted response rates	69.7%	77.1%	80.3%	57.9%

ATX = atomoxetine; CI = confidence interval; GXR = guanfacine extended release; vs. = versus.

Critical Appraisal of Matched-Adjusted Indirect Comparison
The quality of the manufacturer's matched-adjusted indirect comparison was assessed according the recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[59] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 21.

Limitations

Before matching, many of the baseline characteristics of the three trials were different (e.g., mean age, gender percentage, ADHD subtype, and ADHD-RS total score). After matching, the GXR patient samples had similar baseline characteristics as those in the ATX trial. However, the sizes of the GXR dose groups were very small after matching (low dose n = 49, mid-dose n = 16, high dose n = 38). This could limit the generalizability of the results.

No quality assessment was performed for the trials included in the analysis.

The guanfacine trials included patients aged six to seven years, whereas the atomoxetine trials included patients who had reached the age of eight years. The manufacturer made attempts to adjust for this difference by matching mean age and standard deviation for age.

While some information was provided on the trial populations, no information was provided on patient withdrawal and whether follow-up rates were comparable across the three studies. This could affect comparability of the trial populations.

The manufacturer did not provide the results of the statistical comparisons very clearly. No confidence intervals were provided for the mean difference of change scores in the ADHD-RS. This meant that reviewers could not assess the variance of the efficacy estimates. The total range of points on the ADHD-RS is 0 to 54.

No comparative data between the placebo groups was provided. This comparison is helpful for evaluating the response in the placebo group between trials and, subsequently, comparability of trial populations.

In Canada, GXR is indicated for children six to 12 years of age. The indirect comparison data included patients from six to 18 years of age. Therefore, the generalizability of the results has some limitations based on age.

This indirect comparison focused on monotherapy. According to the CDR clinical expert for this review, GXR is also likely to be used as adjunctive therapy in Canada.

Strengths

ATX was selected as a relevant comparator for the Canadian setting.

The baseline characteristics were well matched between the GXR and ATX groups.

TABLE 21: CRITICAL APPRAISAL BASED ON ISPOR CHECKLIST

Checklist Item	Details
Are the rationale for the study and the study objectives stated clearly?	• Rationale and objectives were not clearly stated.
Does the methods section include the following? • Description of eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction (validity/quality assessment	• Inclusion and exclusion criteria are presented. • Information source and search terms were identified (used MEDLINE). • Number of trials meeting specific eligibility criteria was clearly presented. • No critical appraisal was provided of the included studies. • Data extraction methods were not explained.

Checklist Item	Details
of individual studies)	• No detailed description given about the duration of ADHD diagnosis at baseline and how many previous therapies had been utilized.
Are the outcome measures described?	• The outcome measure of interest was briefly described (mean change in ADHD Rating Scale-IV total score). • No explanation for why other outcomes were not extracted from the included trials (e.g., adverse event data were obtained from product monographs).
Is there a description of methods for analysis/synthesis of evidence? Do the methods described include the following? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• Matching-Adjusted Indirect Comparison was used. • Brief description of the statistical methods used for matching. • No description of how bias or heterogeneity was dealt with. • Bootstrap methodology was used to obtain standard errors of predicted guanfacine efficacy. • ADHD Rating Scale-IV scores were converted into response rates using modelling.
Are sensitivity analyses presented?	• Baseline ADHD Rating Scale-IV scores were presented for guanfacine low, mid- and high doses, and comparative results were provided for each dose group (guanfacine versus atomoxetine). • Sensitivity analyses not provided for different atomoxetine doses.
Do the results include a summary of the studies included?	• A brief summary is included of baseline characteristics and designs of the three studies.
Are the results of the evidence synthesis presented clearly?	• The results are not presented clearly. • Incomplete data reporting for main outcome of interest (ADHD Rating Scale-IV).
Sensitivity/scenario analyses	• Low, mid- and high guanfacine doses.
Does the discussion include the following? • Description/summary of main findings • Internal validity of analysis • External validity • Implications of results for target audience	• Summary of findings was provided. • Some discussion of external validity and generalizability to Canadian treatment setting. • Implications of analysis are largely described in terms of the submitted cost-effectiveness analysis.

ADHD = attention-deficit/hyperactivity disorder.

Source: Jansen et al., 2011[59]

Summary

The manufacturer undertook a systematic review of randomized controlled trials (RCTs) and performed a MAIC of GXR and ATX, both given as monotherapy. The resulting matched sample sizes were small, but the baseline characteristics were well matched between the GXR and ATX groups. There were statistically significant differences in mean change in ADHD-RS scores at end point, favouring GXR. Incomplete reporting of analyses did not allow a full analysis of methods. Shire sponsored two other indirect comparison studies (in 2012 and 2013),[54,57] the conclusions of which are similar to the present report.

Inherent in this MAIC method is the possibility of residual confounding of baseline characteristics that were not accounted for. Although the reported baseline characteristics were well matched, there could be other unreported characteristics that were not well matched. In contrast to the findings of this

indirect comparison, there is one RCT that randomized patients to GXR or ATX (Study 316). This study is included in the body of this CDR Clinical Report. The results of this comparison showed similar reductions in ADHD-RS total score for GXR and ATX, although this study was not statistically powered to detect differences between the two active treatments.

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