Common Drug Review
Pharmacoeconomic 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.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
ADHD-RS	ADHD Rating Scale-IV
AE	adverse event
ATX	atomoxetine
CDR	CADTH Common Drug Review
CEA	cost-effectiveness analysis
CGI-S	Clinical Global Impression–Severity of Illness
GXR	guanfacine hydrochloride extended release
HRQoL	health-related quality of life
LOCF	last observation carried forward
ICUR	incremental cost-utility ratio
MAIC	matching-adjusted indirect comparison
QALY	quality-adjusted life-year

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Guanfacine hydrochloride extended release (Intuniv XR)
Study Question	**Monotherapy:** "A cost-effectiveness analysis (CEA) based on matching-adjusted indirect comparison (MAIC)…comparing guanfacine hydrochloride extended release (GXR) versus atomoxetine (ATX) for the treatment of ADHD in children and adolescents from a Canadian perspective." **Adjunctive therapy:** "a cost-effectiveness analysis (CEA) comparing GXR as an adjunctive therapy to psychostimulants with psychostimulant monotherapy among ADHD children who had a suboptimal response to psychostimulants."
Type of Economic Evaluation	• CEA • Cost-utility analysis
Target Population	**Monotherapy:** Children with ADHD aged 6 to 12 years with a symptom severity score at least 1.5 SD above age- and gender-normative values. **Adjunctive therapy:** Children with ADHD aged 6 to 12 years with suboptimal response to psychostimulants
Treatment	**Monotherapy:** 0.09 mg/kg to 0.12 mg/kg/d or 1 mg to 4 mg/d **Adjunctive therapy:** 0.05 mg/kg to 0.12mg/kg/d or 1 mg to 4 mg/d
Outcome(s)	**Monotherapy:** mean change in ADHD-RS total scores from baseline to end point **Adjunctive therapy:** changes in CGI-S score
Comparators	**Monotherapy:** 1.2 mg/kg/d ATX or non-pharmacological treatment **Adjunctive therapy:** placebo plus psychostimulants
Perspective	Canadian Public Payer
Time Horizon	1 year
Manufacturer's Results (Base Case)	**Monotherapy:** $57,866 per QALY (GXR versus ATX) $53,657 (GXR versus non-pharmacological treatment) **Adjunctive therapy:** $23,720 to $35,669 per QALY
Key Limitations and CDR Stimate(s)	• There is significant uncertainty in translating changes in ADHD-RS and CGI-S scores to health states and assigning quality of life for both analyses. **Monotherapy** • Medical costs for responders may be overestimated. CDR analysis assuming equal medical costs for responders and non-responders results in an ICUR of **$64,449** per QALY. • Uncertainty in relative efficacy. Use of the upper bound of the 95% CI doubled the ICUR (**$130,000** per QALY). Using response rates from a recent active-controlled trial, the ICUR increased to **$93,909** per QALY. Of note, the active-controlled trial showed no differences in utility-based quality of life (HUI2/3) of GXR or ATX versus placebo, although the study was not designed to directly compare GXR with ATX. **Adjunctive Therapy** • Model did not consider other adjunctive drugs (clonidine, atypical antipsychotics, etc.), which may be used in addition to psychostimulants. There is a lack of data on relative efficacy of other drugs, and hence the ICUR for other potential comparators is unknown. • The CDR reference case that assumed equal medical costs for normal and mild states and used the LOCF approach increased the ICUR to **$35,675** per QALY. • Uncertainty in relative effectiveness (CGI-S) was not explored in the original submission, but was provided at CDR request. In this analysis by the manufacturer, the ICUR increases to **$35,669** per QALY when the upper 95% CI is used for psychostimulants only with the ordered logit approach. The ICURs increase to **$57,434** to **$65,528** per QALY when the 95% CI is tested with the LOCF approach.

ADHD = attention-deficit/hyperactivity disorder; ADHD-RS = ADHD Rating Scale-IV; ATX = atomoxetine; CGI-S = Clinical Global Impression–Severity of Illness; CDR = CADTH Common Drug Review; CEA = cost-effectiveness analysis; CI = confidence interval; GXR = guanfacine extended release; HUI2/3 = Health Utilities Index Mark 2 and 3; ICUR = incremental cost-utility ratio; LOCF = last observation carried forward; QALY = quality-adjusted life-year.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

Guanfacine hydrochloride extended release (Intuniv XR; GXR) is being reviewed as monotherapy or adjunctive therapy to psychostimulants for the treatment of attention-deficit/hyperactivity disorder (ADHD) for children aged six to 12 years. The recommended oral dose is 0.05 mg/kg to 0.012 mg/kg daily for both monotherapy and adjunctive therapy. The daily cost of GXR is $[redacted] 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 atomoxetine (ATX), over a one year time horizon from a payer perspective. In a second analysis, GXR was also compared with non-pharmacological treatment/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 an active-controlled trial of GXR compared with ATX [SPD503-316] have since become available; see Section 3.3 CADTH Common Drug Review Analyses.) 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 their respective long-term open-label trials.

Adverse events (AEs) were assumed to occur at treatment initiation and persist through the entire titration period. The rates of the 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 were informed by a UK quality of life study in children with ADHD using the EuroQol Five-Dimension Health-Related Quality of Life 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 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 Clinical Global Impression–Severity of Illness [CGI-S] score ≥ 3). The cost-utility analysis was based on a phase 3, double-blinded, 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 (patient with ADHD 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 and placebo was $53,657 per QALY.

Adjunctive Therapy

The manufacturer reported an incremental cost per QALY for GXR plus psychostimulants compared with psychostimulants only 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% CI was used for

psychostimulants. The LOCF model may be more appropriate, given that it conservatively assumes 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 in the Clinical Review Report). Furthermore, significant uncertainty exists in translating the ADHD-RS and CGI-S scales to a quality of life score. [redacted]
- **Resource utilization costs.** Both models used Guevara et al.'s study[2] to estimate the health care utilization costs for patients with ADHD in the US (since no Canadian data were identified). 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 CEA 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. nalyses on time horizon could not be conducted on provided models. However, 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.

Guanfacine Extended Release 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 was $68,455 per QALY.

Adjunctive Therapy

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 the manufacturer's resubmitted sensitivity analysis ($57,434 to $65,528 per QALY).

Issues for Consideration

- According to the clinical experts consulted for this review, most patients with ADHD are not treated with drugs, and those treated are typically given psychostimulants as first-line treatment. The proportion of patients currently treated using non-psychostimulants 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 implications).
- It is arguable that health-related quality of life (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 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.

Conclusions

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).

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question

a) Monotherapy

"A cost-effectiveness analysis (CEA) based on matching-adjusted indirect comparison (MAIC) comparing guanfacine hydrochloride extended release (GXR) versus atomoxetine (ATX) for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents from a Canadian perspective."

(*Manufacturer's Submission – Study report for cost-effectiveness analysis of GXR versus ATX for the treatment of ADHD*, page 6.)

b) Adjunctive Therapy

"To fully understand the economic value of GXR as an adjunctive therapy in a Canadian context, we conducted a cost-effectiveness analysis (CEA) comparing GXR as an adjunctive therapy to psychostimulants with psychostimulant monotherapy among ADHD children who had a suboptimal response to psychostimulants."

(*Manufacturer's Submission — Study analysis report for CEA model GXR plus psychostimulants as adjunctive therapy versus psychostimulant monotherapy in Canada*, page 6.)

1.2 Treatment

a) Monotherapy

0.09 mg/kg to 0.12 mg/kg per day or 1 mg to 4 mg per day

b) Adjunctive Therapy

0.05 mg/kg to 0.12 mg/kg per day or 1 mg to 4 mg per day

1.3 Comparators

a) Monotherapy

1.2 mg/kg per day ATX; non-pharmacological treatment tested in secondary analysis

According to the clinical expert, GXR or ATX monotherapy is uncommonly used in Canada, as psychostimulants are the standard of care. However, some patients may opt for monotherapy to avoid the use of psychostimulants. In addition, GXR may be less likely to replace ATX, as each is often used for specific comorbidities (GXR for oppositional symptoms and ATX for anxiety), according to the clinical expert.

b) Adjunctive Therapy

Placebo plus psychostimulants (weighted average of long-acting psychostimulants according to Canadian data from IMS Brogan for children up to 12 years of age)

According to the clinical experts, there are other comparators in Canada including ATX plus psychostimulants, clonidine plus psychostimulants, and antipsychotics. Patients with ADHD that is not

well controlled with psychostimulants only are frequently prescribed clonidine or atypical antipsychotics, although these are not approved by Health Canada for the treatment of ADHD.

1.4 Type of Economic Evaluation

A cost-utility analysis was undertaken and is appropriate according to the CADTH guidelines.

The primary perspective used in the two models is that of the Canadian public payer. A secondary analysis was also conducted from the societal perspective, taking into account lost workplace productivity for families of patients with ADHD.

1.5 Population

a) Monotherapy

The population comprised patients six to 17 years old in the pivotal trials. However, since GXR is indicated for treatment of children of six to 12 years old, it was assumed that the clinical efficacy of GXR in the model was similar to that measured in the trials. Hence, the clinical outcomes used in the economic evaluation may not exactly represent the target population of GXR in Canada.

b) Adjunctive Therapy

The target population was children with ADHD aged 6 to 12 years with suboptimal response to psychostimulants. Suboptimal response was defined as treatment with a stable dose of psychostimulant for at least four weeks with improvement but with remaining mild to moderate ADHD symptoms (ADHD Rating Scale–IV [ADHD-RS] score ≥ 24 and Clinical Global Impression–Severity of Illness [CGI-S] score ≥ 3). The phase 3 trial also comprised children six to 17 years, old and, again, the clinical efficacy of GXR in the model was assumed to be similar to that measured in the trial.

2. METHODS

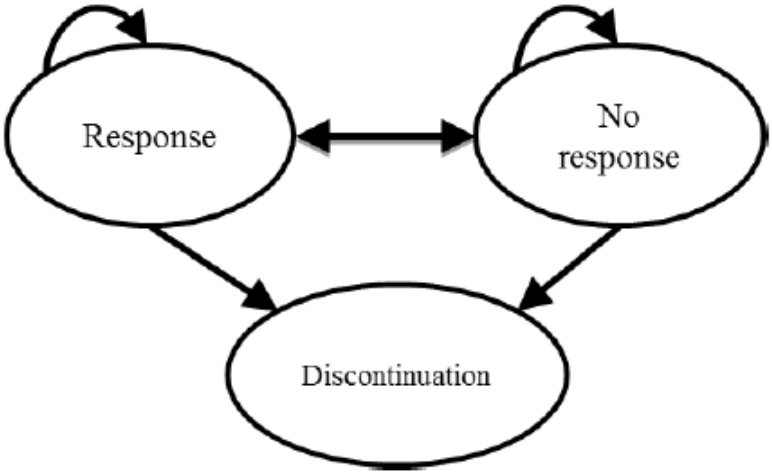
Please see Table 5 for a summary of the key limitations associated with the methodology used by the manufacturer.

2.1 Model Structure

a) Monotherapy

The cost-utility analysis consisted of a one-year Markov model that utilizes efficacy data from the MAIC study. The Markov health states included response, no response, and discontinuation (Figure 1). The cycle length in the Markov model was one week, with a four week drug titration period and a 48 week maintenance period. Rate of treatment response was defined as ≥ 25% reduction in ADHD-RS total score from baseline to end point. Transition probability from no response to response in each cycle during the titration period was estimated using the predicted response rates for GXR and ATX from the published trials. The estimation assumed that response rates were achieved at the end of the titration period and that the transition occurred at a constant rate. The discontinuation rate during the maintenance period was estimated for each treatment based on the two year rate observed in the long-term open-label trials.

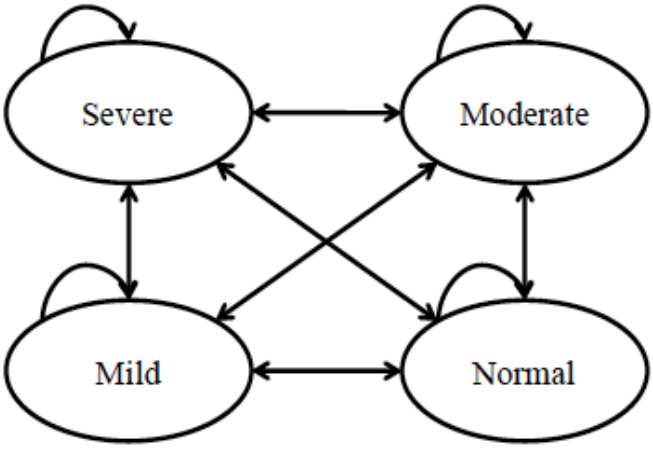
FIGURE 1: MARKOV MODEL (MONOTHERAPY)



b) Adjunctive Therapy

The cost-utility analysis also consisted of a one year Markov model that utilizes efficacy data from a phase 3 randomized controlled trial. The Markov health states included 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"; Figure 2). The cycle length in the Markov model was also one week. The model consisted of two stages: the first stage started from week 0 to week 8, and the second stage spanned from week 9 to week 52. All patients continued their assigned treatments during the first stage. In the second stage, patients in the moderate or severe states were considered to be non-responsive and thus permanently discontinued the treatments. Transition probability was calculated based on patient-level data from the phase 3 trial.

FIGURE 2: MARKOV MODEL (ADJUNCTIVE THERAPY)



2.2 Clinical Inputs

a) Efficacy

Monotherapy

Efficacy outcome was calculated as the mean change in ADHD-RS total scores from baseline to end point in the matching-adjusted indirect comparison (MAIC). MAIC was conducted to compare each GXR weight-based dose with the ATX target dose from pooled patient-level data from the GXR trials (SPD 503-301 and 304 trials) and with summary data published in the ATX trial. Baseline characteristics and trial populations were matched by assigning weights to individual patients in the GXR trials to those reported for the ATX trial. After matching, efficacy outcomes for GXR were predicted for a comparable ATX trial population. For the response rate estimation used in the model, because the ATX trial included in the MAIC did not report response rate as an end point, a prediction model was developed based on other published ATX trials in order to translate the change in ADHD-RS total score to response rate. The model was developed using data from all treatment groups in the ATX trials that reported baseline ADHD-RS total score, change in ADHD-RS total score, and rate of treatment response, defined as ≥ 25% reduction in ADHD-RS total score from baseline to end point. The prediction model was then applied to estimate treatment response for the three GXR dose groups and the ATX group based on the estimated mean change in ADHD-RS total score from the MAIC. Clinical parameters such as ADHD-RS score from baseline, response rate, and treatment discontinuation for non-pharmacological treatment were obtained from the placebo group.

Adjunctive Therapy

The submission relied upon patient-level data from the phase 3 trial to simulate the clinical efficacy of GXR plus psychostimulants in the first eight weeks. Patients were assigned each week to one of the four health states based on ordered logit models to estimate the transition probabilities, and the health state in the previous week was used to predict the current health state. Transition probabilities were estimated for the psychostimulants-only group and the GXR plus psychostimulants group for morning and evening administration. The estimated transition probabilities were applied throughout the model period for patients remaining on treatment. In the alternative last observation carried forward (LOCF) approach, transition probabilities in each health state observed at week 8 were carried forward to week 52.

b) Harms

Monotherapy

Adverse events (AEs) were assumed to occur during the treatment-initiation period. The rates of AEs applied to the model were based on those observed in the key clinical trials reported in the package inserts of GXR and ATX. Only the AEs with rates of more than 5% were included in the economic model and assumed to result in a utility decrement lasting for four weeks.

Adjunctive Therapy

AEs that impacted at least 5% of all treatment groups were included and assumed to result in a utility decrement lasting for four weeks. AEs included in the model were headache, somnolence, insomnia, fatigue, abdominal pain, dizziness, decreased appetite, and nausea.

c) Quality of Life

Monotherapy

Utilities associated with response and non-response were obtained from a UK study by Coghill et al. (available as poster only).[3] Utilities were estimated in a group of patients with ADHD using the EuroQol Five-Dimension Health-Related Quality of Life Questionnaire filled in by parents of patients.

Adjunctive Therapy

Utility values were obtained from a UK study by Lloyd et al.[4] The utility data were collected from a survey of 100 members of the general public using time trade-off method and a visual analogue scale. Utility values estimated from the time trade-off method were used in the economic model.

More details on how the utility scores were assigned are listed in the next section.

d) Costs

Resource use was considered from the perspective of the public payer in the base case models.

e) Drug Costs

Monotherapy

The cost of GXR ($[redacted] per tablet) was obtained from the manufacturer, and the cost of ATX ($2.03 per tablet) was obtained from the Régie de l'assurance-maladie du Québec and in the Saskatchewan Drug Formulary. The non-pharmacological treatment was assumed to be already captured in the medical costs associated with ADHD, and no additional cost was included.

Adjunctive Therapy

The cost of GXR ($[redacted] per tablet) was obtained from the manufacturer. The long-acting psychomstimulants included in the model were those available in Canada: Adderall XR (amphetamine mixed salts), Concerta (methylphenidate HCI), generic methylphenidate, Biphentin (methylphenidate HCI), and Vyvanse (lisdexamfetamine dimesylate). The daily cost of each long-acting psychostimulant was based on daily dose and number of pills according to Canadian data from IMS Brogan for children up to 12 years old. The final unit cost for long-acting psychostimulants ($2.80) was estimated as a weighted average of drug costs based on the Canadian distribution of psychostimulants for the year 2012 provided by IMS Brogan and was assigned to both treatment groups.

f) Event Treatment Costs

Monotherapy

Health care resource utilization was obtained from an US study by Guevara et al.[2] Incremental health care utilization associated with ADHD management, including primary care visits, mental health visits, emergency department visits, and hospitalizations, was extracted from this retrospective matched cohort study. The model assumed the medical costs for responders to be the same as the costs for children without ADHD, and the costs for non-responders to be the same as the costs for children with ADHD. The unit cost of the health care service, obtained from the Ontario Schedule of Benefits for Physician Services and Ontario Case Costing Initiative, was then applied to obtain a Canadian cost for each service. Given the diagnosis and ongoing treatment, responders are unlikely to have the same utilization as children without ADHD, but very likely to have ongoing primary care and mental health visits. This assumption will be tested in the CADTH Common Drug Review (CDR) reanalysis.

Adjunctive Therapy

Similar to monotherapy, the health care utilization was adopted from the Guevara et al. study,[2] and the unit cost was derived from Canadian sources. In order to allocate costs according to disease severity, the model assumed the annual medical costs for the "normal" state to be the same as the median costs for patients without ADHD ($245), and the costs for "severe" state to be two times the mean medical costs as those for patients with ADHD ($1,476). The average cost for the "mild" state ($248) was determined assuming a linear distribution. The average cost for the "moderate" state ($709) was calculated using the cost estimates of the "mild" and "severe" states and by retrieving the original mean cost estimated from the Guevara et al. study. Again, patients with the "normal" state are unlikely to have the same

utilization as children without ADHD. In addition, the Guevara et al. study recruited children who had at least one ambulatory visit or hospitalization during the study period; the study participants are likely to have a more severe health state, and the medical costs might be overestimated in the model.

g) Utilities

Monotherapy

Utilities associated with response (0.837) and non-response (0.773) were obtained from the study by Coghill et al. presented as a conference poster.[3] Unfortunately, the CDR did not have access to the poster and could not determine whether the response and non-response were the same for the trials and the utility study.

Adjunctive Therapy

Utility values were obtained from the UK study by Lloyd et al.[4] Health states based on the CGI-S score were defined similarly to the ones used in the model, with the exception that the "severe" state excluded CGI-S scores 7. The utility data were collected from a survey of 100 members of the general public in the UK. Participants rated each health state with short descriptions developed based on the clinical trial analysis and interviews with children with ADHD.

h) Time Horizon

Both models used a one year time horizon and claimed that this time horizon has been commonly used in other CEAs of ADHD treatments. However, the CDR clinical experts stated that it is normal to treat patients ADHD for at least two to three years, or until adolescence or adulthood in clinical practice.

i) Discounting

Costs and outcomes were not discounted in either model because the time horizon did not exceed one year.

j) Validation

Information on model validation was not provided in the submission.

3. RESULTS

3.1 Manufacturer's Base Case

a) Monotherapy

In the reference case, the manufacturer reported that the total cost for GXR was $938, an incremental cost of $400 compared with ATX. GXR resulted in additional drug costs of $445, but led to reduced medical costs (–$45) compared with ATX. Treatment with GXR resulted in 0.798 total QALYs, an additional 0.007 QALY compared with ATX. Hence, the incremental cost per QALY gained was $57,866.

For the comparison of GXR and non-pharmacological treatment and placebo, the manufacturer reported that the total cost for GXR was $938, an incremental cost of $589 compared with placebo. GXR resulted in additional drug costs of $753, but led to reduced medical costs (–$163) compared with placebo. Treatment with GXR resulted in 0.798 total QALYs, an additional 0.011 QALY compared with placebo. Hence, the incremental cost per QALY gained was $53,657.

b) Adjunctive Therapy

In the reference case (based on ordered logit model), the manufacturer reported that the total cost for GXR plus psychostimulants was $1,617, an incremental cost of $668 compared with psychostimulants only. GXR plus psychostimulants resulted in additional drug costs of $735, but led to reduced medical costs (–$67) compared with psychostimulants only. Treatment with GXR plus psychostimulants resulted in 0.655 total QALYs, an additional 0.028 QALY compared with psychostimulants only. Hence, the incremental cost per QALY gained was $23,720.

With the LOCF approach (based on trial data), the manufacturer reported that the total cost for GXR plus psychostimulants was $2,339, an incremental cost of $1,197 compared with psychostimulants only. GXR plus psychostimulants resulted in additional drug costs of $1,274, but led to reduced medical costs (–$76) compared with psychostimulants only. Treatment with GXR plus psychostimulants resulted in 0.737 total QALYs, an additional 0.034 QALY compared with psychostimulants only. Hence, the incremental cost per QALY gained was $35,669.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

Monotherapy	Total Costs ($)	Incremental Cost of GXR ($)	Total QALYs	Incremental QALYs of GXR	Incremental Cost per QALY ($/QALY)
GXR	938	400	0.798	0.007	57,866
ATX	537		0.791		
GXR	938	589	0.798	0.011	53,657
Non-pharmacological treatment	348		0.787		
Adjunctive Therapy (Ordered Logit Model)	**Total Costs ($)**	**Incremental Cost of GXR Plus Psychostimulants ($)**	**Total QALYs**	**Incremental QALYs of GXR Plus Psychostimulants**	**Incremental Cost per QALY ($/QALY)**
GXR plus psychostimulants	1,617	668	0.655	0.028	23,720
Psychostimulants only	949		0.627		
Adjunctive Therapy (LOCF)	**Total Costs ($)**	**Incremental Cost of GXR Plus Psychostimulants ($)**	**Total QALYs**	**Incremental QALYs of GXR Plus Psychostimulants**	**Incremental Cost per QALY ($/QALY)**
GXR plus psychostimulants	2,339	1,197	0.737	0.034	35,669
Psychostimulants only	1,141		0.704		

ATX = atomoxetine; GXR = guanfacine extended release; LOCF = last observation carried forward; QALY = quality-adjusted life-year.
Source: Manufacturer's submission.[5]

3.2 Summary of the Manufacturer's Sensitivity Analyses

Uncertainty was addressed using Monte Carlo simulation and one-way deterministic sensitivity analyses, which varied model parameters by using alternative values.

a) One-Way Sensitivity Analyses

Monotherapy

A series of one-way sensitivity analyses (95% confidence interval of the parameter, unless specified) were conducted by the manufacturer, including response rate; GXR dose (0.046 mg/kg to 0.075 mg/kg per day); rate of treatment discontinuation during maintenance (no discontinuation, observed rates, ATX rates to both groups); drug cost (for lowest and highest dose); medical cost and productivity loss (± 25%); utility (± 25%); and disutility (± 25%).

The reference case result for GXR compared with ATX was $57,866 per QALY. The following parameters increased the incremental cost per QALY gained by more than 25% for GXR:

- Decreased utility associated with response by 25% (base case 0.837), cost per QALY was $81,441
- Increased ATX response rate (upper 95% CI), cost per QALY was $127,471
- Decreased GXR response rate (lower 95% CI), cost per QALY was $130,000
- All patients received highest dosing of GXR (4 mg), cost per QALY was $86,073.

No sensitivity analysis was performed on GXR versus non-pharmacological treatment.

Adjunctive Therapy

A series of one-way sensitivity analyses (95% confidence interval of the parameter, unless specified) were conducted by the manufacturer, including transition probabilities (no transitions from week 9 to week 52); drug costs (lower dose or higher dose of each psychostimulant, 100% patients on each psychostimulant); medical costs/productivity losses (normal –25% to severe +25%); utility; AEs (at baseline, two, and eight weeks); and initial distribution (100% mild, moderate, or severe).

The reference case result for GXR plus psychostimulants compared with psychostimulants alone was $23,720 per QALY. None of the parameters increased the incremental cost per QALY gained by more than 25% for GXR plus psychostimulants in the original sensitivity analysis. However, when the observed transition probabilities (LOCF) from trial data were used (estimates from ordered logit model were used in the base case), the cost per QALY increased to $35,669. There were substantial differences between the two approaches: the ordered logit model assumed patients with ADHD experience a deterioration in health state over time, with only 1% to 5% of patients in the normal health state by the end of the year. With the LOCF approach, the percentage of patients in each health state at week 8 was carried forward, and thus 15% to 25% of patients were in the normal state at the end of model duration (week 52). Actual/predicted transition probabilities from the trial were used in the model; the sensitivity analysis of the variance in relative efficacy was resubmitted at CDR request. The following parameters increased the incremental cost per QALY gained by more than 25% for GXR plus psychostimulants in the resubmitted sensitivity analysis:

- Decreased the transition probabilities for psychostimulants only with the LOCF approach (lower 95% CI), cost per QALY was $65,528
- Increased the transition probabilities for GXR plus psychostimulants with the LOCF approach (upper 95% CI), cost per QALY was $57,434
- Increased the transition probabilities for psychostimulants only with the ordered logit approach (upper 95% CI), cost per QALY was $36,181.

GXR was also compared with short- and intermediate-acting psychostimulants in a complementary analysis for provinces where access to long-acting psychostimulants was limited. The cost per QALY was $20,663.

b) Probabilistic Sensitivity Analysis

Monotherapy

According to the acceptability curves from the probabilistic sensitivity analyses, there is a 60.83% probability that the incremental cost-effectiveness ratio would fall below the $50,000 per QALY threshold for GXR versus ATX. Probabilistic sensitivity analyses were not performed for GXR versus non-pharmacological treatment.

Adjunctive Therapy

According to the acceptability curves from the probabilistic sensitivity analyses in the resubmission, there is a 96.68% probability that the incremental cost-effectiveness ratio would fall below the $50,000 per QALY threshold for GXR plus psychostimulants versus psychostimulants only.

3.3 CADTH Common Drug Review Analyses

a) Monotherapy

Guanfacine Extended Release Versus Atomoxetine

- **Medical costs:** The cost of patients with ADHD with full response is assumed to be the same as those of children without ADHD; the additional medical cost for non-responders is reduced to test this assumption. When the additional medical cost for non-responders is reduced by 50 % ($7 to $3.50), the incremental cost-utility ratio (ICUR) increases to $61,156 per QALY. When the annual medical cost is the same for both responders and non-responders, the ICUR increases to $64,449 per QALY.
- **Response rate:** Predicted response rates rather than actual trial response rates were used in the model. If the response rate for ATX is increased by 10% and 20% (relative risk [RR] 0.637 and 0.695 instead of 0.579), the ICUR increases to $85,456 and $173,045 per QALY, respectively. In addition, if the CGI-S improvement rate from the active-controlled trial (SPD503-316, GXR 67.9% versus ATX 56.3%) is used as a proxy for response rate, the ICUR is $86,699 per QALY.
- **Quality of life:** The new active-controlled trial (SPD503-316) reported no significant improvement in quality of life among GXR, ATX, and placebo when assessed by Health Utilities Index Mark 2 and 3 (see Clinical Report Table 12). When quality of life is assumed to be the same by treatment strategy, ATX dominates GXR.
- **Higher dose of GXR:** As a higher dose might be used in patients with a higher body mass, when the dosing is changed to 8 mg per day, the ICUR is $166,722 per QALY.

Guanfacine Versus Non-pharmacological Treatment

- **Medical costs:** When the additional medical cost for non-responders is reduced by 50 % ($7 to $3.50), the ICUR increases to $61,000 per QALY. When the annual medical cost is the same for both responders and non-responders, the ICUR increases to $68,455 per QALY.
  Note: the ICURs were manually calculated by CDR, as the medical cost is assumed to be the cost of non-pharmacological treatment in the model; therefore, the medical cost was kept constant although the parameters have been changed.
- **Response rate:** Predicted response rates rather than actual trial response rates were used in the model. If the response rate for non-pharmacological treatment is increased by 10% and 20% (RR 0.362 and 0.395 instead of 0.329), the ICUR increases to $62,181 and $73,503 per QALY, respectively.
- **Higher dose of GXR:** As a higher dose might be used in patients with a higher body mass, when the dosing is changed to 8 mg per day (above maximum recommended dose), the ICUR is $122,173 per QALY.

b) Adjunctive Therapy

- **Medical costs:** The cost of normal state was assumed to be the same as the cost in children without ADHD. To test this assumption, the medical cost for normal state was set to be the same as the cost of the mild state, and the ICUR slightly increased to $23,726 per QALY as a result. When the medical cost for all health states are equal to the cost of the mild state, the ICUR increases to $26,095 per QALY. When the LOCF approach is used (which may be most appropriate), the ICUR is $36,675 per QALY if the medical cost for normal state is set to be the same as the cost of the mild state. When the medical cost for all health states are equal to the cost of the mild state, the ICUR increases to $37,929 per QALY.
- **Higher dose of GXR:** CDR is unable to change the dosing parameter. However, when the daily cost of GXR is doubled, the ICUR is $45,855 per QALY. If the drug cost is doubled in the new CDR base case, the ICUR is $69,682 per QALY.

TABLE 3: CDR REANALYSIS ICURS FOR GXR AS MONOTHERAPY AND ADJUNCTIVE THERAPY

Monotherapy		
ICURs of GXR Versus ATX ($/QALY)		
	Base-Case Analysis Submitted by Manufacturer	**Reanalysis by CDR, Assuming Same Medical Costs For Both Responders And Non-Responders**
Base case	57,866	64,449
Same utilities for responders and non-responders	ATX dominates	ATX dominates
RR of response for ATX increased by 10%	85,456	92,507
RR of response for ATX increased by 20%	173,045	181,579
RR of response from active-controlled trial	86,699	93,909
Doubled doses (8 mg/day)	166,722	173,305
ICURs of GXR Versus Non-pharmacological Treatment ($/QALY)		
	Base-Case Analysis Submitted By Manufacturer	**Reanalysis by CDR, Assuming Same Medical Costs For Both Responders and Non-Responders[a]**
Base case	53,657	68,455
Same utilities for responders and non-responders	13,549	17,310
RR of response for placebo increased by 10%	62,181	78,438
RR of response for placebo increased by 20%	73,503	90,723
Doubled doses (8 mg/d)	122,173	136,818
Adjunctive Therapy		
ICURs of GXR Plus Psychostimulants Versus Psychostimulants Only ($/QALY)		
	Base-Case Analysis Submitted By Manufacturer (Logit Model)	**Reanalysis by CDR, LOCF and Same Medical Costs For Normal and Mild States**
Base case	23,720	35,675
100% morning administration	26,096	38,818
100% evening administration	21,832	33,028
Same medical costs for all health states	26,095	37,929
Doubled drug cost for higher dosage (8 mg/d)	45,855	69,682

ATX = atomoxetine; CDR = CADTH Common Drug Review; GXR = guanfacine extended release; ICUR = incremental cost-utility ratio; LOCF = last observation carried forward; QALY = quality-adjusted life-year; RR = relative risk.
[a] ICURs calculated by CDR.

TABLE 4: CDR ANALYSIS OF ICURS BASED ON VARIOUS PRICE REDUCTION SCENARIOS FOR MONOTHERAPY

Scenario	ICUR ($/QALY) Based on Manufacturer's Analysis	Revised ICUR[a] ($/QALY) Based on CDR Most Likely Scenario[b]
GXR Versus ATX		
Manufacturer's base case ($[redacted])	57,866	64,449
10% price reduction ($[redacted])	46,968	53,551
20% price reduction ($[redacted])	36,084	42,667
30% price reduction ($[redacted])	25,200	31,783
40% price reduction ($[redacted])	14,315	20,899
50% price reduction ($[redacted])	3,431	10,014
60% price reduction ($[redacted])	GXR dominates	GXR dominates
GXR Versus Non-pharmacological Treatment and Placebo		
Manufacturer's base case ($[redacted])	53,657	68,455
10% price reduction ($[redacted])	46,798	61,545
20% price reduction ($[redacted])	39,947	54,727
30% price reduction ($[redacted])	33,098	47,909
40% price reduction ($[redacted])	26,246	41,091
50% price reduction ($[redacted])	19,395	34,182
60% price reduction ($[redacted])	12,544	27,364
70% price reduction ($[redacted])	5,694	20,545
80% price reduction ($[redacted])	GXR dominates	13,727

ATX = atomoxetine; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility review; GXR = guanfacine extended release; QALY = quality-adjusted life-year.
Note: Price reduction analysis for adjunctive therapy not presented since the ICUR is already lower than $50,000 per QALY.
[a] **ICURs calculated by CDR.** [b] Most likely scenario refers to assuming the same medical costs for both responders and non-responders.

4. DISCUSSION

The key limitations associated with the manufacturer's economic submission are summarized in Table 5. While the limitations in Table 5 are specific, they collectively illustrate the major issue of uncertainty related to the estimates of ICURs. A major challenge is interpreting the relative efficacy of the treatments being compared. While several scales are commonly used in the research setting to adjudicate outcomes in patients with ADHD, their clinical validity and clinical significance are not well established (see Clinical report Appendix 5). Furthermore, complex data modelling, including ordered logit models, were used to correlate these scales to health states (based on approach and face validity of model transitions, CDR believes that the LOCF approach may be most appropriate). Additional mapping of the health state to utility-based quality of life scores was conducted, adding yet another layer of uncertainty. There are no identifiable data to reduce this uncertainty, and therefore the true ICUR may be materially different than those presented here. This is exemplified when uncertainty in one parameter — the probability of response and transition through health states — is modified more than its 95% confidence interval in both the monotherapy and adjunctive therapy models, leading the ICUR to approximately double.

In addition to the issues noted above, there may be other issues that are unique to this disorder. Unlike other conditions that may be associated with high health care resource utilization, or more traditional measures of illness (pain, disability, poor functional status, etc.), one of the major goals of therapy according to the clinical experts in ADHD is to control behaviour, particularly in controlled settings such as in school, and to enhance school performance. To what extent these are captured in traditional HRQoL measures (such as QALY) is unclear. Therefore, traditional cost-effectiveness analyses may be challenging to apply to diseases such as ADHD. From the price-reduction scenarios in this report, a price reduction of at least 20% to 30% would be needed to increase confidence in the ICUR being < $50,000 per QALY for monotherapy.

TABLE 5: KEY LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter/Assumption	Issue	Impact
Quality of life improvement	Symptom control may not lead to improvement in quality of life	Overestimated ICUR; comparators become dominant
Translating CGI-S scores into health states with corresponding quality of life	Probabilities in each health state were predicted using the ordered logit model rather than directly derived from trial. Quality of life scores were obtained from literature rather than from trials.	ICUR unknown. The range of cost-effectiveness is likely to be very large given significant uncertainty in the true difference in quality of life.
Relative efficacy in adjunctive model is assumed to be the same as that from the trial.	Failure to conduct sensitivity analysis on variance of relative efficacy in the original adjunctive model	The ICUR is $65,528 per QALY from the manufacturer's resubmitted sensitivity analysis. If relative efficacy attenuates over time, ICUR is likely to increase even more.
Medical costs	Costs for responders and "normal" state are assumed to be the same as those of children without ADHD	Overestimated cost saving; CDR estimate of ICUR is $61,156 per QALY for monotherapy, and $26,095 per QALY for adjunctive therapy.

ADHD = attention-deficit/hyperactivity disorder; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

According to the clinical experts, the majority of patients with ADHD in Canada receive no pharmacologic treatment, and in those treated, psychostimulants are most commonly prescribed. For patients with ADHD not well controlled by psychostimulant therapy, adjunctive therapy, such as the use of clonidine and atypical antipsychotics, may be employed. While adjunctive drugs may not be approved by Health Canada, economic evaluations should consider "usual care" in the comparator. If the costs of atypical antipsychotics or other treatments are lower than GXR, and efficacy is similar, then the attractiveness of GXR may be materially different. However, there are no data to inform the relative efficacy of these other treatments, and hence the ICUR is unknown.

Furthermore, non-psychostimulant pharmacologic treatment may be preferred by patients and providers. For this proportion of patients, GXR versus usual (non-drug) care, or GXR versus psychostimulants, may be valid comparators (the latter is not included in this submission). In the opinion of the clinical expert, ATX may not be a good comparator, as GXR and ATX are often selectively used to treat associated symptoms (GXR for oppositional disorder and ATX for anxiety).

The health care resource utilization costs are likely biased toward GXR, as patients with well-controlled ADHD are still likely to have greater health care resource utilization than children without the diagnosis, as patients with this disease receiving therapy are likely to require continued monitoring. However, given the relatively low costs of mental health care, primary care, and emergency department visits with this disorder, this only had a minor impact on results.

Issues for Consideration

- According to the clinical experts, most patients with ADHD are not treated with drugs, and those treated are typically given psychostimulants as first-line treatment. The proportion of patients treated using adjunctive therapy is likely to be small. As some patients or 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 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 should be captured in HRQoL outcomes, it is not clear how completely these are integrated in this measure. In addition, QALY may not capture all the purported benefits of treatment.

Patient Input

Symptom control (treatment response) and reduced AEs are important outcomes that were included by the manufacturer in the economic submission. Caregiver costs were also considered from the societal perspective (monotherapy: GXR dominates ATX; adjunctive therapy: $11,845 per QALY).

5. CONCLUSIONS

For the treatment of ADHD, the manufacturer suggests that GXR is likely to have a cost per QALY of approximately $58,000 for monotherapy and $24,000 for adjunctive therapy for a one year time horizon. In patients with ADHD that is not well controlled with psychostimulant therapy, other adjunctive treatments may be used, including clonidine or atypical antipsychotics, but the relative cost-effectiveness of GXR versus other adjunctive therapies to psychostimulants is unknown.

In the CDR reference case, in which medical costs for responders and normal state are assumed to be equal, the ICUR increases 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 (the latter using the LOCF approach).

The major issue with the economic analysis is uncertainty. It is not clear how clinical trial outcomes translate into health state and attendant quality of life, given poor quality of data. Hence, 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 analyses 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 between $57,434 and $65,528 per QALY when the 95% confidence interval was explored for the LOCF approach. The ICUR also increased to $35,181 per QALY for the ordered logit approach.

APPENDIX 1: COST-COMPARISON TABLE

Clinical experts have deemed the comparators presented in Table 6 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 6: COST COMPARISON TABLE FOR GUANFACINE HYDROCHLORIDE

Drug/Comparator	Strength	Dosage Form	Price ($)	Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Guanfacine hydrochloride (Intuniv XR)	**1 mg 2 mg 3 mg 4 mg**	**ER tab**	[redacted][a]	**1 to 4 mg once daily**	[redacted] **to**	[redacted] **to**
Long-Acting (Once Daily) Formulations						
Atomoxetine (Strattera)	10 mg 18 mg 25 mg 40 mg 60 mg 80 mg 100 mg	cap	2.6514[b] 3.0196[b] 3.3885[b] 3.8214[b] 4.2710[b] 4.5850[b] 5.0367[b]	10 to 80 mg (1.2 mg/kg/d)	2.65 to 4.58	968 to 1,674
Lisdexamfetamine (Vyvanse)	20 mg 30 mg 40 mg 50 mg 60 mg	cap	2.5500 3.0500 3.5500 4.0500 4.5500	30 mg to 60 mg	3.05 to 4.05	1113 to 1,478
Methylphenidate – controlled release (Biphentin)	10 mg 15 mg 20 mg 30 mg 40 mg 50 mg 60 mg 80 mg	ER cap	0.6950 0.9940 1.2850 1.7630 2.2460 2.7240 3.1700 4.1840	10 mg to 60 mg	0.70 to 3.17	256 to 1,157
Methylphenidate OROS (generics)	18 mg 27 mg 36 mg 54 mg	ER tab	1.0197 1.1768 1.3339 1.6480	18 mg to 54 mg	1.02 to 1.65	372 to 602
Mixed amphetamine salts (Adderall XR)	5 mg 10 mg 15 mg 20 mg 25 mg 30 mg	ER cap	2.1068 2.3942 2.6817 2.9692 3.2566 3.5443	10 mg to 30 mg	2.39 to 3.54	874 to 1,394

Drug/Comparator	Strength	Dosage Form	Price ($)	Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Short- and Intermediate-Acting Formulations						
Dextroamphetamine (Dexedrine)	5 mg	tab	0.6379	5 mg to 40 mg in divided doses	0.64 to 5.10	233 to 1,863
Dextroamphetamine (Dexedrine Spansules)	10 mg 15 mg	ER cap	0.9149 1.1186	10 mg to 40 mg once daily or divided doses	0.91 to 3.15	334 to 1,151
Methylphenidate (generics)	10 mg 20 mg	tablet	0.0816 0.1142[a]	20 mg to 60 mg in divided doses	0.16 to 0.34	60 to 125
Methylphenidate SR (generics)	20 mg	ER tab	0.2820	20 mg to 60 mg in divided doses	0.28 to 0.85	103 to 309

Cap = capsule; ER = extended release; OROS = Osmotic Controlled Release Delivery System; SR = sustained release; tab = tablet; XR = extended release.
Note: All prices are from the Ontario Drug Benefit Formulary (accessed February 2013), unless otherwise indicated, and do not include dispensing fees.
[a] Manufacturer's confidential submitted price.
[b] Saskatchewan Formulary (January 2014).

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS GXR AS MONOTHERAPY OR ADJUNCTIVE THERAPY?

GXR Versus ATX	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life			X			
ICER or net benefit calculation	Manufacturer's base case $57,866/QALY CDR reanalysis					
GXR plus Psychostimulants Versus Psychostimulants Only	**Attractive**	**Slightly Attractive**	**Equally Attractive**	**Slightly Unattractive**	**Unattractive**	**NA**
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
ICER or net benefit calculation	Manufacturer's base case $23,720/QALY and $35,669/QALY CDR reanalysis					

ATX = atomoxetine; CDR = CADTH Common Drug Review; GXR = guanfacine extended release; ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.

The above is based on both the manufacturer's results and the CADTH Common Drug Review reanalysis.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 8: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	**X**		
Comments	None		
Was the material included (content) sufficient?		**X**	
Comments	Efficacy was not tested in the original sensitivity analysis for the adjunctive therapy.		
Was the submission well organized and was information easy to locate?	**X**		
Comments	None		

TABLE 9: AUTHOR INFORMATION

Authors	Affiliations		
Jean Lachaine and Karine Mathurin	PeriPharm Inc.		
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

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