CDEC FINAL RECOMMENDATION

GUANFACINE HYDROCHLORIDE EXTENDED RELEASE
(Intuniv XR — Shire Canada Inc.)
Indication: Attention Deficit Hyperactivity Disorder

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that guanfacine hydrochloride extended release (GXR) not be listed.

Reasons for the Recommendation:
1. There was insufficient evidence from randomized controlled trials (RCTs) to assess the comparative clinical benefit of GXR as monotherapy relative to other less costly treatments for attention deficit hyperactivity disorder (ADHD).
2. Evidence for the use of GXR as adjunctive therapy in ADHD is limited to one RCT (SPD503-313; N = 461) of only eight weeks duration. Although there is an absence of treatments approved for use as adjunctive therapy in ADHD, the single included study provided insufficient evidence to adequately assess the overall and longer-term clinical benefit of GXR in this patient population.

Of Note:
CDEC noted that there is an unmet need for patients with ADHD requiring adjunctive therapy; however, the available evidence for GXR is limited to a single, short-term RCT that was insufficient to support a listing recommendation.

Background:
Guanfacine hydrochloride is a selective alpha$_{2A}$-adrenergic receptor agonist. GXR is indicated as monotherapy or as adjunctive therapy to psychostimulants (PSY) for the treatment of ADHD in children, aged 6 to 12 years, with a suboptimal response to PSY. The product monograph recommends a starting dose for both GXR monotherapy and as adjunct therapy to PSY of 1 mg once per day. The dose should be adjusted, depending on clinical response and tolerability, in increments of no more than 1 mg per week up to a maximum daily dose of 4 mg. GXR is available as 1 mg, 2 mg, 3 mg, and 4 mg tablets.

Summary of CDEC Considerations
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of GXR, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients and caregivers.

Patient Input Information

The following is a summary of information provided by one patient group that responded to the CDR call for patient input.

- Daily activities and quality of life are affected in children with ADHD. Children often experience significant impairments in academic performance, emotional regulation, and psychosocial well-being.
- Most parents and caregivers experience increased stress, increased conflict with their child/spouse, and an increased financial burden.
- Various ADHD medications are available; however, many children with ADHD do not have their symptoms satisfactorily controlled.

Clinical Trials

The CDR systematic review included seven double-blind, placebo-controlled RCTs of children with ADHD as monotherapy: study 301 (N = 345), study 304 (N = 324), study 307 (N = 217), study 314 (N = 340), study 315 (N = 316), study 316 (N = 338), and study 206 (N = 182). In addition to GXR and placebo groups, study 316 also included an atomoxetine (ATX) group. One double-blind, placebo-controlled RCT (study 313 [N = 461]) investigated GXR co-administered with a PSY. The double-phase of most of the trials ranged from 6.5 to 10 weeks; however, the double-blind phase of study 315 was 26 weeks in duration.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Change from baseline in ADHD-Rating Scale-IV total score (ADHD-RS-IV) — an instrument used to measure the behaviours of children with ADHD. The ADHD-RS-IV consists of 18 items designed to reflect current symptoms of ADHD based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Each item is scored from 0 (no symptoms) to 3 (severe symptoms) with total scores ranging from 0 to 54.
- Change from baseline in Conners' Parent Rating Scale-Revised (CPRS-R) and Conners' Teacher Rating Scale-Revised (CTRS-R) — scales completed by parent/caregiver or teacher to measure a cross-section of ADHD-related symptoms and problem behaviours.
- Clinical Global Impression of Severity (CGI-S) — a seven-point scale ranging from 1 (no symptoms) to 7 (very severe symptoms).
- Clinical Global Impression of Improvement (CGI-I) — a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).
- Change from baseline in Weiss Functional Impairment Rating Scale (WFIRS).
- Change from baseline in Child Health Questionnaire (CHQ).
- Change from baseline in Health Utilities Index-Mark 2 and Mark 3 (HUI-2/3).
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

Change in ADHD-RS-IV total score was the primary endpoint in study 301, study 304, study 314, study 316, and study 313.

Efficacy

Monotherapy

- Compared with placebo, the least square mean difference (95% confidence interval [CI]) in change from baseline in ADHD-RS-IV total score was reported as follows:
  - GXR 1 mg: –6.75 (–11.3 to –2.2) in study 304
  - GXR 2 mg: –5.41 (–9.9 to –0.9) in study 304 and –7.42 (–12.07 to –2.77) in study 301
  - GXR 3 mg: –7.31 (–11.8 to –2.8) in study 304 and –7.52 (–12.19 to –2.85) in study 301
  - GXR 4 mg: –7.88 (–12.3 to –3.4) in study 304 and –9.99 (–14.67 to –5.32) in study 301
  - GXR 1 mg to 4 mg: –12.3 (–16.2 to –8.5) in study 307, –6.24 (–9.01 to –3.48) in study 315, and –8.9 (–11.9 to –5.8) in study 316; and –9.4 (–12.8 to –6.0) and –9.8 (–13.1 to –6.4) in study 314 (a.m. and p.m., respectively).
- Results in the subgroup of children aged six to 12 years were consistent with the overall population.
- In the six-month trial (study 315), the mean ADHD-RS-IV total score increased (worsened) in both GXR and placebo over six months, although the scores in the GXR group had a slower increase than placebo.
- GXR was statistically superior to placebo for the outcomes of CTRS-R, CPRS-R, and CGI.
- GXR was superior to placebo for WFIRS in studies 314 and 316; however, there was no statistically significant difference in CHQ or HUI-2/3.
- Both GXR and ATX were statistically significantly better than placebo for improving ADHD symptoms; however, no statistical comparisons were made between the two active treatments.

Adjunctive Therapy

- Compared with placebo, the least square mean difference in change from baseline in ADHD-RS-IV total score was reported as follows:
  - GXR (a.m.) plus PSY: –4.5 (95% CI, –7.5 to –1.4)
  - GXR (p.m.) plus PSY: –5.3 (95% CI, –8.3 to –2.3).
- A statistically significantly greater proportion of patients receiving GXR showed improvement, based on CGI-I scores, compared with placebo for both the a.m. (P = 0.024) and p.m. (P = 0.003) dosing regimens.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one adverse event was reported as follows:
  - Monotherapy: GXR 1 mg (80.3%), GXR 2 mg (range: 61.5% to 77.0%), GXR 3 mg (range: 69.2% to 88.4%), GXR 4 mg (range: 84.6% to 87.2%), GXR 1 mg to 4 mg (range: 56.7% to 83.8%), placebo (range: 48.1% to 75.8%), and ATX (67.9%).
  - Adjunctive therapy: GXR 1 mg to 4 mg plus PSY (76.3% to 77.3%) and placebo plus PSY (63.4%).
- Somnolence, headache, sedation, and fatigue were the most commonly reported adverse events in the GXR groups.
- The proportion of patients who experienced at least one serious adverse event was reported as follows:

  - Monotherapy: GXR 1 mg (0%), GXR 2 mg (0%), GXR 3 mg (range: 1.2% to 1.5%), GXR 4 mg (range: 0% to 1.2%), GXR 1 mg to 4 mg (range: 0% to 1.8%), placebo (range: 0% to 2.5%), and ATX (0%).
  - Adjunctive therapy: GXR 1 mg to 4 mg plus PSY (0.7% and 1.3%) and placebo plus PSY (0%).
- The proportion of patients who withdrew due to adverse events was reported as follows:
  - Monotherapy: GXR 1 mg (3.3%), GXR 2 mg (range: 3.1% to 10.3%), GXR 3 mg (range: 9.2% to 15.1%), GXR 4 mg (range: 13.8% to 23.3%), GXR 1 mg to 4 mg (range: 1.9% to 8.8%), placebo (range: 0% to 7.6%), and ATX (4.5%).
  - Adjunctive therapy: GXR 1 mg to 4 mg plus PSY (2.7% to 3.9%) and placebo plus PSY (0.7%).

Cost and Cost-Effectiveness

The manufacturer submitted two cost-utility analyses (one for monotherapy and one for adjunctive therapy) for children aged 6 to 12 with ADHD. Both analyses were based on similar Markov models that used a one-year time horizon and a payer's perspective. For the monotherapy analysis, the manufacturer compared GXR to ATX (1.2 mg/kg/day; $968 to $1,674 annually) and GXR to non-pharmacological treatment/placebo. For the adjunctive therapy analysis, the manufacturer compared GXR plus PSY therapy to PSY therapy alone (average unit cost of $2.80, or $1,022 annually). For the monotherapy analysis, a matching-adjusted indirect comparison was used to estimate relative efficacy, using patient-level data from the GXR trials (studies 301, 304, and 316) to adjust for differences in observed baseline characteristics between trials. For the adjunctive analysis, treatment efficacy was based on study 313. The manufacturer reported that for monotherapy, the incremental cost-utility ratio (ICUR) for GXR compared with ATX was $57,866 per quality-adjusted life-year (QALY), while the ICUR for GXR compared to non-pharmacological treatment (or placebo) was $53,657 per QALY. For adjunctive therapy, the ICUR for GXR plus PSY compared with PSY alone was $23,720.

CDR noted that a major limitation with the manufacturer's pharmacoeconomic analyses was uncertainty in the cost-effectiveness estimates due to a lack of clarity regarding how outcomes derived from clinical trials were translated into health states and improvements in health-related quality of life. In addition, the manufacturer's analyses potentially overestimated the reduction in resource utilization costs attributable to GXR treatment. CDR re-analyses of the manufacturer's models to explore uncertainty related to the relative efficacy of GXR led to substantially higher ICURs for both monotherapy and adjunctive therapy. Further, CDR noted that the manufacturer's economic submission failed to consider other (potentially much less costly) comparators, such as methylphenidate ($60 to $1,157 annually), lisdexamfetamine ($1,113 to $1,478 annually), mixed amphetamine salts ($874 to $1,394 annually), and dextroamphetamine ($233 to $1,863 annually).

GXR is available for once-daily oral administration in 1 mg ($3.00), 2 mg ($3.65), 3 mg ($4.30), and 4 mg ($4.95) tablets. The recommended oral dose is 0.05 to 0.012 mg/kg/day, at a daily cost of $3.00 to $4.95 per patient, compared with daily costs of $2.65 to $4.58 for ATX; $3.05 to $4.05 for lisdexamfetamine; $2.39 to $3.54 for mixed amphetamine salts; $0.70 to $3.17 for long-acting methylphenidate; $0.16 to $0.85 for short and intermediate-acting methylphenidate; and $0.64 to $3.15 for dextroamphetamine.

Other Discussion Points:
CDEC noted the following:

- The comparative clinical benefit of GXR relative to the current standard therapy is unclear, as there were no direct comparisons against ATX or PSY.
- CDEC considered GXR for patients with ADHD and inadequate control with methylphenidate or an amphetamine or for whom these drugs are contraindicated or inadvisable; however, there was insufficient evidence to support a recommendation in this population.
- Validated, minimal clinically important differences have not been conclusively established for many of the scales used in the RCTs, including the CPRS-R, CTRS-R, and WFIRS.
- A current controlled or uncontrolled psychiatric diagnosis was an exclusion criterion, which makes it unlikely that the study populations are representative of the majority of children with ADHD.

Research Gaps:
CDEC noted that there is an absence of evidence regarding the following:

- Direct evidence comparing GXR with other active treatments, including PSY.
- Long-term efficacy and safety data for the use of GXR.
- Efficacy and safety data for patients who are in the lower body weight categories.

September 17, 2014 Meeting:

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets: None.

Conflicts of Interest: None.

May 21, 2014 Meeting:

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

Regrets: None

Conflicts of Interest: The CDEC Chair recused himself and did not participate in the deliberations. The Vice-Chair acted as the Chair for this drug review.

About This Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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