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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

TAPENTADOL HYDROCHLORIDE (NUCYNTA EXTENDED-RELEASE — PALADIN LABS INC.)
Indication: Management of pain severe enough to require daily, continuous, long-term opioid treatment, and: that is opioid responsive; and for which alternative treatment options are inadequate.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that tapentadol extended-release not be reimbursed for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and: that is opioid responsive; and for which alternative treatment options are inadequate.

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TAPENTADOL HYDROCHLORIDE (NUCYNTA EXTENDED-RELEASE — PALADIN LABS INC.)

Indication: Management of pain severe enough to require daily, continuous, long-term opioid treatment, and: that is opioid responsive; and for which alternative treatment options are inadequate.

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that tapentadol extended release (ER) not be reimbursed for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and: that is opioid responsive; and for which alternative treatment options are inadequate.

Reasons for the Recommendation:

1. All eight randomized controlled trials (RCTs), including five in non-cancer pain (comparing tapentadol ER with oxycodone controlled release [CR] or oxycodone plus naloxone prolonged release [PR]) and three in cancer-related pain (comparing tapentadol ER with oxycodone CR, morphine sustained release [SR], or morphine CR), contained numerous limitations that impact the validity of the results. These limitations included high and unbalanced withdrawal rates with corresponding missing data, short duration, lack of blinding of active controls, lack of statistical testing or control of multiplicity, and differential use of concomitant rescue analgesics. These limitations may have biased the comparative measure of effect in reducing pain intensity and resulted in significant uncertainty regarding the magnitude of the effect of tapentadol.
2. Despite evidence from the aforementioned trials to suggest that tapentadol ER may be associated with fewer adverse events (AEs), AEs were reported in more than 65% of all active treatment groups in seven of eight trials. In addition, the observed differences in gastrointestinal AEs that favoured tapentadol ER were potentially impacted by the rapid titration of opioids and the apparent lack of specific bowel management regimens in the trials, neither of which are reflective of clinical practice in the treatment of chronic pain.
3. Direct comparisons were not available for several long-acting opioids, such as oral hydromorphone or methadone, transdermal fentanyl, or transdermal or buccal film buprenorphine, tramadol ER, or codeine CR. Although two indirect treatment comparisons (ITCs) were provided, these were associated with serious limitations and failed to provide clarity regarding the relative benefit of tapentadol ER versus other treatments for chronic pain requiring long-term opioid treatment.
4. There was insufficient evidence to suggest that tapentadol ER fulfills an unmet need within the current treatment landscape for chronic pain in reducing the potential for opioid use disorder, misuse, overdose, or diversion, compared with other available opioids.

Discussion Points:

- The committee noted that the reviewed trials did not describe specific bowel management regimens to manage the expected gastrointestinal AEs of opioid treatment, which would be standard practice when prescribing opioids for the treatment of chronic pain in clinical practice. Thus, the frequency of gastrointestinal AEs and the associated withdrawals in the trials are likely overestimated, and the comparative effects are uncertain.
- The committee discussed that Nucynta ER was designed with the intention of making the product tamper resistant. It was noted that other products have also been developed to incorporate a tamper-resistant mechanism, but that Health Canada has not approved tamper-resistant labelling for any opioid formulations marketed in Canada, and there is insufficient evidence to suggest that Nucynta ER would address issues related to the opioid crisis in Canada.

Background:

Nucynta ER has a Health Canada indication for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and: that is opioid responsive; and for which alternative treatment options are inadequate. Nucynta ER is an opioid analgesic. It is available as 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg ER tablets and the Health Canada–approved dose is 100 mg to 250 mg twice daily, taken approximately every 12 hours.

Submission History:

A formulation of tapentadol, bioequivalent to Nucynta ER, known as Nucynta CR was previously reviewed for the management of moderate-to-moderately-severe pain in adults who require continuous treatment for several days or more. It received a recommendation that it not be listed (see Notice of CEDAC Final Recommendation, September 28, 2011; revised March 25, 2014). Since Nucynta CR and Nucynta ER are considered by Health Canada to be bioequivalent, the term "tapentadol ER" is used in this document to refer to either of the formulations.

Summary of Evidence Considered by CDEC:

The committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of phase III or IV RCTs of tapentadol ER, and a critique of two ITCs and the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with chronic pain, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Six patient groups, The Chronic Pain Association of Canada, The Canadian Arthritis Patient Alliance, Arthritis Consumer Experts, The Halton/Hamilton Chronic Pain Support Group, Action Atlantic Pain Society, and the Chronic Pain Support Group of Sarnia-Lambton community in Ontario provided input for this submission. Patient perspectives were obtained through a call for patient input, interactions with patients suffering from pain (monthly meetings, survey, or emails), communications with professionals, discussions with scientific members of the patient groups, relationships with other patient groups, and ongoing research. The following is a summary of key input from the perspective of the patient groups:

- Pain has negative impacts on almost all aspects of day-to-day life, such as family relationships, social outings, workplace settings, and the ability to carry out daily activities. Patients' quality of life (QoL) is greatly impaired by pain and patients may feel depressed, isolated, and helpless. Consequences of the negative impacts of pain include the inability to find gainful employment or the need to retire earlier than expected, which both also have financial implications.
- Many patients taking medications to treat their pain experience side effects of the drugs, most commonly constipation.
- Patients have difficulty accessing non-pharmaceutical treatments, such as physiotherapy and psychological treatment, in the public system, with significant costs associated with accessing such treatments privately.
- Medical training on pain management is very limited in Canada and it is a challenge to find a doctor who will treat pain. In most cases, patients have to wait 18 to 24 months to see a pain specialist.
- Based on input from one of the patient groups, it was felt that there are insufficient treatments for chronic pain, and that pharmaceutical options have the potential for serious risks and side effects that are often difficult to manage.
- In general, patients expect to see safer and more effective treatments for pain relief. They want new treatments that can relieve pain and improve function, are non-addictive and won't cause withdrawal, have long-lasting effects, have fewer side effects, and can improve their QoL.
- Some patients who had experience with Nucynta reported an overall improvement in their QoL, including finding fewer side effects with Nucynta than with other medications, including non-opioid drugs.

Clinical Trials

The systematic review included five RCTs of patients with chronic non-cancer pain and three RCTs of patients with cancer-related pain:

- Three 15-week, double-blind (DB) RCTs in patients with knee osteoarthritis (Study PAI-3008, N = 1,030; Study PAI-3009, N = 990) or non-malignant low back pain (Study PAI-3011, N = 981) randomized (1:1:1) to one of placebo, tapentadol ER (100 mg to 250 mg twice daily), or oxycodone CR (20 mg to 50 mg twice daily). The proportions of patients who discontinued the study in the tapentadol ER group versus the oxycodone CR group were 47% versus 65% in Study PAI-3008, 44% versus 64% in Study PAI-3009, and 48% versus 59% in Study PAI-3011.

- One one-year, open-label (OL) RCT (Study PAI-3007, N = 1,121) in patients with knee or hip osteoarthritis or non-malignant low back pain randomized (4:1) to tapentadol ER (100 mg to 250 mg twice daily) or oxycodone CR (20 mg to 50 mg twice daily). There were no formal statistical comparisons between treatment groups. The proportions of patients who discontinued the study in the tapentadol ER and oxycodone CR groups were 54% and 65%, respectively.
- One 12-week, OL, non-inferiority phase IIIb/IV RCT (Baron 2016, N = 258) in patients with low back pain with a neuropathic component randomized (1:1) to tapentadol ER (50 mg to 250 mg twice daily) or oxycodone/naloxone PR (10 mg/5 mg to 40 mg/20 mg plus 10 mg oxycodone PR twice daily). The proportions of patients who discontinued the study in the tapentadol ER and oxycodone/naloxone PR groups were 34% and 63%, respectively. Patients in the oxycodone/naloxone PR group could switch to a separate tapentadol ER escape arm at any time, but patients in the tapentadol ER group could not switch to another group.
- One four-week, DB, non-inferiority RCT (Imanaka 2013; N = 343) in patients with cancer pain randomized (1:1) to tapentadol ER (25 mg to 250 mg twice daily) or oxycodone CR (5 mg to 40 mg twice daily). The proportions of patients who discontinued the study in the tapentadol ER and oxycodone CR groups were 33% and 29%, respectively.
- One eight-week, OL RCT (Imanaka 2014; N = 100) in patients with cancer pain whose pain was already controlled with an opioid and who were randomized (1:1) to tapentadol ER (25 mg to 250 mg twice daily) or morphine SR (10 mg to 70 mg twice daily). The proportions of patients who discontinued the study in the tapentadol ER and morphine SR groups were 44% and 42%, respectively.
- One six-week, DB RCT (Kress 2014; N = 505) in patients with cancer pain. Patients were initially randomized (2:1) to tapentadol ER (100 mg to 250 mg twice daily) or morphine sulphate CR (40 mg to100 mg twice daily) for a two-week, parallel-group titration phase followed by a randomized withdrawal maintenance phase for patients originally randomized to tapentadol ER. Thus, comparisons of tapentadol ER with morphine sulphate CR were limited to two weeks. The proportion of patients who discontinued during the titration phase was 18% in both treatment groups.

In the five chronic non-cancer pain trials, randomization was preceded by washout of prior analgesic medication. Informative direct comparisons between tapentadol ER and long-acting opioids were only available for oxycodone CR and oxycodone/naloxone PR. Statistical comparisons between tapentadol ER and oxycodone CR were not controlled for multiplicity and were considered exploratory in studies PAI-3008, PAI-3009, and PAI-3011. Further, the comparison with morphine SR (Imanaka 2014) was limited by the lack of a formal statistical comparison, and the comparison with morphine CR (Kress 2014) was limited by the two-week treatment duration.

The common limitations potentially significantly impacting internal validity were: substantial and unbalanced amounts of missing data from early study discontinuations, short durations of most of the trials (with titration periods shorter than would be expected in clinical practice), lack of blinding in some trials coupled with the use of subjective outcomes, lack of control for type I error, and potential biases introduced by approaches for imputing missing data. In the non-cancer pain trials, the most common reasons for discontinuing treatment were AEs, lack of efficacy, and patient choice with withdrawal due to AEs (WDAEs) accounting for most of the imbalances between treatment groups.

It is unclear whether the patients in the non-cancer pain trials would be considered appropriate candidates for continuous, long-term opioid therapy in the current Canadian setting. Only one of these trials (Baron 2016) specified in the entry criteria that patients had to require treatment with an opioid analgesic according to the investigator. In the cancer pain trials, the intervention may not be relevant to the clinical setting as treatment durations were eight weeks or less and substantial proportions of patients received dosages of tapentadol ER that were below the minimum recommended dosage.

No trials comparing tapentadol ER with hydromorphone CR, methadone, transdermal fentanyl, transdermal or buccal film buprenorphine, tramadol ER, or codeine CR met the review criteria.

Outcomes

Outcomes were defined *a priori* in the CDR systematic review protocol. Of these, the committee discussed the following: pain intensity (using an 11-point numeric rating scale [NRS]), health-related QoL (variously including the 36-Item Short Form Health Survey [SF-36], EuroQol 5-Dimension 3-Level [EQ-5D-3L], and the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]), AEs, gastrointestinal symptoms, and WDAEs. The primary outcome in five trials (PAI-3008, PAI-3009, PAI-3011, Baron 2016, and Imanaka 2013) was change in pain intensity on an 11-point NRS. In Baron 2016, change in Patient Assessment of Constipation Symptoms (PAC-SYM) total score was a co-primary outcome. The primary outcome in Imanaka 2014 was the

proportion of patients who maintained pain control (based on an 11-point NRS pain intensity score and rescue medication use) and the primary outcome in Kress 2014 was pain control during the randomized withdrawal phase. Study PAI-3007 measured change in 11-point NRS pain intensity, but was primarily a safety study.

- The 11-point NRS for pain intensity is an ordinal scale from 0 to 10 with 0 corresponding to "no pain" and 10 corresponding to "pain as bad as you can imagine." Estimated minimal clinically important differences (MCIDs) range from 1.1 to 2.2 points in patients with various types of chronic pain.
- The EQ-5D-3L is a generic health-related QoL measure, which includes an index score, on which scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Estimates of MCID for the EQ-5D-3L index score in general have ranged from 0.033 to 0.074 and MCIDs specific to patients with chronic pain were not found. The EQ-VAS is a 20 cm visual analogue scale (VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." An MCID for the EQ-VAS in patients with chronic pain was not found by CDR.
- The SF-36 is a 36-item, general health status instrument that can provide two component summaries, the physical component summary (PCS) and the mental component summary (MCS). The PCS and MCS scores range from 0 to 100 with higher scores indicating better health status. The MCID for the SF-36 MCS and PCS is typically between 2.5 and 5 points. MCIDs in patients with chronic pain were not found for the SF-36 MCS and PCS.
- The WOMAC consists of 24 self-administered items rated on an ordinal scale of 0 to 4, with 0 corresponding to the lowest level of symptoms of physical disability. The subscales assess pain, physical function, and joint stiffness due to knee and hip osteoarthritis. The global score ranges from 0 to 96, with higher scores indicating greater levels of symptoms or physical disability and MCIDs of 0.51 to 1.33 for worsening and 0.67 to 0.75 for improvement.
- The PAC-SYM is a self-administered instrument containing 12 items with a recall period of two weeks. Each item asks about the severity of a symptom and is rated on a 5-point categorical scale ranging from "absent" (0) to "very severe" (4).The overall and subscale scores are calculated as the mean score of the individual items, yielding a possible range of 0 to 4 for each score. Estimates of the MCID for the PAC-SYM overall score range from –0.52 to –0.63.

Efficacy

Pain Intensity, Non-Cancer Pain Trials

In studies PAI-3008 and PAI-3009, a reduction in pain intensity (based on 11-point NRS) was greater in the tapentadol ER groups compared with the oxycodone CR groups; least squared mean differences (LSMDs) were –0.3 (95% confidence interval [CI], –0.66 to –0.00) and –0.4 (95% CI, –0.68 to –0.05), which were less than the MCID of 1.1 to 2.2, and were not controlled for multiplicity. In Study PAI-3011, pain intensity change was not statistically different for the tapentadol ER and oxycodone CR groups. In all three trials, substantial proportions of early study discontinuations, which were unbalanced across treatment groups, comprised a significant source of potential bias that contributed a large amount of uncertainty to the results. In Baron 2016, reduction in pain intensity was statistically greater for tapentadol ER compared with oxycodone/naloxone PR, LSMD of –0.9 (97.5% CI, –1.8 to –0.2) but the difference was not considered clinically meaningful. In Study PAI-3007, tapentadol ER and oxycodone CR lowered pain intensity by similar amounts, though statistical testing was not conducted.

Pain Intensity, Cancer Pain Trials

In Imanaka 2013, tapentadol ER was noninferior to oxycodone CR; LSMD –0.06 (95% CI, –0.51, 0.38). In Imanaka 2014, mean pain intensity did not change appreciably in either group (tapentadol ER or morphine SR) from baseline to the end of treatment. In Kress 2014 mean pain intensity at the end of the two-week DB titration phase was greater in the tapentadol ER group compared with the morphine CR group; 4.1 (standard deviation of 1.8) versus 3.7 (standard deviation of 1.8) despite similar baseline scores. In addition, immediate release morphine as rescue therapy was used by more patients (72% versus 58%) and in larger amounts as measured by the mean of the mean total daily dose (13.3 mg versus 8.9 mg as morphine equivalent dose in the tapentadol ER group versus the morphine CR group). There were no formal comparisons in Imanaka 2014 or Kress 2014 between tapentadol ER and either morphine SR or morphine sulphate CR, respectively.

Other Efficacy Outcomes

The other efficacy outcomes were subject to the same limitations as identified for pain intensity and statistical tests were not conducted for most comparisons between tapentadol ER and active comparators. There was no control for multiplicity in any of the trials for these outcomes and between-group differences were not conclusive due to the risk of type I error. Results for the EQ-5D-3L index score showed clinically meaningful differences in improvement in favour of tapentadol ER in three of the five chronic non-cancer pain trials. The EQ-VAS and the SF-36 (or SF-12) MCS and PCS showed consistently greater improvements in the tapentadol ER groups in the five chronic non-cancer pain trials, though the differences were less than the MCIDs for the respective instruments. In studies PAI-3008 and PAI-3009, improvements from baseline to the end of the maintenance phase in the global pain subscale and physical function subscale scores of the WOMAC were similar between the tapentadol ER and oxycodone CR groups, though no formal comparisons of the two active treatments were made.

Harms (Safety)

Adverse Events

In all eight of the RCTs, the tapentadol ER group had lower proportions of patients experiencing at least one AE than the active comparator group. The most common AEs were constipation, nausea, vomiting, and somnolence in both non-cancer and cancer pain trials. In the non-cancer pain RCTs, AEs occurred in 67% to 76% of patients in the tapentadol ER group and 85% to 87% in the oxycodone CR groups in the DB efficacy RCTs; 77% and 84% in the tapentadol ER and oxycodone/naloxone PR groups in the OL efficacy RCT (Baron 2016); and 86% and 91% in the tapentadol ER and oxycodone CR groups in the one-year, OL RCT (Study PAI-3007). In the cancer pain trials, AEs occurred in 88% and 90% of the tapentadol ER and oxycodone CR groups in Imanaka 2013, 90% and 94% of the tapentadol ER and morphine SR groups in Imanaka 2014, and 50% and 64% of the tapentadol ER and morphine CR groups in the titration phase of Kress 2014.

In the non-cancer pain RCTs, lower proportions of patients in the tapentadol ER groups versus the oxycodone CR and oxycodone/naloxone PR groups experienced WDAEs. WDAEs occurred in 17% to 19% of the tapentadol ER groups and 32% to 43% of the oxycodone CR groups in the DB efficacy RCTs, 22% and 42% of the tapentadol ER and oxycodone/naloxone PR groups in Baron 2016, and 22% and 37% of the tapentadol ER and oxycodone CR groups in Study PAI-3007. In the cancer pain RCTs, WDAEs occurred in 13% and 17% of the tapentadol ER and oxycodone CR groups in Imanaka 2013 and 28% and 38% of the tapentadol ER and morphine SR groups in Imanaka 2014, while the proportions of WDAEs during the titration phase in Kress 2014 were similar between the tapentadol ER and morphine sulphate CR groups (9% and 7%).

Serious AEs (SAEs) were reported in no more than 4% of patients in the short-term, non-cancer pain trials and in no more than 6% of patients in the one-year trial. SAEs occurred more frequently in the cancer pain trials, with disease progression and vomiting being the most common SAEs in the Imanaka 2013 and 2014 RCTs and neoplasm-related SAEs being the most common in Kress 2014.There were no notable differences in SAEs between tapentadol ER and its comparators.

The AE profile in the OL extension trial was similar to that in the non-cancer pain RCTs and no new safety signals were apparent.

Notable Harms

Gastrointestinal AEs, which mainly comprised constipation, nausea, and vomiting, occurred in 42% to 44% of patients in the tapentadol ER group and 62% to 68% in the oxycodone CR groups in the DB efficacy RCTs; 45% and 52% in the tapentadol ER and oxycodone/naloxone PR groups, respectively, in Baron 2016; and 52% and 64% in the tapentadol ER and oxycodone CR groups, respectively, in Study PAI-3007. In the cancer pain RCTs, gastrointestinal AEs occurred in 55% and 67% of the tapentadol ER and oxycodone CR groups in Imanaka 2013, 38% and 54% of the tapentadol ER and morphine SR groups in Imanaka 2014, and 30% and 47% of the tapentadol ER and morphine sulphate CR groups during titration in Kress 2014.

In the three DB non-cancer pain RCTs, the PAC-SYM overall score results favoured tapentadol ER over oxycodone CR. The magnitude of the between-group differences, ranging from 0.2 to 0.3, was less than the lower limit of the range of MCIDs found for the outcome (0.52 to 0.63). As with the other outcomes, the PAC-SYM results were limited by substantial and unbalanced amounts of missing data from early study discontinuations, as well as the lack of control for multiplicity. In the OL trial comparing tapentadol ER with oxycodone/naloxone PR, the PAC-SYM overall score was similar with both treatments. It was unclear if observed differences

in the gastrointestinal AEs would translate to clinical practice where there may be more gradual titration and concurrent measures to mitigate gastrointestinal effects.

The systematic review did not identify sufficient evidence on the risks of long-term opioid use, such as tolerance and hyperalgesia. An additional search by CDR for studies comparing the potential risks of opioid use disorder, misuse, overdose, or diversion between tapentadol ER and the relevant comparators yielded four observational studies that were not informative because of their retrospective nature and uncertain generalizability to the Canadian context.

Indirect Treatment Comparisons

Due to the lack of sufficient head-to-head trials of tapentadol versus opioids other than oxycodone CR, oxycodone/naloxone PR, morphine SR, and morphine sulphate CR for chronic pain management, a search for ITCs was conducted to provide indirect evidence on the efficacy and safety of the available opioids in the study population. Two network meta-analyses (NMAs) were identified for this review. Different approaches and statistical models were adopted in the two NMAs; however, a major limitation of both NMAs was the decision to combine all doses and formulations of each drug and treat them as a single intervention in the analysis. The combination of immediate and ER formulations in the NMAs provides no evidence specific to tapentadol ER, the study drug under review; thus, the usefulness of the results of these analyses is compromised.

Cost and Cost-Effectiveness

Tapentadol ER tablets are available in 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg strengths. The submitted price of tapentadol ER is based on dose: 50 mg ($1.04), 100 mg ($1.56), 150 mg ($2.09), 200 mg ($2.71), and 250 mg ($3.75). At the recommended dose range of 100 mg to 250 mg twice daily, the cost of tapentadol ER is $3.12 to $7.50 per day, or $1,140 to $2,738 per year.

The manufacturer submitted a probabilistic Markov state-transition cost-utility analysis comparing tapentadol ER with long-acting oral preparations of oxycodone, hydromorphone, and morphine in adult patients with pain severe enough to require daily, continuous, long-term opioid use that is opioid responsive and for which alternative treatment options are inadequate. The model consisted of five health states: treatment with no AEs, treatment with tolerant AEs, lack of efficacy discontinuation, AE discontinuation, and treatment switch. Transitions between health states were derived from a head-to-head RCT (PAI-3011) for tapentadol ER and oxycodone, and a published NMA for hydromorphone and morphine. The perspective was that of a Canadian health care payer, with weekly cycles over a one-year time horizon. Due to the short time horizon, no discounting was applied to costs or clinical outcomes. In their probabilistic base case, the manufacturer estimated that tapentadol ER was associated with more quality-adjusted life-years (QALYs) and lower costs than oxycodone, and was thus dominant over oxycodone. When compared with hydromorphone and morphine, tapentadol ER was associated with an incremental cost-utility ratio of $1,721 per QALY and $15,833 per QALY, respectively.

CADTH identified a number of limitations with the model submitted by the manufacturer:

- The relative treatment effects between tapentadol ER, hydromorphone, and morphine were derived by using odds ratios from an NMA. The NMA combined all doses and formulations of each drug as a single intervention and did not provide comparative clinical evidence specific to long-acting opioid formulations.
- The drug costs provided were inconsistent with the doses used to determine efficacy in the model, biasing costs in favour of tapentadol ER.
- The utility value assigned to the treatment switch health state was set to baseline utility values reported in the trials, in effect, assuming patients would gain no clinical benefit from switching to a new opioid despite incurring the costs of the new treatment for the remaining duration of the model.
- Assumptions pertaining to opioid switching in patients who discontinue therapy due to lack of efficacy or AEs do not align with clinical practice, including: instantaneous switching, averaging the costs of all comparators to determine drug costs within the switch state, and patients continuing on the same morphine equivalent dose after switching.
- Transition probabilities and event rates were assumed linear despite clinical data suggesting otherwise. Event rates observed in the 15-week trial were extrapolated to one year, thereby overestimating discontinuation in the later cycles of the model, which may bias against the comparators.
- Some long-acting opioid comparators that may be of interest were absent.

Given the uncertainty associated with the available clinical data for tapentadol ER compared with long-acting formulations of morphine and hydromorphone, the CADTH base-case reanalysis focused on the pairwise comparison between oxycodone CR and tapentadol ER for which direct clinical evidence was available. CADTH reanalysis further revised drug dosages to be consistent with the trial, assumed a higher utility value for patients who switch opioids, adjusted post-switching treatment costs, and revised rates of discontinuation beyond week 15 to reflect the available clinical trial data.

Based on CADTH reanalysis, the incremental cost-utility ratio for tapentadol ER was $45,847 per QALY gained when compared with oxycodone CR, over a one-year time horizon. At a willingness-to-pay threshold of $50,000 per QALY, the probability of tapentadol ER being cost-effective was 52%. The long-term cost-effectiveness of tapentadol ER remains unknown. The economic analysis could only consider the cost-effectiveness of tapentadol ER with long-acting formulations of morphine and hydromorphone in an exploratory analysis, and was unable to address its cost-effectiveness compared with long-acting oral formulations of tramadol or codeine.

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

September 19, 2018 Meeting

Regrets:

Two CDEC members did not attend.

Conflicts of Interest:

None