CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Tapentadol Hydrochloride Extended-Release Tablet (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. Tapentadol extended-release tablet is not indicated as an as-needed (prn) analgesic.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse event
CDR	CADTH Common Drug Review
CR	controlled release
ER	extended release
ICUR	incremental cost-utility ratio
GP	general practitioner
MED	morphine-equivalent dose
NMA	network meta-analysis
ODB	Ontario Drug Benefit
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomized controlled trial
WTP	willingness to pay

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Tapentadol hydrochloride extended-release tablet (Nucynta Extended-Release)
Study Question	What is the cost-effectiveness of tapentadol ER compared with long-acting oral formulations of oxycodone, hydromorphone, and morphine as a treatment option in adults 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 from the perspective of the publicly funded health care payer?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adults with pain severe enough to require daily, continuous, long-term opioid treatment and that is opioid responsive, and for which alternative treatment options are inadequate.
Treatment	Tapentadol ER
Outcome	Quality-adjusted life-years (QALYs)
Comparator(s)	Long-acting oral formulations of: • oxycodone • hydromorphone • morphine.
Perspective	Canadian public health care payer
Time Horizon	1 year
Results for Base Case	Tapentadol ER was: • less costly and more effective than oxycodone (dominant) • associated with an ICUR of $1,721 per QALY compared with hydromorphone • associated with an ICUR $15,833 per QALY compared with morphine.
Key Limitations	• The relative treatment effects between tapentadol ER and oxycodone were based on the PAI-3011 randomized controlled trial (RCT), while those between tapentadol ER, hydromorphone, and morphine were derived by using odds ratios from a network meta-analysis (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 of the treatment switch health state (the absorbing state) was too low, 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. • Inappropriate assumptions pertaining to opioid switching were considered, which 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 (MED) after switching. • Transition probabilities and event rates were assumed linear despite clinical data suggesting otherwise. Furthermore, event rates observed in the 15-week trial were extrapolated to one year; thereby, overestimating discontinuation in the later cycles of the model and biased against the comparators. • Absence of some long-acting opioid comparators that may be of interest.

CDR Base-Case Estimates	The CDR base-case reanalysis corrected dosages of all comparators to be consistent with the trial data that informed relative safety and efficacy estimates, assigned drug costs equivalent to the mean of the other three comparators and reduced the MED by 25% when a patient switched from their first opioid, assigned a higher utility weight to the switch state, and assumed a lower rate of discontinuation after the first 15 weeks of the model to reflect the observed rates from an extension study. Furthermore, the base-case reanalysis was restricted to the comparison of tapentadol ER with long-acting oxycodone in which treatment effects were based on direct evidence. Based on these revisions, CDR found that: • Tapentadol ER vs. oxycodone: $45,847 per QALY gained.

CDR = CADTH Common Drug Review; ER = extended release; ICUR = incremental cost-utility ratio; vs. = versus.

Drug	Tapentadol hydrochloride extended-release tablet (Nucynta Extended-Release)
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. Nucynta Extended-Release is not indicated as an as-needed (prn) analgesic.
Reimbursement Request	As per indication
Dosage Forms	50 mg, 100 mg, 150 mg, 200 mg, and 250 mg tablets
NOC Date	October 31, 2013
Manufacturer	Paladin Labs Inc.

Executive Summary

Background

Tapentadol ER (Nucynta Extended-Release) is indicated for the management of patients with pain severe enough to require daily, continuous, long-term opioid treatment, and that is opioid responsive, and for which alternative treatment options are inadequate. 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).[1] The recommended initial dose for opioid-naive patients is 50 mg twice daily, titrated to an optimal dose within the therapeutic range of 100 mg to 250 mg twice daily. A switch to tapentadol ER for patients currently taking another opioid analgesic should be accompanied by a 50% reduction in the calculated morphine-equivalent daily dose, followed by adjustments to an optimal dose, recommended as 100 mg to 250 mg twice daily.[1] At the recommended dose range, the cost of tapentadol ER is $3.12 to $7.50 per patient, per day, or $1,140 to $2,738 per patient, per year.

CADTH's Common Drug Review (CDR) previously reviewed tapentadol controlled-release (Nucynta CR) for the management of moderate-to-moderately-severe pain in adults who require continuous treatment for several days or more. The CADTH Canadian Drug Expert Committee recommended that tapentadol CR not be listed, based on a lack of sufficient evidence establishing the relative efficacy between tapentadol CR and oxycodone CR.[2]

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.[3] The model consisted of five health states: treatment with no adverse events (AEs), treatment with tolerant AEs, lack of efficacy discontinuation, AE discontinuation, and treatment switch. The perspective was that of a Canadian health care payer, with weekly cycles over a one-year time horizon. A half-cycle correction was applied, but due to the short time horizon, no discounting was applied to costs or clinical outcomes. Transitions between health states were derived from a head-to-head randomized controlled trial[4] for tapentadol ER and oxycodone CR, and a network meta-analysis (NMA)[5] for long-acting hydromorphone and

morphine. Patients who discontinued therapy due to a lack of efficacy or AEs switched to another opioid treatment and remained in that state for the remaining duration of the model, accruing the average cost of all four comparators thereafter. Utilities were obtained from a cost-utility analysis conducted in the UK.[6] Doses used for comparators, as well as the average number of units used per day, were derived from IQVIA PharmaStat market share data over an unspecified period.

In their base case, the manufacturer reported that tapentadol ER was dominant (i.e., less costly and more effective) compared with oxycodone CR, and was associated with an incremental cost-utility ratio of $1,721 per quality-adjusted life-year (QALY) compared with hydromorphone CR and $15,833 per QALY compared with long-acting morphine.

Summary of Identified Limitations and Key Results

CDR identified a number of limitations with the model submitted by the manufacturer. The relative efficacy and safety of tapentadol ER versus its comparators was uncertain, particularly for those with inputs derived from the NMA.[7] The NMA reported the combined relative effects of long- and short-acting opioids together; therefore, the comparative treatment effects specific to long-acting opioids are unclear.[4] Drug costs were not consistent with the doses from which the efficacy and safety effects were derived, biasing costs in favour of tapentadol ER. The manufacturer assumed that patients switching opioids would have a quality of life equivalent to baseline utility values from trials,[6] which suggests that patients would not derive any clinical benefit upon switching to their new opioid. After switching, despite Canadian guideline recommendations to reduce the morphine-equivalent dose by 25% to 50% between comparators,[8] the manufacturer assumed patients would remain on an average cost of all four comparators at the same doses, including the drug that was just discontinued. The manufacturer derived linear transition probabilities and AE rates from the proportion of patients experiencing the events over the course of the 15-week PAI-3011 randomized controlled trial.[4] However, the occurrences of events were not linearly distributed over time in the trial. Furthermore, these rates were extrapolated to the model's full year time horizon.

In addition to the above limitations, CDR identified several limitations that could not be addressed. The manufacturer's time horizon was one year, which, given the chronic nature of pain severe enough to require continuous treatment, is unlikely to be sufficient in capturing all outcomes of interest when determining the most cost-effective opioid therapy. Additionally, long-acting oral formulations of tramadol and codeine may also be comparators of interest, as tapentadol ER may replace their use in some patients. The cost-effectiveness of tapentadol ER compared with codeine or tramadol is unknown.

Given the uncertainty associated with the available clinical data for tapentadol ER compared with long-acting formulations of morphine and hydromorphone, the CDR base-case reanalysis focused on the pairwise comparison between oxycodone CR and tapentadol ER for which direct clinical evidence was available. An exploratory analysis was conducted to assess the potential cost-effectiveness of tapentadol ER against long-acting hydromorphone and morphine by assuming equal treatment efficacy and safety between long-acting oxycodone, hydromorphone, and morphine. In addition, to account for other limitations identified in the manufacturer's economic analysis, the CDR reanalysis included revisions to drug dosages to be consistent with the PAI-3011 trial data; the assumption that patients who switched and continued on a second opioid had a quality of life equivalent to those with tolerable AEs on their first opioid within the model; the adjustment of post-switching costs to exclude the

previous opioid and integrated an MED reduction; and set rates of discontinuation beyond week 15 to reflect the available clinical trial data.

Conclusions

Based on CDR reanalysis, tapentadol ER was associated with an additional benefit of 0.010 QALYs at an additional cost of $449, for an incremental cost-utility ratio of $45,847 per QALY gained when compared with oxycodone CR, over a one-year time horizon. The probability of tapentadol ER being cost-effective at a willingness-to-pay threshold of $50,000 per QALY, when compared with oxycodone CR, was 52%.

The long-term clinical effectiveness and cost-effectiveness of tapentadol ER remain unknown. Furthermore, the economic analysis could only consider the cost-effectiveness of tapentadol ER compared 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.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's PE Submission

The manufacturer submitted a Markov state–transition model comparing tapentadol extended-release (ER) with long-acting 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.[3] The model consisted of five health states: treatment with no adverse event (AE), treatment with tolerant AE, lack of efficacy discontinuation, AE discontinuation, and treatment switch. The perspective was that of a Canadian health care payer, with weekly cycles over a time horizon of one year, with a half-cycle correction applied. Due to the short time horizon, no discounting was applied to costs or clinical outcomes (i.e., quality-adjusted life-years [QALYs]).

All patients in the cohort started in the treatment with no AE health state. At each cycle, they could move from treatment with no AE to treatment with tolerable AEs, or pass through one of two transient states (i.e., lack of efficacy discontinuation or AE discontinuation) and proceed onto the treatment switch health state. In the manufacturer's base case, 100% of patients who discontinued their initial treatment due to either AEs or a lack of efficacy instantaneously entered the treatment switch health state, and remained there for the remaining duration of the model (Figure 1, Appendix 5). Patients in the switch state were assumed to accrue the average cost of all four comparators thereafter.

For the comparison between tapentadol ER and oxycodone controlled-release (CR), efficacy and safety data informing the transition probabilities and AE rates within the model were derived from a randomized controlled trial (RCT) (PAI-3011)[4] where patients were randomized to receive tapentadol ER, oxycodone CR, or placebo over 15 weeks. In the manufacturer's base case, these transition probabilities and AE rates were also extrapolated to weeks 16 to 52. Odds ratios for long-acting hydromorphone and morphine versus tapentadol were derived from a published network meta-analysis (NMA)[7] and applied to treatment effects derived from PAI-3011 for tapentadol ER to determine the relative efficacy and safety of long-acting hydromorphone and morphine. Change in pain intensity, the primary end point of the PAI-3011 trial, was not directly captured in the model; however, lesser pain relief would be reflected in the higher rates of discontinuation due to a lack of efficacy. With the one-year model time horizon, mortality was not incorporated. Additionally, no demographic-specific baseline data such as patient age or gender were incorporated into the economic model.

Health state utility weights were derived from a UK cost-utility analysis by Ikenberg et al.,[6] which mapped EuroQol 5-Dimensions questionnaire results from three RCTs comparing tapentadol ER with oxycodone CR[4,9,10] (Table 11). Patients in the treatment with no AEs, treatment with tolerable AEs, and two discontinuation health states were assigned utility weights consistent with those definitions from Ikenberg, while patients in the absorbing treatment switch state were assumed to have the same quality of life (QoL) as patients who were on their fourth line of opioid therapy due to severe AEs or a lack of efficacy. In Ikenberg's economic model, the utility weight for the fourth line of opioid therapy was assumed to be equivalent to the baseline utility values that were reported within the trials.

Unit costs for the comparators were based on Ontario Drug Benefit (ODB) Formulary list prices when reimbursed or IQVIA Delta PA when not, while those for tapentadol ER were the

manufacturer's submitted prices. To calculate a weighted average drug cost, doses used for comparators, as well as the average number of units used per day, were derived from IQVIA PharmaStat market share data from Ontario, while those for tapentadol ER were based on IQVIA PharmaStat data for all of Canada, both over an unspecified period. Other costs were divided into two categories: i) health-state specific costs based on number of general practitioner (GP) visits per cycle or during transition between health states, and ii) AE-specific costs that, with the exception of chronic constipation, were applied as one-time costs. GP visit costs were based on the Ontario Schedule of Benefits for Physician Services,[11] while costing of each AE was based on a US costing study,[12] the Ontario Case Costing Initiative,[3] a Canadian Institute for Health Information survey,[13] and ODB Formulary list prices[14] (Table 12).

Manufacturer's Base Case

The manufacturer's probabilistic base case was presented from a health care payer perspective (Table 2). The use of tapentadol ER was associated with a one-year cost of $2,205 and QALY gains of 0.555. Tapentadol ER was associated with more QALYs at a lower cost than oxycodone CR, and was thus dominant over oxycodone CR. When compared with long-acting hydromorphone and morphine, the manufacturer reported that tapentadol ER was associated with an incremental cost-utility ration (ICUR) of $1,721/QALY and $15,833/QALY, respectively. A more detailed cost breakdown can be found in Table 15, Appendix 5.

Table 2: Summary of Results of the Manufacturer's Probabilistic Base Case

	Tapentadol ER	Oxycodone CR	Hydromorphone CR	Morphine SR/ER
Total cost ($)	2,205	2,790	2,154	1,815
Total QALYs	0.555	0.521	0.525	0.530
ICUR, tapentadol ER vs. comparator ($/QALY)	Reference	Tapentadol ER dominant	1,721	15,833

CR = controlled release; ER = extended release; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SR = sustained release; vs. = versus.

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted several scenario analyses that included considering a societal perspective; using clinical data from Wild et al. 2010;[15] dosages based on the product monographs; removal of extra GP visits associated with AEs; assuming that only 90% of patients who discontinue due to lack of efficacy switch to another treatment while none switch for those discontinuing due to AEs; and modelling a total of three lines of treatment rather than two.

Specifically, for the scenario that explored different clinical management upon initial opioid discontinuation, it was assumed that those who do not switch to another opioid (i.e., 10% of patients who discontinue due to lack of efficacy and all who discontinue due to AEs) would withdraw from opioid therapy entirely. In such a scenario, the manufacturer reported that tapentadol ER was dominant over oxycodone CR, with ICURs of $22,888 and $50,460 per QALY compared with long-acting hydromorphone and morphine, respectively.

Limitations of Manufacturer's Submission

1. **Relative efficacy and safety uncertain:** Head-to-head trials comparing tapentadol ER with oxycodone CR exist, including the PAI-3011 RCT, which was used by the manufacturer to inform both transition probabilities and the probability of AEs in the model.[4] However, this trial was associated with significant limitations, increasing uncertainty in the treatment effects modelled. It was reported that 22% of patients had a major protocol violation, with the most common involving concomitant medication use and poor treatment compliance. Furthermore, the short titration period of three weeks for the oxycodone CR arm may not reflect current clinical practice. According to the clinical expert consulted for this review, patients in a real-world setting are titrated and monitored continuously and provided a longer time to acclimatize or develop tolerance to side effects. Discontinuation rates may therefore be lower in a real-world setting as patients may be encouraged to stay on therapy and acclimatize to the side effects under a more flexible titration regimen (see Clinical Report for details). Given these limitations with the clinical trial, this introduces uncertainty into the economic model as to the true relative treatment effects of tapentadol ER compared with oxycodone CR.

   Although head-to-head trials comparing tapentadol ER to long-acting morphine also exist, the trial durations were shorter (eight weeks or shorter) and limited to patients with cancer pain.[16,17] The manufacturer relied instead on a published network meta-analysis (NMA)[5] to estimate the relative efficacy and safety of hydromorphone CR and morphine sustained-release (SR)/ER to tapentadol ER. The NMA had several limitations that hampered the applicability of its results to those of the modelled population. By pooling both long- and short-acting formulations, the relative treatment effects of tapentadol ER compared with other long-acting opioid formulations is unclear. The NMA was carried out using a regression model that was claimed to be a straightforward generalization of the fixed-effects meta-analysis. However, significant heterogeneity was noted by CADTH Common Drug Review (CDR) clinical reviewers across the included trials, such as study duration, formulations and dosages of the study drugs, and patient's prior opioid experience (see Clinical Report, Appendix 7). Given the concerns with the NMA and the approach taken to incorporate the NMA findings to the economic model, there is uncertainty on the comparative clinical efficacy and safety of tapentadol ER compared with long-acting hydromorphone and morphine.

   CDR's base-case reanalysis only compared tapentadol ER with oxycodone CR as the baseline characteristics informing the efficacy and safety inputs were considered balanced between these treatment groups. CDR further conducted an exploratory analysis in which the efficacy and safety of long-acting morphine and hydromorphone were assumed equivalent to the oxycodone CR treatment group in PAI-3011. This was aligned with the assumption made by the manufacturer in cases where efficacy and safety data were not available from the Riemsma study to inform model inputs for long-acting morphine and hydromorphone.

2. **Calculation of average drug costs inconsistent with doses used for efficacy data:** Weighted average drug costs were calculated using Ontario and national IQVIA PharmaStat utilization data, while the efficacy and safety inputs in the model were based on the doses used in the clinical trials. In the PAI-3011 RCT,[4] the average daily doses of tapentadol ER and oxycodone CR over the entire double-blind period were 313 mg and 53 mg respectively, while the averages over the last two weeks of the maintenance period were 393 mg and 75 mg, respectively. Using the submitted utilization data from IQVIA

PharmaStat, the weighted average daily dose used in the economic model was 266 mg for tapentadol ER and 106 mg for oxycodone CR. Efficacy and safety of an opioid are expected to be related to its dosage. Although utilization data, if appropriately incorporated into the economic evaluation, may better reflect real-world costs than calculating drug costs based on the doses used in the RCTs, the efficacy of each therapy as observed in the clinical trials would no longer be presumed to apply as doses are no longer similar. Applying a lower dose for tapentadol ER and a higher dose for oxycodone CR, while assuming the efficacy and safety as reported in the PAI-3011 trial, biases the average cost of therapy in favour of tapentadol ER, while the relative safety and efficacy impacts on QoL outcomes at such doses is unknown. In the CDR reanalysis, doses for both tapentadol ER and oxycodone CR were assumed to be based on the dose distributions reported in PAI-3011. This limitation also applies to the doses assumed for long-acting hydromorphone and morphine; in the scenario analyses conducted by CDR, long-acting hydromorphone and morphine were assumed to be used in the same dose distribution as reported in the oxycodone CR arm of PAI-3011, converted using morphine-equivalent doses (MEDs) that are reported in a current Canadian clinical practice guideline.[8]

3. **Utility weight too low in absorbing treatment switch health state:** The manufacturer's base-case model used a utility weight of 0.422 for patients who had discontinued therapy and switched to another medication, where they remained for the duration of the model. This value is from a UK cost-utility analysis[6] and corresponds to the QoL of a patient in need of a fourth line of opioid therapy. The value itself was derived from patients' EuroQol 5-Dimensions questionnaire scores measured at baseline of the included clinical trials; i.e., patients who were currently unsatisfied enough with their pain control to enter a clinical trial. By using it to represent the absorbing health state of patients who switch therapies, the manufacturer is implying that all such patients receive no improvement of symptoms upon discontinuation of their failing therapy and switching to an alternate opioid therapy, yet continue to accrue the costs of the alternate opioid therapy. The approach taken by the manufacturer underestimates the potential clinical benefits of switching opioids, while accounting for the potential cost impacts. Results are thus biased in favour of therapies with fewer discontinuations in the model; i.e., tapentadol ER. In the CDR reanalysis, utility weight of the treatment switch health state was assumed to correspond to the health state of treatment with AEs (i.e., 0.583) that was reported in the same publication. CDR considered this approach to better align with the fact that patients would derive some clinical benefits from switching to another opioid, while still having a lower QoL than those who did not suffer AEs or loss of efficacy on their original treatment (0.695).

4. **Assumptions pertaining to opioid switching:** The manufacturer's submitted economic evaluation assumed that all patients would immediately switch to a new opioid. According to the clinical expert consulted as part of this CDR review, this does not reflect current clinical practice. Whether patients switch to a new opioid is likely dependent on the reason for treatment discontinuation as, in the case of intolerable AEs, clinicians may attempt to address the AEs by decreasing the opioid dose and rarely will switch patients to a new opioid treatment. In cases where discontinuation is due to poor efficacy, instantaneous discontinuation does not reflect clinical practice as patients would require tapering from one opioid to another, or be off opioid therapy entirely. Proportions of patients switching opioids after discontinuation and the timelines on which they do so are likely to vary among clinicians.

Another concern in how switching was modelled by the manufacturer is in how drug costs were calculated within the treatment switch state. In the submitted model, once a patient had switched from their initial opioid therapy, drug costs were assumed to be the average of all four comparators, including the opioid that had been discontinued. This biases results in favour of comparators that are less expensive (i.e., hydromorphone and morphine) as their post-switch treatment costs should be higher than those switching from a higher-cost opioid to a lower cost opioid. In CDR's reanalysis, after switching from the original opioid, patients accrue the average cost of the other three opioids included in the model.

Additionally, current Canadian guidelines[8] and opioid product monographs (including tapentadol ER's[1]) recommend that when switching from one opioid to another, physicians should consider reducing the calculated MED by 25% to 50% to minimize the risk of overdose. The clinical expert consulted by CDR considered this practice vital, specifying that patients on initial higher doses should have their new opioid doses reduced by 50%, while those discontinuing at lower doses should have their new opioid dose reduced by 25%. Given the short one-year time horizon, CDR considered an estimated average 25% reduction in MED to be an appropriate balance between patients on high doses who would require greater reductions, and patients who may require uptitrating after such switches.

5. **Linearity in event rates:** The manufacturer derived the transition probabilities and AE rates for tapentadol ER and oxycodone CR used in the economic model from the proportions of patients experiencing the respective events over the course of the 15-week PAI-3011 trial.[4] In the manufacturer's base case, these rates were then extrapolated beyond to weeks 16 to 52. However, as seen in PAI-3011, event rates are not linear over time; most events occur in the first few weeks on the new treatment. This is also evident from the Buynak 2015 extension study,[18] which included patients who had completed studies PAI-3008,[9] PAI-3007,[15]-PAI-3011,[18] or a seven-week phase IIIb crossover trial between tapentadol immediate-release and ER.[19] Patients in the extension study who had not previously received tapentadol were titrated to dosages between 100 mg and 250 mg twice daily, while those who had previously received tapentadol did not require titration. Rates of AEs and withdrawals due to lack of efficacy were lower than seen in PAI-3011.

   CDR reviewers considered the methods for modelling event rates in the Ikenberg et al. economic evaluation[6] to be more appropriate, where transition probabilities are greatest in the first four weeks after treatment initiation, and reduced at weeks 4, 8, 12, and 16, as observed within the clinical trials. However, the manufacturer's model was not sufficiently flexible to incorporate time-dependent event rates during the three-week titration and subsequent 12-week maintenance period. In CDR's reanalysis, long-term discontinuation beyond the first 15 weeks was adjusted to reflect the rates reported for tapentadol ER in the extension study for weeks 16 to 52,[18] with discontinuation rates for oxycodone CR derived by incorporating relative risks versus tapentadol ER, as programmed by the manufacturer, based on a 2015 Cochrane review.[20]

6. **Long-term cost-effectiveness uncertain:** Given the chronic nature of pain severe enough to require continuous treatment, a one-year time horizon is too short to capture all potential differences in costs and outcomes when determining the most cost-effective choice of opioid therapy, as laid out in CADTH's *Guidelines for the Economic Evaluation of Health Technologies*.[21] The manufacturer deemed the one-year time horizon appropriate given that the rates of treatment discontinuation and switching in the patient

population would makes it unlikely that patients would continue on a single opioid therapy for many years. In clinical practice, patients and their physicians may require months to find the optimal dosage of an opioid and to manage side effects, rather than the weeks allowed within a clinical trial, and according to the clinical expert consulted on this review, they may be less likely to switch or withdraw than if following a trial protocol. Downstream clinical and cost effects of opioid choice may continue past one year, and by constraining the time horizon to one year, this introduces uncertainty in the long-term cost-effectiveness of tapentadol ER. CDR was unable to analyze the cost-effectiveness of tapentadol ER relative to its comparators beyond one year after initiating treatment.

7. **Not all comparators considered:** According to the clinical expert consulted on this CDR review, there is some overlap in the indications between tapentadol ER and long-acting formulations of "weak" opioids, tramadol and codeine.[1,22,23] In clinical practice, patients with moderate long-term pain may receive any of the weak or strong opioids (See the Clinical Report's Potential Place in Therapy section). Tramadol is not routinely covered by public drug plans in Canada; however, tapentadol ER may replace some use of oral long-acting codeine, which is reimbursed by public payers, and thus long-acting codeine can be considered a potential comparator of interest. The relative efficacy and safety and thus cost-effectiveness of tapentadol ER compared with codeine or tramadol is unknown; however, the annual cost of tapentadol ER is similar to that of long-acting oral codeine and brand-name tramadol, but more expensive than generic tramadol (see Table 7).

CADTH Common Drug Review Reanalyses

The results of the CDR reanalyses are presented in Table 3. These reanalyses addressed several limitations that were previously identified. These include:

1. The comparison of tapentadol ER to oxycodone CR was limited given that the relative efficacy and safety data were derived from a trial with balanced baseline characteristics.
2. Dose distributions for tapentadol ER and oxycodone CR were taken from the total daily dose in the last two weeks of the maintenance period reported in PAI-3011.[4]
3. Utility weight of the treatment switch health state was assumed to be consistent with treatment with AEs (0.583) health state.
4. Drug costs for each comparator after switching were the average of the other three comparators. Furthermore, after switching, doses of subsequent drugs were assumed to be 25% lower.
5. Transition probabilities from week 16 to 52 were derived from the Buynak 2015 extension study.[18]
6. In addition, CDR's reanalysis also entailed revising comparator pricing to reflect per-unit prices based on the ODB Formulary, as of June 2018. While the manufacturer did not specify when they cited ODB for their drug costs, several changes were made to formulary list prices in April 2018 after the manufacturer's submission was received by CDR.

Compared with the manufacturer's results, the CDR's base-case reanalysis reported numerically higher QALY gains for both comparators, but a smaller difference in incremental QALYs for tapentadol ER, as well as higher costs for tapentadol ER and lower costs for oxycodone. Tapentadol ER was associated with a one-year cost of $2,392 and QALY gains of 0.611. Tapentadol ER was more costly but also more effective than long-acting oxycodone, with an ICUR of $45,847 per QALY gained. At a willingness-to-pay (WTP) threshold of

$50,000 per QALY, tapentadol ER was cost-effective 52% of the time, compared with oxycodone CR (more than 5,000 iterations).

Table 3: CADTH Common Drug Review Reanalysis of Limitations

	Scenario	Treatments	QALYs	Cost ($)	ICUR ($ Per QALY) Tapentadol ER vs. Oxycodone CR
	Base case, submitted by manufacturer	Tapentadol ER	0.555	2,205	**Dominant**
		Oxycodone CR	0.521	2,790	Reference
1	**Switch utility same as treatment with AEs**	Tapentadol ER	0.603	2,207	**Dominant**
		Oxycodone CR	0.597	2,790	Reference
2	**Dosage distributions from PAI-3011 trial**	Tapentadol ER	0.555	2,729	**6,791**
		Oxycodone CR	0.521	2,499	Reference
3	**Week 16+ transition probabilities from Buynak 2015**	Tapentadol ER	0.579	2,128	**Dominant**
		Oxycodone CR	0.546	2,824	Reference
4	**Post-switch drug costs are the average of the other three drugs**	Tapentadol ER	0.555	2,202	**Dominant**
		Oxycodone CR	0.521	2,628	Reference
5	**Dose of new opioid is reduced by 25% after switch**	Tapentadol ER	0.555	2,101	**Dominant**
		Oxycodone CR	0.521	2,622	Reference
6	**ODB list prices updated to June 2018**	Tapentadol ER	0.555	2,233	**Dominant**
		Oxycodone CR	0.521	2,954	Reference
1 to 6	**CDR base case**	Tapentadol ER	0.611	2,392	**45,847**
		Oxycodone CR	0.601	1,943	Reference

AEs = adverse events; CDR = CADTH Common Drug Review; CR = controlled release; ER = extended release; ICUR = incremental cost-utility ratio; ODB = Ontario Drug Benefit; QALY = quality-adjusted life-year; vs. = versus.

As noted, there is considerable uncertainty in terms of the comparative clinical efficacy and safety of long-acting hydromorphone and morphine against tapentadol ER given that the NMA combined all doses and formulations of a drug and treated them as a single intervention in the analysis.[5] Given this issue, CDR conducted an exploratory analysis that, in addition to those changes outlined in the previously mentioned CDR base-case analysis, also assumed long-acting hydromorphone and morphine had equal efficacy and safety as oxycodone CR, as reported in PAI-3011.[4] In this scenario, tapentadol ER was associated with ICURs of $69,009 per QALY compared with hydromorphone CR, and $107,536 per QALY compared with morphine SR/ER (see Table 4). When considered sequentially, hydromorphone CR and oxycodone were dominated by long-acting morphine (having equivalent benefit at higher costs); thus, the ICUR of interest is that of tapentadol ER compared with long-acting morphine: $107,536 per QALY gained.

Table 4: CDR Exploratory Analyses, Including Hydromorphone and Morphine

Scenario	Treatments	Total QALYs	Total Cost ($)	ICUR ($ Per QALY) Tapentadol ER vs. Comparator	Sequential ICUR ($ Per QALY)
CDR exploratory analysis, assuming efficacy and safety data from hydromorphone and morphine are equivalent to that of oxycodone	Morphine SR/ER	0.601	1,364	107,536	Reference
	Tapentadol ER	0.611	2,394	Reference	107,536
	Hydromorphone CR	0.601	1,754	69,009	Dominated by long-acting morphine
	Oxycodone CR	0.601	1,942	45,714	Dominated by long-acting morphine

CDR = CADTH Common Drug Review; CR = controlled release; ER = extended release; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SR = sustained release.

Price-reduction analyses were not conducted on the CDR base-case reanalysis as the ICUR for tapentadol ER was already below $50,000 per QALY when compared with oxycodone CR. However, price-reduction analysis on CDR's scenario analysis that incorporated long-acting hydromorphine and morphine as comparators found that the price of tapentadol ER would need to be reduced by approximately 11% when compared with hydromorphone CR and 32% when compared with morphine SR/ER to be considered cost-effective at a WTP of $50,000 per QALY (see Table 5).

Table 5: CADTH Common Drug Review Reanalysis Price-Reduction Scenarios

ICURs of Tapentadol ER Versus Oxycodone CR (Cost Per QALY, CDR Base Case)		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR (Based on CDR Exploratory Analysis)**
Submitted	Dominant	45,714
10% reduction	Dominant	28,201
20% reduction	Dominant	10,550
30% reduction	Dominant	Dominant
40% reduction	Dominant	Dominant
50% reduction	Dominant	Dominant
60% reduction	Dominant	Dominant
70% reduction	Dominant	Dominant
ICURs of Tapentadol ER Versus Hydromorphone CR (Cost Per QALY)		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR (Based on CDR Exploratory Analysis)**
Submitted	1,721	69,009
10% reduction	Dominant	52,021
20% reduction	Dominant	34,746
30% reduction	Dominant	15,917
40% reduction	Dominant	Dominant
50% reduction	Dominant	Dominant
60% reduction	Dominant	Dominant
70% reduction	Dominant	Dominant

ICURs of Tapentadol ER Versus Morphine SR/ER (Cost Per QALY)		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR (Based on CDR Exploratory Analysis)**
Submitted	15,833	107,536
10% reduction	11,571	90,228
20% reduction	7,841	72,665
30% reduction	3,581	54,412
40% reduction	Dominant	36,627
50% reduction	Dominant	18,472
60% reduction	Dominant	612
70% reduction	Dominant	Dominant

CDR = CADTH Common Drug Review; CR = controlled release; ER = extended release; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SR = sustained release.

Issues for Consideration

The confidential nature of the negotiated effective price for pharmaceuticals means CDR is unable to assess the impact of potentially lower prices of comparators on the results. Thus, it is unknown if the reduced effective price of comparators would lead to differing conclusions than the current analysis, based on list prices.

Patient Input

Input regarding tapentadol ER was received from 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. One group noted that there were no respondents in their submission who met the manufacturer's requested reimbursement criteria.

Many patients who were taking medications to treat their pain experienced side effects, with constipation being the most common in two submissions. Other reported side effects were tiredness, drowsiness, nausea, stomach upset, kidney and liver damage, weight gain or loss, loss of appetite, anxiety, hyperactivity, feelings of being unwell, dizziness, headache, dry mouth, mood swings, brain fog, insomnia, irritability, and paranoia (note that the manufacturer considered constipation, nausea, vomiting, dizziness, pruritus, diarrhea, fatigue, insomnia, somnolence, headache, and dry mouth as AEs within the model). In general, all patient groups expected to see safer and more effective treatments for pain relief. They wanted new treatments that will relieve pain and improve function, are non-addictive and won't cause withdrawal symptoms, have long-lasting effects, have the fewest side effects, and can improve their QoL. They also emphasized that the drug should be affordable and accessible for those who need it. These groups reported issues for patients in accessing non-pharmaceutical treatments such as physiotherapy and psychological treatment in the public system, with significant costs associated with accessing such services privately (see Clinical Report, Appendix 1, for more detail).

Conclusions

To account for the limitations identified in the manufacturer's economic analysis, the CDR base-case reanalysis assumed dosages to be consistent with the clinical trial, incorporated a higher QoL benefit in patients switching to another opioids, applied a lower discontinuation probability in later modelled cycles, excluded the cost of the previous opioid following treatment switching, and assumed a 25% MED reduction upon opioid switching. This led to tapentadol ER being associated with an ICUR of $45,847 per QALY gained compared with oxycodone CR, over a one-year time horizon. The probability of tapentadol ER being cost-effective at a WTP of $50,000 per QALY was 52% when compared with oxycodone CR.

The long-term clinical effectiveness and cost-effectiveness of tapentadol ER remain unknown. Furthermore, the economic analysis could only consider the cost-effectiveness of tapentadol ER against 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.

Appendix 1: Cost Comparison

The comparators presented in the tables below have been deemed to be appropriate by clinical experts. 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. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 6: CDR Cost Comparison Table for Long-Acting Opioid Analgesics for Chronic Pain

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Cost of 90 MED ($)	Annual Drug Cost at 90 MED[a] ($)
Tapentadol ER (Nucynta ER)	**50 mg 100 mg 150 mg 200 mg 250 mg**	**ER tablet**	**1.0412[a] 1.5612[a] 2.0893[a] 2.7085[a] 3.7508[a]**	**Opioid naive** 50 mg twice daily, titrated to 100 mg to 250 mg twice daily (increments of 50 mg twice daily every 3 days) **Opioid experienced** 100 mg to 250 mg twice daily, taking into account previous opioid dosages[b]	**300 mg as 150 mg twice daily: 4.18**	**1,525**
Main Comparators Considered by Manufacturer						
Hydromorphone (Hydromorph Contin)	3 mg 4.5 mg 6 mg 9 mg 12 mg 18 mg 24 mg 30 mg	CR capsule	0.8030 0.9700 1.2040 1.5900 2.0870 3.0120 3.8550[c] 4.6180[c]	Usual initial dose: 3 mg every 12 hours, titrated in 48 hour intervals Convert from previous opioid medication[b]	18 mg as 9 mg twice daily: 2.41	879
Morphine sulphate (generics)	15 mg 30 mg 60 mg 100 mg 200 mg	SR tablet	0.2317 0.3500 0.6167 2.4600 4.5738[d]	Most frequent initial dose is 30 mg every 12 hours Convert from previous opioid dose[b]	90 mg as 45 mg twice daily: 1.16	425
Morphine sulphate (Kadian SR)	10 mg 20 mg 50 mg 100 mg	SR capsule	0.4014 0.7795 1.4751 2.5730	Convert from previous opioid dose.[b] Maximum 90 mg daily for non-cancer, non-palliative pain	90 mg once daily: 3.03	1,107
Morphine sulphate (M-Eslon)	10 mg 15 mg 30 mg 60 mg 100 mg	ER capsule	0.3200 0.3700 0.5510 0.9800 2.1130	Most frequent initial dose is 30 mg every 12 hours Convert from previous opioid dose[b]	90 mg as 45 mg twice daily: 1.84	672
Oxycodone	10 mg	CR tablet	0.9265	Usual initial dose is	60 mg as 30 mg twice	1,342

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Cost of 90 MED ($)	Annual Drug Cost at 90 MED[a] ($)
(OxyNEO)	15 mg 20 mg 30 mg		1.1200 1.3900 1.8380	10 mg every 12 hours Convert from previous opioid dose.[b] Maximum 60 mg daily for non-cancer, non-palliative pain	daily: 3.68	

CDR = CADTH Common Drug Review; CR = controlled release; ER = extended release; MED = morphine-equivalent dose; SR = sustained release.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2018) unless otherwise indicated and do not include dispensing fees. Morphine-equivalent dosage calculated according to *2017 Canadian Guidelines for Opioids for Chronic Non-Cancer Pain*.[8]

[a] Manufacturer-submitted price.[3]

[b] When switching between opioid products, it is recommended to initially reduce morphine-equivalent dose by 25% to 50% to reduce risk of overdose, and then to uptitrate to the optimal dose as needed.

[c] Ontario Drug Benefit Exceptional Access Program list price (June 2018).[24]

[d] Wholesale price, IQVIA Delta PA (June 2018).[25]

Table 7: CDR Cost Comparison Table for Additional Long-Acting Opioid Analgesics for Chronic Pain

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Cost of 90 MED ($)	Annual Drug Cost at 90 MED ($)
Codeine (Codeine Contin)	50 mg 100 mg 150 mg 200 mg	CR tablet	0.3660 0.7320 1.0380 1.4640	Usual initial dose: 50 mg every 12 hours, titrate to maintenance dose up to 300 mg twice daily	600 mg as 300 mg twice daily: 4.15	1,515
Fentanyl (generics)	12 mcg/hr 25 mcg/hr 50 mcg/hr 75 mcg/hr 100 mcg/hr	Trans dermal patch	2.2310[a] 3.6582 6.8838 9.6817[a] 12.0512[a]	One patch every 3 days	25 mcg/hr: 1.22[b]	445
Methadone (Metadol)	1 mg 10 mg 25 mg 1 mg/mL 10 mg/mL	Tablet Oral liquid	0.1869 1.0213 1.7963 0.1187 0.4288	2.5 to 10 mg every 4 hours for first three to five days, then a fixed dose every 8 to 12 hours thereafter Maintenance dosage is highly individualized, but typically 50 mg to 60 mg per day[c]	Dose equivalence not established Typical dose[c] 50 to 60 mg daily: 3.59 to 4.61	1,311 to 1,684

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Cost of 90 MED ($)	Annual Drug Cost at 90 MED ($)
Tramadol (generics)	100 mg 200 mg 300 mg	ER tablet	0.7853[a] 0.9244[a] 1.2854[a]	Usual initial dose: 100 mg daily Maximum: 300 mg to 400 mg daily[d]	Equivalent to 540 mg, which exceeds guideline dosage 300 mg to 400 mg daily: 1.29 to 2.92[d]	469 to 1,067
Tramadol (Zytram XL)	75 mg 100 mg 150 mg 200 mg 300 mg 400 mg	ER tablet	0.9910[a] 1.2850[a] 1.8870[a] 2.4790[a] 3.5800[a] 4.7220[a]	Usual initial dose: 100 mg daily Maximum: 300 mg to 400 mg daily[d]	Equivalent to 540 mg, which exceeds guideline dosage 300 mg to 400 mg daily: 3.58 to 4.72[d]	1,306 to 1,724

CDR = CADTH Common Drug Review; CR = controlled release; ER = extended release; MED = morphine-equivalent dose.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2018) unless otherwise indicated and do not include dispensing fees. Morphine-equivalent dosage calculated according to *2017 Canadian Guidelines for Opioids for Chronic Non-Cancer Pain*,[8] unless otherwise indicated.

[a] Ontario wholesale price, IQVIA Delta PA (June 2018).[25]

[b] Patients using 60 mg to 134 mg of oral morphine daily should be converted to 25 mcg/hr fentanyl patch, fentanyl product monograph.[26]

[c] Typical maintenance dose is based on expert opinion.

[d] Note that product monograph specified dose should not exceed 300 mg daily, while *2017 Canadian Guidelines for Opioids for Chronic Non-Cancer Pain*[8] recommend not more than 400 mg daily.

Appendix 2: Summary of Key Outcomes

Table 8: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is Tapentadol Extended-Release Relative to Oxycodone CR?

Tapentadol ER vs. Oxycodone CR	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Manufacturer's base case: dominant (less costly, more effective) CDR base case: $45,847 per QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; ER = extended release; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.

Appendix 3: Additional Information

Table 9: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments Reviewer to provide comments if checking “no”	None		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking “poor”	None		

Table 10: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of global model/Canadian model done by the manufacturer

☐ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer

☒ Other (please specify) De novo model

	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

CDR = CADTH Common Drug Review.

Appendix 4: Other HTA Agencies

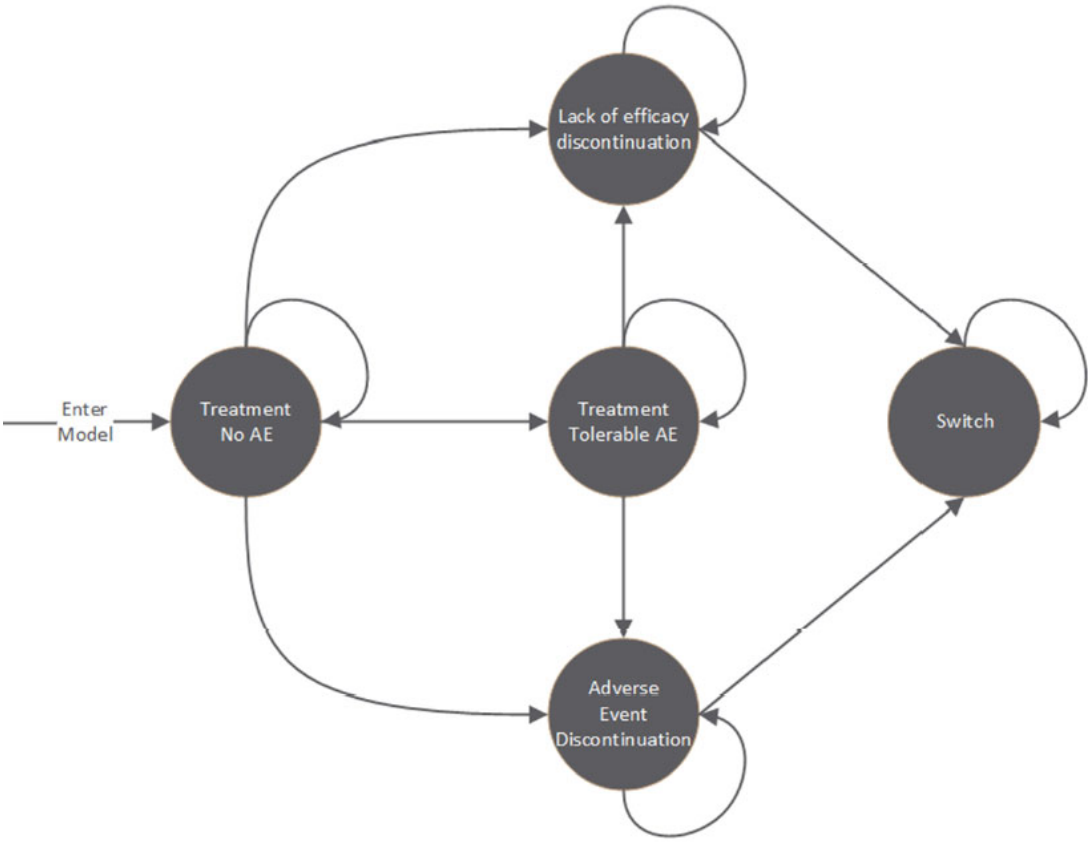
No other health technology assessment agencies have reviewed tapentadol extended-release for the requested CADTH Common Drug Review indication.

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer undertook a Markov state–transition model comparing tapentadol extended-release (ER) to long-acting oral formulations of oxycodone, hydromorphone, and morphine in adult patients with pain severe enough to require daily, continuous, long-term opioid treatment, and that is opioid responsive, and for which alternative treatment options are inadequate. Health states and the possible transitions between them are illustrated in Figure 1.

Figure 1: Manufacturer's Model Structure



Source: Manufacturer's economic submission, Figure 2.[3]

The manufacturer's health state utility weights were derived from a UK cost-utility analysis by Ikenberg et al.,[6] which mapped EuroQol 5-Dimensions questionnaire results from three randomized controlled trials comparing tapentadol ER with oxycodone controlled-release (CR) (i.e., Buynak, Afilalo, Lange).[4,9,10] The utility for each one-week cycle was calculated by dividing the annual utility (or annual utility draw for the probabilistic analysis) by 52 weeks (Table 11). As the model treated discontinuation due to adverse events (AEs) or lack of efficacy as transient, instantaneous states, the utility weights assigned for those health states do not impact the manufacturer's base-case results.

Table 11: Manufacturer's Modelled Utility Weights

Health State	Annual Utility (SD)	Utility per 1-Week Cycle
Treatment with no AEs	0.695 (0.016)	0.0133
Treatment with AEs	0.583 (0.007)	0.0112
Discontinuation due to AEs	0.503 (0.012)	0.0096[a]
Discontinuation due to lack of efficacy	0.405 (0.031)	0.0078[a]
Switch	0.422 (0.032)	0.00871

AE = adverse events; SD = standard deviation.

[a] Has no impact on results as these health states are instantaneous within the model.

Transition probabilities for tapentadol ER and oxycodone CR during the titration and maintenance phase (i.e., cycles 1 to 15) were derived using the proportion of patients experiencing treatment-emergent AEs, discontinuations due to AE, and discontinuations due to lack of efficacy in PAI-3011[4] and transformed into a weekly rate. Individual AE rates were similarly calculated. The proportion of patients using specific health care resources due to each AE were based on a US costing study comparing tapentadol ER with oxycodone CR for chronic non-cancer pain by Neil et al. 2013,[12] while the costs associated with those resources were based on the Ontario Schedule of Benefits for Physician Services for general practitioner visits,[11] the Ontario Case Costing Initiative for nausea and vomiting,[3] a Canadian Institute for Health Information survey on the cost of one day in the emergency room,[13] and Ontario Drug Benefit Formulary list prices for treatments for nausea, constipation, and pruritus (Table 12).[14] All states were associated with a $10.59 cost per week to account for regular general practitioner visits.

Table 12: Manufacturer's Base-Case Transition Probabilities and Incidence of Adverse Events

	Derived from PAI-3011		Derived Using OR vs. Tapentadol ER From Reimsma[a]		Associated Cost ($)
	Tapentadol ER % (SD)	Oxycodone CR % (SD)	Hydromorphone CR % (SD)	Morphine SR/ER % (SD)	
Transition Probabilities (Cycles 1 to 15 and Cycles 16 to 52)					**One-Time Cost**
Treatment without AEs	Starting health state				10.59 for all states per week
Treatment with AEs	0.755 (0.024)	0.848 (0.02)	0.783 (0.078)	0.817 (0.082)	91.80
DC due to AE	0.160 (0.021)	0.326 (0.026)	0.313 (0.031)	0.279 (0.028)	91.80
DC due to lack of efficacy	0.041 (0.011)	0.021 (0.008)	0.026 (0.003)	0.025 (0.002)	91.80
AE Incidence (Cycles 1 to 15 and Cycles 16 to 52)					**One-Time Cost**
Constipation	0.138 (0.019)	0.268 (0.025)	0.33 (0.033)	0.358 (0.036)	46.88[b]
Nausea	0.201 (0.022)	0.345 (0.027)	0.349 (0.035)	0.305 (0.03)	130.64
Vomiting	0.091 (0.016)	0.192 (0.022)	0.204 (0.02)	0.294 (0.029)	130.64
Dizziness	0.119 (0.018)	0.171 (0.021)	0.064 (0.006)	0.113 (0.011)	6.23
Pruritus	0.072 (0.015)	0.168 (0.021)	0.168 (0.021)	0.168 (0.021)	5.07
Diarrhea	0.06 (0.013)	0.024 (0.009)	0.024 (0.009)	0.024 (0.009)	0.00
Fatigue	0.066 (0.014)	0.073 (0.015)	0.073 (0.015)	0.073 (0.015)	0.00
Insomnia	0.041 (0.011)	0.076 (0.015)	0.076 (0.015)	0.076 (0.015)	0.00
Somnolence	0.132 (0.019)	0.162 (0.021)	0.18 (0.018)	0.235 (0.024)	3.47
Headache	0.198 (0.022)	0.168 (0.021)	0.168 (0.021)	0.168 (0.021)	0.00
Dry mouth	0.082 (0.015)	0.037 (0.011)	0.037 (0.011)	0.037 (0.011)	0.00

AE = adverse event; CR = controlled release; DC = discontinuation; ER = extended release; OR= odds ratio; SD = standard deviation; SR = sustained release; vs. = versus.

[a] Odds ratios not available for pruritus, diarrhea, fatigue, insomnia, headache, and dry mouth, assumed equal to oxycodone.

[b] Chronic constipation was also associated with a weekly cost of $1.06 per week.

Source: Manufacturer's pharmacoeconomic model.[3]

Table 13: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Patient characteristics are not explicitly considered.	Unclear. Patient age, gender, or other health or demographic indicators may impact effectiveness or quality of life assumptions.
Efficacy	PAI-3011 RCT[4] for tapentadol ER vs. oxycodone CR, assumed to be linear and extrapolated from 15 weeks to the entire 52 week time horizon. Odds ratios vs. tapentadol from Riemsma NMA[7] used to calculate relative transition probabilities for long-acting hydromorphone and morphine.	Per week transition probabilities derived by transforming total proportion of patients experiencing TEAEs and discontinuations during the 15-week PAI-3011 trial to weekly probabilities. The approach to transform transition probabilities assumes a linear rate, which is not supported by trial data itself, and is not appropriate when extracting over a longer time horizon. Reimsma NMA combines long-acting and immediate-release formulations of both tapentadol and comparators. Treatment effects for long-acting hydromorphone and morphine were calculated by applying odds ratios from the NMA to tapentadol-related probabilities from a single RCT. This approach fails to account for the potential differences in the baseline characteristics, severity and type of disease, drug formulations, dosages, or length of therapy between the studies in the NMA and the tapentadol ER clinical study in question.
Natural history	Time horizon of one year. All patients assumed to instantaneously switch upon efficacy failure or intolerable AEs in base case, assumption.	Likely insufficient to capture all long-term outcomes subsequent to the choice of one opioid over another, given the chronic nature of the condition. Unlikely to reflect clinical practice according to the expert consulted by CDR. Patients would need time to switch given the complexity and possibility of withdrawal symptoms. According to the clinical expert consulted on this review and clinical practice guidelines, patients with AEs would likely have their doses lowered upon the development of AEs rather than switching. Patients who have lost efficacy may be tapered and discontinued from opioids or switched to another opioid. However, given the model's short duration, it did not adequately capture the impact of losing efficacy while switching treatment.
Utilities	Derived from a UK cost-utility analysis[6] using mapped EQ-5D indices from three tapentadol RCTs of osteoarthritis and lower back pain patients using unspecified methodology. Three of four health states use similar definitions to the source model; however the absorbing switch state used the utility for fourth-line therapy after three failures.	Appropriate, with the exception of the use of 0.422 for the switch utility, which was the baseline utility measurement of the clinical trials and represented the utility value for individuals in the fourth-line therapy health state in the UK CUA.[6] Patients who switched to another opioid and remained on therapy for the duration of the model should not be presumed to derive no benefit if they are still on opioid treatment.
Adverse events	Rates for tapentadol ER and oxycodone CR were derived from PAI-3011;[4] those of long-acting hydromorphone and morphine were calculated using odds ratios versus	Model considered the following adverse events: constipation, nausea, vomiting, dizziness, pruritus, diarrhea, fatigue, insomnia, somnolence, headache, and dry mouth. Per week event rates were transformed from total proportion

Data Input	Description of Data Source	Comment
	tapentadol from the Reimsma NMA,[5] where available, or assumed equal to oxycodone CR where data were not available.	of patients experiencing each AE in PAI-3011 during 15 weeks of the trial and extrapolated to the entire year. This was considered inappropriate, as event rates did not happen linearly within the trial and thus cannot be extrapolated beyond the 15 weeks of the trial period.
Mortality	Not incorporated due to short time horizon	Acceptable.
Resource Use and Costs		
Drug	Doses are weighted based on IQVIA Pharmastat[27] market share data (National for tapentadol ER, Ontario for comparators) over an unspecified time period.	Inappropriate; doses should be based on those used in the trials from which the modelled efficacy and safety data came. Relative efficacy and safety at real-world opioid doses is unknown.
Administration	Not included.	Appropriate.
AEs	Proportion of patients utilizing resources were from Neil 2013,[12] while costs were derived from the Ontario SoB for Physicians Services for GP visit, the OCCI for nausea and vomiting, the ODB Formulary for drug treatments, [14] and Dawson & Zinck for ER costs.[13]	Acceptable. AEs were considered one-time events with the exception of chronic constipation.
Health state or event-specific costs	Patients were assumed to visit a GP every 12 weeks for all health states. Switching to another medication due to discontinuation triggered an additional two GP visits.	Deemed appropriate by clinical expert.

AE = adverse event; CDR = CADTH Common Drug Review; CR = controlled release; CUA = cost-utility analysis; EQ-5D = EuroQol 5-Dimensions questionnaire; ER = extended release; GP = general practitioner; NMA = network meta-analysis; OCCI = Ontario Case Costing Initiative; ODB = Ontario Drug Benefit; RCT = randomized controlled trial; SoB = schedule of benefits; TEAE = treatment-emergent adverse events; vs. = versus.

Table 14: Manufacturer's Key Assumptions

Assumption	Comment
Baseline characteristics of cohort in the model match the patient characteristics in PAI-3011 and in the NMA	Inappropriate. Important patient characteristics were not reported within the Riemsma NMA (such as previous opioid use) and there was considerable heterogeneity between patient populations in the studies.[5]
Mortality not included	Acceptable, given the short time horizon.
NMA data, including IR formulations can inform relative efficacy and safety of long-acting opioids, hydromorphone, and morphine, compared with tapentadol ER	Inappropriate. CDR clinical review team critically appraised the NMA informing the relative treatment effects of hydromorphone and morphine. The NMA used by the manufacturer to incorporate efficacy data for hydromorphone and morphine combines long-acting and immediate-release formulations; therefore, the relative effect of tapentadol ER to long-acting opioid comparators is unclear. To incorporate treatment effects for long-acting hydromorphone and morphine, the approach taken involved incorporating odds ratios based on the NMA (i.e., indirect evidence) and direct evidence from an individual study rather than considering the relative efficacy and safety incorporating all comparators in a single NMA. Given this limitation, CDR excluded long-acting hydromorphone and morphine from the base-case analysis, and conducted an exploratory analysis where both hydromorphone CR and morphine SR/ER were assumed to have the same efficacy and safety inputs as oxycodone CR (i.e., derived from the oxycodone CR results of the PAI-3011 trial), consistent with the manufacturer's assumptions where NMA data were not available.
Doses are derived from utilization data	Inappropriate. Although utilization data, if appropriately incorporated into the economic evaluation, may better reflect real-world costs than calculating drug costs based on the doses used in RCTs, the efficacy of each therapy as observed in clinical trials can no longer be presumed to apply, as dosages are no longer similar, and the population using opioids is unknown. Calculating treatment costs based on the doses reported in a Canadian utilization database, which differed considerably from the doses observed in the PAI-3011 trial, greatly increases uncertainty in the modelled treatment effect relative to the assumed costs of therapy. Addressed as a limitation to ensure costs and efficacy reflect the same population within the model.
Discontinuation states are transient	Likely inappropriate, per clinical expert. Although both discontinuation health states have utility values assigned to them, the model appears to consider them transient. Despite the one-week cycles, no patients are ever reported as being in either discontinuation state, thus the assigned utilities are never applied. In reality, it is likely that discontinuation would not be instantaneous as patients would need to schedule an appointment to see their provider and may experience a lower QoL in the meantime before their pain management is adjusted in response to either a lack of efficacy or intolerable adverse events.
Patients who have switched remain in the switch health state for the remainder of the model at a low utility	Inappropriate. While the absorbing switch state is acceptable given the short time horizon, at a utility of 0.422 (source described previously), patients experience a lower quality of life than they did on their previous medication with AEs or while discontinuing their medication due to AEs. Presumably a patient whose QoL caused them to discontinue one therapy would also discontinue the new therapy if their QoL was even lower, however patients continue to accrue the cost of switched therapy in the model. This unrealistically biases the QoL results toward whichever medication has the least discontinuations, which in the base case is tapentadol ER. In CDR reanalyses, patients who switched to a new therapy were assumed to have the same QoL post-switch as

Assumption	Comment
	patients with tolerable AEs (i.e., the state with the lowest QoL where patients remained on their current therapy), while a sensitivity analysis explored a utility consistent with more severe baseline pain and treatment with tolerable AEs.
All patients switch to a new therapy immediately upon discontinuation due to lack of efficacy or adverse events	Unrealistic, according to the clinical expert consulted by CDR; patients are only switched when necessary, and after dose escalation, in the case of loss of efficacy, or reductions and concomitant medications are tried in the case of intolerable AEs. In the case of a complete lack of efficacy (an early discontinuation due to lack of efficacy), the patient might be presumed to be non-responsive to opioids and also not be switched. CDR included sensitivity analyses where the proportion of patients who discontinued due to a lack of efficacy and due to intolerable AEs, were assumed to be 90% and 0%, respectively, to align with the manufacturer's similar scenario analysis, and 50% and 80%, to explore CDR's clinical expert's conclusion.
AEs assumed to occur at same rate throughout model	Inappropriate, as discontinuations did not occur at the same rate over the course of the PAI-3011 trial[4] (most occurred early, especially those due to AEs), nor did the CUA on which the utilities are based use a linear discontinuation rate.[6] CDR was unable to adequately model decreasing discontinuation rates over time, due to inflexibility in the model, but considered incorporating the model option to use the lower discontinuation rates derived from the Buynak 2015 extension study[18] and a Cochrane review [20] for weeks 16 to 52 to be preferable to extending the mean PAI-3011 discontinuation rates over the entire time horizon.
Average cost of four opioids used as cost of "switched" therapy	Inappropriate. A random draw proportion or a flat average of the other three comparator costs would be a more appropriate choice. Reanalyses by CDR consider the average cost of the other three opioids when a patient switches from their first.

AE = adverse event; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; ER = extended release; IR = immediate release; NMA = network meta-analysis; QoL = quality of life; SR = sustained release.

Manufacturer's Results

See Table 2 for manufacturer's overall results. A breakdown of individual costs can be found in Table 15.

Table 15: Cost Breakdown of Manufacturer's Deterministic Base-Case Results

Comparator	Initial Opioid ($)	Post-Switch Opioid ($)	Resources ($)	AEs ($)	Total Cost ($)
Tapentadol ER	1,049	428	599	131	2,207
Oxycodone CR	1,296	678	621	194	2,790
Hydromorphone CR	658	662	620	214	2,154
Morphine SR/ER	341	609	616	249	1,815
Differences					
Tapentadol ER vs. oxycodone CR	–248	–250	–22	–63	–583
Tapentadol ER vs. hydromorphone CR	390	–235	–20	–82	52
Tapentadol ER vs. morphine SR/ER	707	–182	–16	–118	391

AEs= adverse events; CR = controlled release; ER = extended release; SR = sustained release; vs. = versus.

CDR's Reanalyses

The main CADTH Common Drug Review (CDR) reanalyses can be found in Table 3, Table 4, and Table 5.

In order to explore uncertainty in the assumptions made in the CDR exploratory analysis, additional sensitivity analyses were conducted and are reported in Table 16. This included assuming:

- dose inputs from alternate time points from PAI-3011[4] (sensitivity analyses 1 and 2)
- a lower utility of 0.535 for the switch health state, based on the utility weight for patients with more severe pain at baseline who were on treatment with tolerable AEs[6] (sensitivity analysis 3)
- no reduction in morphine-equivalent dose (MED) when switching from one opioid to another (sensitivity analysis 4)
- that the proportions of patients who switched to an alternate opioid after discontinuing due to a lack of efficacy or intolerable AEs were 90% and 0%, respectively, consistent with one of the manufacturer's scenario analyses and based on their clinical expert's opinion (sensitivity analysis 5)
- that the proportions of patients who switched to an alternate opioid after discontinuing due to a lack of efficacy or intolerable AEs were 50% and 80%, respectively, which is an exploration of the opinion provided by the clinical expert consulted by CDR. According to this clinical expert, many patients who had discontinued due to a lack of efficacy would stop opioid therapy, whereas more of the patients who had discontinued due to an AE would try an alternate opioid (analysis 6).

CDR's scenario analysis was sensitive to the use of a lower utility for the switched state, which lowered the incremental cost-utility ratio of tapentadol ER relative to all three comparators (sensitivity analysis 3, Table 16), as well as to the manufacturer's assumption regarding the proportion of patients switching opioid therapy (sensitivity analysis 5). However, the substitution of doses from other time points in the PAI-3011 trial for tapentadol ER and oxycodone CR with MED conversions for long-acting morphine and hydromorphone (sensitivity analyses 1 and 2) did not substantially alter results, nor did assuming that no reduction in MED would occur when patients switched to a new opioid (sensitivity analyses 4), nor in assuming that only half of patients who discontinued due to a lack of efficacy continued onto a new opioid, while 80% of those discontinuing due to AEs would switch to a new opioid (sensitivity analysis 6).

Table 16: CDR Sensitivity Analyses Around CDR Exploratory Analysis

	Scenario	Treatments	QALYs	Cost ($)	ICUR ($ Per QALY) Tapentadol ER vs. Comparator	Sequential ICUR ($ Per QALY)
	CDR exploratory analysis, with long-acting hydromorphone and morphine inputs equivalent to oxycodone CR	Morphine SR/ER	0.601	1,364	107,536	Reference
		Tapentadol ER	0.611	2,394	**Reference**	**107,536**
		Oxycodone CR	0.601	1,942	45,714	Dominated by morphine
		Hydromorphone CR	0.601	1,754	69,009	Dominated by morphine
1	**Tapentadol ER (313 mg) and oxycodone CR (53 mg) dosage based on overall average during PAI-3011; long-acting hydromorphone and morphine converted by MED from oxycodone CR dose[4]**	Morphine SR/ER	0.601	1,163	92,199	Reference
		Tapentadol ER	0.611	2,065	**Reference**	**92,199**
		Oxycodone CR	0.601	1,594	48,105	Dominated by morphine
		Hydromorphone CR	0.601	1,432	64,546	Dominated by morphine
2	**Tapentadol ER (357 mg) and oxycodone CR (67 mg) dosage based on average first two weeks of maintenance during PAI-3011; long-acting hydromorphone and morphine converted by MED from oxycodone dose[4]**	Morphine SR/ER	0.601	1,281	98,271	Reference
		Tapentadol ER	0.611	2,241	**Reference**	**98,271**
		Oxycodone CR	0.601	1,823	42,756	Dominated by morphine
		Hydromorphone CR	0.601	1,621	63,403	Dominated by morphine
3	**Switch utility assumed to be equivalent to severe pain subgroup treatment with AEs utility from Ikenberg (0.535)[6]**	Morphine SR/ER	0.585	1,335	64,002	Reference
		Tapentadol ER	0.601	2,384	**Reference**	**64,002**
		Oxycodone CR	0.584	1,942	26,915	Dominated by morphine
		Hydromorphone CR	0.585	1,711	41,060	Dominated by morphine
4	**No dose reduction assumed when switching to a second opioid**	Morphine SR/ER	0.601	1,337	106,132	Reference
		Tapentadol ER	0.611	2,378	**Reference**	**106,132**
		Oxycodone CR	0.601	1,937	44,983	Dominated by morphine
		Hydromorphone CR	0.601	1,711	67,777	Dominated by morphine
5	**Long-acting hydromorphone and morphine inputs derived using Reimsma odds ratios where available**	Morphine SR/ER	0.603	1,399	133,451	Reference
		Hydromorphone CR	0.605	1,733	117,262	183,536
		Tapentadol ER	0.611	2,392	Reference	117,262
		Oxycodone CR	0.601	1,943	45,847	Dominated by morphine and hydromorphone
6	**90% of those discontinuing due to lack of efficacy assumed to switch, 0% of those with intolerable adverse events**	Morphine SR/ER	0.575	1,337	47,078	Reference
		Tapentadol ER	0.597	2,383	Reference	47,078
		Oxycodone CR	0.575	1,932	20,317	Dominated by

	Scenario	Treatments	QALYs	Cost ($)	ICUR ($ Per QALY) Tapentadol ER vs. Comparator	Sequential ICUR ($ Per QALY)
						morphine
		Hydromorphone CR	0.575	1,710	30,288	Dominated by morphine
7	**50% of those discontinuing due to lack of efficacy assumed to switch, 80% of those with intolerable adverse events**	Morphine SR/ER	0.594	1,334	101,707	Reference
		Tapentadol ER	0.604	2,392	Reference	101,707
		Oxycodone CR	0.594	1,943	43,196	Dominated by morphine
		Hydromorphone CR	0.594	1,720	64,894	Dominated by morphine

AE = adverse events; CDR = CADTH Common Drug Review; CR= controlled release; ER = extended release; ICUR = incremental cost-utility ratio; MED = morphine-equivalent dose; QALY = quality-adjusted life-year; SR = sustained release; vs. = versus.

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