CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Buprenorphine extended-release injection (Sublocade)

(Indivior Canada, Ltd.)

Indication: For the management of moderate-to-severe opioid use disorder in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product.

Service Line:	CADTH Common Drug Review
Version:	Final
Publication Date:	July 2019
Report Length:	33 Pages

CADTH

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.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

Tables

Figure

Abbreviations

AE	adverse event
BUP-ER	buprenorphine extended-release
HR	hazard ratio
ICUR	incremental cost-utility ratio
ITC	indirect treatment comparison
LST	low-serum testosterone
OAT	opioid agonist therapy
OUD	opioid use disorder
QALY	quality-adjusted life-year
WTP	willingness-to-pay

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Buprenorphine extended-release injection (BUP-ER; Sublocade)
Study Question	From the perspective of a Canadian publicly funded health care payer, what is the cost-effectiveness of BUP-ER compared with generic buprenorphine/naloxone, and methadone for the treatment of moderate-to-severe opioid use disorder (OUD) in adults?
Type of Economic Evaluation	Cost-utility analysis (CUA)
Target Population	Adult patients with moderate-to-severe OUD
Treatment	300 mg for the first two months, followed by 100 mg or 300 mg BUP-ER every 28 days in patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product
Outcome	QALYs
Comparators	Generic buprenorphine/naloxone Methadone
Perspective	Canadian public health care payer
Time Horizon	5 years
Results for Base Case	In a sequential analysis: • 100 mg BUP-ER was associated with an incremental cost-utility ratio (ICUR) of $61,165 per QALY gained compared with generic buprenorphine/naloxone. • 300 mg BUP-ER was associated with an ICUR of $190,242 per QALY gained compared with 100 mg BUP-ER. • Methadone was dominated by generic buprenorphine/naloxone.
Key Limitations	• Uncertainty in the comparative clinical evidence leads to corresponding uncertainty in the results of the economic analysis. Comparative treatment effects were informed by the manufacturer's indirect treatment comparison and through naive comparison from observational studies. The indirect treatment comparison involved studies with sparse baseline data without assessment of inconsistency or sufficient adjustment for potential confounders. Further, the patient population in the trials may not be consistent with the Canadian population. • The clinical trial for BUP-ER (Study 13-0001) recruited a selectively more stable patient population. The potential cost-effectiveness of BUP-ER in a less stable population is unknown. • Long-term outcomes were not adequately captured in the model, resulting in uncertainty in the long-term cost-effectiveness. • Estimation of model parameters did not reflect real-world clinical management and patient experience with OUD. This included applying a treatment-specific proportion of patients using opioids at baseline; assuming a constant month-to-month proportion of illicit opioid use based on aggregate estimates; overestimating the cost of non-fatal overdose; specific to methadone, the number of fatal overdoses could exceed the number of all-cause deaths; and, underestimating the duration of opioid agonist therapy. Combined, these biases generally favoured BUP-ER.

CDR Estimates	• To better reflect the clinical pathway of OUD in Canada, CADTH assumed all patients were using opioids at the start of the model, incorporated weekly urinalysis data to model patients using opioids while on OAT, reduced non-fatal overdose cost and fatal overdose rates, and delayed when abstinence could occur until at least one year after treatment. Furthermore, CADTH considered BUP-ER as described in the recommended dosage schedule (300 mg injection per month for the first two months followed by monthly 100 mg injections) as a single treatment comparator rather than separately as 100 mg and 300 mg treatments. • In the CADTH base case, BUP-ER was dominated by generic buprenorphine/naloxone (associated with greater expected costs and fewer expected QALYs). • A price reduction of at least 73% is required for BUP-ER to be the cost-effective intervention at a willingness-to-pay threshold of $50,000 per QALY gained.

BUP-ER = buprenorphine extended-release injection; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; ICUR = incremental cost-utility ratio; OAT = opioid agonist therapy; OUD = opioid use disorder; QALY = quality-adjusted life-year.

Drug	Buprenorphine extended-release injection (Sublocade)
Indication	For the management of moderate-to-severe opioid use disorder in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product. Sublocade should be used as part of a complete treatment plan that includes counselling and psychosocial support. Sublocade must only be administered subcutaneously in the abdominal region by a health care provider.
Reimbursement Request	As per indication. Sublocade should be used as part of a complete treatment plan that includes counselling and psychosocial support. Sublocade must only be administered subcutaneously in the abdominal region by a health care provider.
Dosage Forms	Solution for subcutaneous injection, 100 mg/0.5 mL and 300 mg/1.5 mL
NOC Date	November 21, 2018
Manufacturer	Indivior Canada Ltd.

Executive Summary

Background

Buprenorphine extended-release injection (BUP-ER; Sublocade) is indicated for the management of moderate-to-severe opioid use disorder (OUD) in adult patients who have been inducted and clinically stabilized on the equivalent of 8 mg per day to 24 mg per day of transmucosal buprenorphine-containing product in combination with counselling and psychosocial support.[1] BUP-ER is available as 100 mg and 300 mg single-use pre-filled syringe at a submitted price of $550 for either dose. The recommended dosage schedule is 300 mg injection per month for the first two months followed by maintenance on monthly 100 mg injections.[1] The monthly maintenance dose may be increased to 300 mg if the patient does not demonstrate satisfactory response and can tolerate the 100 mg dose, although the 300 mg maintenance dose in clinical trials did not provide additional efficacy compared with the 100 mg dose and was associated with a higher incidence of adverse events and study discontinuations.[1]

The manufacturer submitted a cost-utility analysis comparing 100 mg and 300 mg BUP-ER (i.e., 300 mg BUP-ER every four weeks for two doses followed by 100 mg or 300 mg BUP-ER monthly) to oral methadone and generic buprenorphine/naloxone in adults with moderate-to-severe OUD.[2] The analysis was conducted from the Canadian publicly funded health care payer perspective over a five-year time horizon, with future costs and benefits discounted at 1.5%. The model structure defined seven health states that reflected the status of illicit opioid use and opioid agonist therapy (OAT) use (i.e., “OAT, not using,” “OAT, using on top,” “abstinent” [reflecting off treatment, not using], and “off treatment, using”), long-term relapse health states (i.e., “post-abstinent” and “subsequent treatment”), and death. At the start of the model, patients entered either of the two OAT health states (i.e., “OAT, not using” and “OAT, using on top”). The proportion of patients in each health state at

baseline was treatment-dependent and remained constant over the course of treatment. Patients who remained on OAT had a higher probability of achieving abstinence (i.e., entering the "abstinent" health state) while patients who dropped out of OAT entered the "off treatment, using" health state where they were assumed to continue using opioids illicitly. To model relapse and return to OAT, after a fixed period in the off treatment health states (i.e., "abstinent" and "off treatment, using"), patients could transition to the long-term relapse health states ("post-abstinent" and "subsequent treatment," respectively). The key clinical outcomes in the model were proportion using opioids and time to treatment dropout, both of which were derived from the manufacturer-submitted indirect treatment comparison (ITC).[3] Input from key opinion leaders was used to define the long-term relapse health states that reflected a composite health state defined by opioid use and OAT status. In the manufacturer's base case, adverse events were not modelled, with the exception of treatment-specific overdose, which could be fatal or non-fatal. Treatment-specific mortality was further incorporated based on a 10-year Australian retrospective study.[4] Health state utilities were based on a UK study,[5] except for abstinence, which was assumed to reflect the utility value of a general Canadian population.[6] Health care resource use and cost inputs were primarily informed by the manufacturer's commissioned chart review of Canadian OUD practices and public pricing databases.[7]

In the manufacturer's probabilistic sequential analysis, 100 mg and 300 mg BUP-ER doses were considered separately (i.e., 300 mg per month in the first two months of maintenance followed by either 100 mg or 300 mg monthly). The manufacturer reported that the incremental cost-utility ratio of 100 mg BUP-ER was $61,165 per quality-adjusted life-year (QALY) gained compared with generic buprenorphine/naloxone, while the incremental cost-utility ratio of 300 mg BUP-ER was $190,242 per QALY gained compared with 100 mg BUP-ER. At a willingness-to-pay threshold of $50,000 per QALY, 100 mg and 300 mg BUP-ERs were associated with, respectively, a 25% and 5% probability of being the most likely cost-effective intervention compared with the other comparators.

Summary of Identified Limitations and Key Results

CADTH identified several key limitations with the manufacturer's economic evaluation. Relative treatment effects were uncertain. The comparative clinical evidence of BUP-ER was modelled based on Study 13-0001, the manufacturer-submitted ITC, and observational studies. Overall, the ITC for proportion on top use and time to treatment dropout were informed by studies with sparse baseline data. Consistency was not assessed and sufficient adjustments were not made to correct for potential confounders. Observational studies used in the model were also not adequately adjusted for potential confounders. Furthermore, there are concerns regarding the generalizability of the economic findings to the target population as treatment outcomes for BUP-ER were primarily based on Study 13-0001, which selectively recruited a more stable population, and the patient population in the trials that informed the ITC and the observational studies may not reflect the Canadian population.

Furthermore, the approach taken to model long-term outcomes did not adequately reflect the remitting and relapsing nature of the condition as long-term relapse health states was modelled as a weighed health state that remained constant over time.

The manufacturer's assumptions for the parameter values in the economic model did not adequately reflect the clinical pathway and management of OUD. Specifically, concerns were noted on four key aspects: illicit opioid use, overdose, health care resource use, and duration of the treatment phases (i.e., induction, stabilization, and maintenance). The

proportion of patients using opioids illicitly on top of OAT ("using on top") differed by treatment at the start of the model despite the clinical expectation that the population indicated for treatment would all be using illicit opioids at baseline. Over time, the proportion of patients using opioids while on OAT also remained fixed to the baseline proportions. This proportion reflected a summary measure of the proportion of positive urinalysis test collected over the study duration, and may not capture the variability in how monthly proportion of on top use may change with longer treatment exposure. In addition, the cost of non-fatal overdose was overestimated by assuming that it would be managed in an in-patient setting, which would be rare according to the clinical expert consulted by CADTH. Specific to methadone, inconsistencies were noted as the number of fatal overdoses could exceed the number of all-cause deaths estimated within a modelled cycle. Finally, according to the clinical expert consulted by CADTH, the duration of each phase of treatment did not always reflect clinical practice. Specifically, the average duration of OAT was underestimated by allowing patients to successfully complete OAT and become abstinent starting as early as after the stabilization phase (i.e., one month of OAT). This is in contrast to the experience of the clinical expert who noted that patients would remain stable on OAT for at least a year before entering the "abstinent" health state. Overall, the choice of these model parameters favoured BUP-ERs by reducing drug costs, increasing the expected costs of the comparators, and improving the clinical benefits of BUP-ERs.

The CADTH reanalysis considered BUP-ER according to the recommended dosage schedule in the product monograph[1] rather than considering 100 mg and 300 mg doses as separate treatment options. The CADTH reanalyses of the manufacturer's model further revised the OUD clinical pathway to better reflect Canadian practice. This included the following changes: all patients were assumed to be using opioids on top at baseline; the proportion of patients using on top while on treatment varied weekly based on the manufacturer's regression analysis of weekly urinalysis data; ensuring the validity of values by selecting fatal overdose rates from the same study that reported treatment-specific all-cause mortality rates; assuming non-fatal overdoses would be managed in outpatient care; and permitting patients to progress to the "abstinent" health state only after at least one year of OAT. CADTH could not address the limitations associated with the manufacturer's submitted ITC that still informed time to treatment dropout in the CADTH reanalyses.

Conclusions

In adults with moderate-to-severe OUD, CADTH estimated that BUP-ER would be dominated by generic buprenorphine/naloxone (i.e., produces fewer QALYs at a higher cost). Based on CADTH reanalysis, a price reduction of more than 73% would be required for BUP-ER to be the cost-effective intervention at a willingness-to-pay threshold of $50,000 per QALY gained.

It should be noted that considerable uncertainty remains on the comparative treatment effects between BUP-ER and generic buprenorphine/naloxone and methadone; as such, the interpretation of the economic results warrants careful consideration. The cost-effectiveness of BUP-ERs in less stable patients (i.e., more comorbidities) remains unknown. The average drug cost per month during the maintenance phase is estimated to be $550 for BUP-ER, which is greater than generic buprenorphine/naloxone ($72 to $77).

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's PE Submission

The manufacturer submitted a cost-utility analysis that compared two different doses of buprenorphine extended-release injection (BUP-ER; 100 mg and 300 mg) with two other opioid agonist therapies (OATs; generic methadone and buprenorphine/naloxone) in adults with moderate-to-severe opioid use disorder (OUD).[2] The model was conducted from the perspective of a Canadian publicly funded health care payer under a five-year time horizon with costs and clinical outcomes (quality-adjusted life-years [QALYs]) discounted at 1.5% per annum. A cohort of patients with moderate-to-severe OUD who had a mean age of 39.7 years and was 33.8% women was modelled based on the patient characteristics from Study 13-0001, which investigated the efficacy of BUP-ERs compared with placebo.[8]

The submission was based on a Markov cohort state-transition model with monthly cycles. Seven health states were defined that reflected the status of first-line OAT and illicit opioid use (specifically: "OAT, using on top" [i.e., on OAT, using opioids], "OAT, not using" [i.e., on OAT, not using opioids], "abstinent" [i.e., not on OAT, not using opioids], and "off treatment, using" [i.e., not on OAT, using opioids]), long-term relapse health states ("post-abstinent" and "subsequent treatment"), and death (Figure 1). Detailed descriptions of each health state can be found in Table 9. At the start of the model, patients entered either of the two treatment health states (i.e., "OAT, using on top" if concurrently using illicit opioid, or "OAT, not using" if not concurrently using illicit opioid) to begin OAT induction. The proportion of patients with illicit opioid use at baseline was treatment-dependent and was informed by either the manufacturer's submitted indirect treatment comparison (ITC) for BUP-ER and buprenorphine/naloxone or based on a single study (unadjusted) for methadone.[9] While on OAT, the relative proportion of patients using illicit opioids was assumed to match baseline values and remained constant over time. The proportion of patients remaining on OAT at the end of each cycle reflected the rates of treatment retention reported in the manufacturer's ITC,[3] with those dropping out transitioning to the "off treatment, using" health state. Patients who remained on treatment were assumed to have a higher probability of achieving abstinence with the transitions to the "abstinent" health state informed by a Public Health England report.[10] A relative risk of abstinence in patients who did not use illicit opioids versus those who used illicit opioids while on treatment was estimated by expert opinion.

The following approach was taken to model long-term relapse. For patients who reached the "abstinent" health state, the manufacturer assumed that 70% of abstinent patients would relapse after three months and enter the "post-abstinent" health state. For patients who reached the "off treatment, using" health state, 80% who were using illicit opioids would seek treatment after two months and enter the "subsequent treatment" health state. Both of the long-term relapse health states ("post-abstinent" and "subsequent treatment") reflected composite health states. Specifically, these states were comprised of a weighted average of four health states: "OAT, not using," "OAT, using on top," "abstinent," and "off treatment, using." The proportion of patients in each of these health states did not differ by treatment and were assumed to remain constant throughout the modelled time horizon. Expert opinion was extensively used to inform model parameters for these states. Patients receiving OAT in the "post-abstinent" and "subsequent treatment" states were assumed to have an equal chance of receiving 100 mg BUP-ER, buprenorphine/naloxone, or methadone regardless of the prior OAT they were on.

Although adverse events (AEs) were not modelled in the base case, state- and treatment-dependent fatal and non-fatal overdose rates were modelled for OAT and "off treatment, using" health states based on a 10-year Australian retrospective study.[4] Patients could also transition to death at each cycle within the model and mortality was assumed to be health state– and treatment-dependent according to the meta-analysis by Sordo et al.[11] Treatment benefits were therefore captured by both a decline in mortality and an improvement in health-related quality of life.

Health state utilities were informed by a utility valuation study based on 22 UK residents,[5] except for the "abstinent" health state in which patients were assumed to have the equivalent quality of life as general Canadians.[6] Furthermore, non-fatal overdose was assumed to incur a health utility decrement equivalent to a week-long depressive disorder episode.[12]

Direct medical costs, including drug acquisition, dispensing, administration, and monitoring, were considered for the induction/stabilization and maintenance phases separately. Furthermore, state- and treatment-dependent health care resource utilization (i.e., physician office visit, psychosocial visit, urinalysis, and blood test) were modelled based on the manufacturer's review of the charts of Canadian patients with OUD.[7] "Off treatment, using" and "abstinent" health states were assumed to not incur any health care resource use based on expert opinion. Costs estimates were obtained from provincial formularies,[13] databases,[14] or the manufacturer's chart review.[7] The manufacturer did not explicitly note the year in which costs were considered.

Manufacturer's Base Case

The manufacturer's base-case probabilistic results are presented in Table 2 with the 100 mg and 300 mg BUP-ER doses considered separately. In a sequential analysis, BUP-ER 100 mg was found to produce an incremental 0.09 QALYs at an additional cost of $5,676 compared with generic buprenorphine/naloxone, resulting in an incremental cost-utility ratio of $61,165 per QALY gained. BUP-ER 300 mg was associated with 0.01 additional QALYs at an additional cost of $1,121 compared with the 100 mg BUP-ER, with an incremental cost-utility ratio of $190,242 per QALY gained. At a willingness-to-pay (WTP) threshold of $50,000 per QALY, 100 mg BUP-ER had a 25% probability and 300 mg BUP-ER had a 5% probability of being the most likely cost-effective intervention compared with the other comparators.

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

	Total Costs ($)	Incremental Cost ($)[a]	Total QALYs	Incremental QALYs[a]	Incremental Cost per QALY ($)
BUP/NAL	23,926		3.40		
Methadone	24,424	498	3.38	– 0.02	Dominated
100 mg BUP-ER	29,602	5,676	3.49	0.09	61,165
300 mg BUP-ER	30,723	1,121	3.50	0.01	190,242

BUP-ER = buprenorphine extended-release injection; BUP/NAL = generic buprenorphine/naloxone; QALY = quality-adjusted life-year.

[a] Derived from the manufacturer's submission.[2]

Summary of the Manufacturer's Sensitivity Analyses

Parameter uncertainty was addressed through the use of probabilistic analysis while methodological and structural uncertainties were addressed using scenario analyses (i.e., time horizon, perspective, discount rate, alternate distribution for treatment retention curve, incorporation of diversion). Specifically, the manufacturer's scenario analyses were reported as pairwise comparisons between BUP-ER and either generic buprenorphine/naloxone or methadone.

Based on the manufacturer's scenario analyses, the results of the pharmacoeconomic model were found to be most sensitive to the inclusion of low-serum testosterone as an AE that would be associated with both costs and annual utility decrements of 0.06 (reflective of impotence and erectile dysfunction).[15] Specifically, the manufacturer assumed that low-serum testosterone is an AE that occurs more frequently in patients treated with methadone. CADTH replicated these analyses to report sequential results. The incremental cost-utility ratio for BUP-ER 100 mg was found to be $31,963 per QALY gained compared with generic buprenorphine/naloxone, while the incremental cost-utility ratio for BUP-ER 300 mg was found to be $153,881 per QALY gained compared with BUP-ER 100 mg.

Limitations of Manufacturer's Submission

CADTH identified the following key limitations in the submission:

- **Uncertain comparative evidence:** The clinical trial evidence on BUP-ER is based on Study 13-0001, which was a placebo-controlled trial.[8] To compare buprenorphine with other OATs, relative treatment effects were informed by either the manufacturer's submitted ITC or through observational studies.

  The ITCs captured the following clinical outcomes that were incorporated into the economic model: proportion on top use (for buprenorphine/naloxone and BUP-ER) and time to treatment dropout (for all treatment).[3] However, the results of the manufacturer's ITC were based on sparse baseline data without assessment of consistency or sufficient adjustments made to address potential confounders. Furthermore, the population in these studies may not be consistent with the Canadian population expected to use BUP-ER. The CADTH clinical report noted that the comparative efficacy of BUP-ER is uncertain based on the submitted ITCs.[16] The manufacturer incorporated the potential treatment effects of BUP-ER 100 mg directly from Study 13-0001 rather than adjusting the treatment effects based on the findings of its ITC. Naive estimates were also directly taken from an observational study[9] to determine the potential effects of methadone in terms of the proportion of patients with on top use while on treatment.

  Observational studies were used to inform the probability of abstinence,[10] treatment-specific mortality,[11] and treatment-specific overdose rates.[4] As noted in the CADTH clinical report,[16] these studies were limited for a variety of reasons. For studies that reported treatment-specific parameters, patient population between treatment arms may have been different and some potential confounders were not controlled for. In the meta-analyses of observational studies, patient cohorts from as far back as 1965 were included, with only one study conducted in a Canadian population.[11] Generalizability of the clinical evidence from these studies remains unclear due to potential differences in treatment practice and patient populations between countries and over time. Furthermore, the clinical expert consulted by CADTH identified that overdose rates for

patients who withdrew from OAT (i.e., the "off treatment, using" health state of the model) would not differ as was modelled in the manufacturer's base case. All of these limitations increase the uncertainty in the comparative treatment effects assumed in the manufacturer's submitted economic model results. CADTH conducted exploratory analyses with alternate distributional forms for treatment dropout and abstinence inputs to address some of this uncertainty.

- **The modelled population does not reflect the indication:** The exclusion criteria in Study 13-0001 was extended to patients with any concurrent substance use disorder; those meeting *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* criteria for either moderate or severe cocaine, alcohol, or cannabis use disorder; and those with uncontrolled psychiatric comorbidities (i.e., depression, post-traumatic stress disorder, anxiety).[8] According to the clinical expert consulted by CADTH, concurrent substance use disorders and uncontrolled psychiatric comorbidities are common in this patient population. In addition, the study's baseline characteristics seem to indicate a selective patient population that is more likely to achieve positive clinical outcomes. The clinical expert consulted by CADTH noted concerns that the population studied in Study 13-0001 may not be representative of the patient population with moderate-to-severe OUD in Canada. As the treatment outcomes for BUP-ER are derived from this study and incorporated into the economic model, it is unclear how generalizable the model's results are to a less stable patient population, to marginalized or socially disadvantaged populations, or to certain high-risk populations of interest (i.e., youth or Indigenous peoples, and those with chronic pain).
- **Long-term outcomes were not adequately captured in the model:** Although the time horizon of the manufacturer's model was five years in order to capture the long-term costs and benefits for patients with OUD, the approach taken to model long-term relapses was inappropriate. Composite health states were used to represent the average state of patients who relapsed following abstinence or who returned to treatment following illicit opioid use; these were derived based on weighting the probability in which patients would be in one of four health states: "OAT, not using," "OAT, using on top," "abstinent," and "off treatment, using" (Table 9). Potential treatment switching was further inadequately captured in these health states according to the clinical expert consulted by CADTH. All patients were assumed to have an equal chance of receiving 100 mg BUP-ER, buprenorphine/naloxone, or methadone, regardless of their past OAT exposure. This approach to modelling long-term relapse does not accurately capture the remitting and relapsing nature of the condition as the proportion of patients in each state remained constant over time. Given the potential uncertainty introduced with this approach to model long-term outcomes, an exploratory analysis was conducted in which the time horizon was truncated to 14 months to explore the impact of this limitation on the cost-effectiveness findings (Table 12).
- **Estimation of model input values does not accurately capture real-world clinical management and patient experience with OUD:** Parameter values that were incorporated into the manufacturer's economic model assumed clinical management and patient experience that differed from the account of a clinical expert consulted by CADTH on four key aspects: illicit opioid use, overdose, health care resource use, and duration of the treatment phases (i.e., induction, stabilization, and maintenance).

  There are several concerns to how opioid use has been incorporated into the model. First, the proportion of patients using opioids at baseline was treatment-specific. This does not align with the treatment indication as all patients would be using opioids at baseline by virtue of an OUD diagnosis. Second, to model the temporal change in on

top use during OAT (i.e., transitions between "OAT, not using" and "OAT, using on top"), the manufacturer assumed the proportion of patients with on top use would remain consistent from baseline to the end of the modelled time horizon. For methadone, this was informed by the reported overall proportion of positive urinalysis tests in a 26-week study.[9] For the other treatments considered in the economic model, the odds ratios from the manufacturer's ITC was applied to the overall proportion of positive urinalysis tests reported for the placebo arm of Study 13-0001. As these inputs reflect a summary measure over the entire study duration, this approach is less robust compared with repeated measures. The manufacturer's approach assumed a constant month-to-month proportion of illicit opioid use, whereas literature and clinical experience from the clinical expert consulted by CADTH suggest that the rate of on top use differs by treatment due to different mechanisms of action. Variability would be expected as the monthly proportion of on top use would decrease with longer treatment exposure, which was not considered in the analysis. The use of a summary measure to inform this model's transition probability is therefore inconsistent with the nature of the model parameter. In order to address some of these concerns in the CADTH reanalysis, all patients entered the model in the "OAT, using on top" health state to align with the treatment indication and transitions to "OAT, not using" were informed by a logistic regression equation provided by the manufacturer that described the weekly change in on top use by treatment.

The manufacturer assumed that a non-fatal overdose event would result in hospitalization. The clinical expert consulted by CADTH observed that in-patient management would be rare. Furthermore, there were inconsistencies as overall mortality rates, and fatal overdose rates were estimated from separate sources.[4,11] Transitions into the death health state were informed by the overall mortality rates, while additional costs were associated if death was due to a fatal overdose. However, it was noted that the number of fatal overdoses could exceed the number of all-cause deaths estimated within the manufacturer's model for the methadone arm. To address these limitations, CADTH assumed outpatient management for non-fatal overdose and selected fatal overdose rates from the same source that reported all-cause mortality rates in the CADTH reanalysis.

In consultation with the clinical expert consulted by CADTH, it was noted that the manufacturer's values for resource utilization reflected a multidisciplinary setting that would not be typical of most Canadian practices. Although psychosocial visits were billed separately from office visits in the manufacturer's model, the clinical expert noted that psychosocial visits would occur as part of the office visit to the physician. Blood tests were also noted to occur less frequently than is modelled in most Canadian practices. In response to this observation, CADTH conducted a scenario analysis exploring a less multidisciplinary approach to patient management.

Last, according to the clinical expert consulted by CADTH, the duration of each phase of treatment in some instances did not reflect treatment practices and clinical practice guidelines. The manufacturer assumed a constant duration for the induction and stabilization phases of one week and three weeks, respectively, across all OATs. However, according to the clinical expert consulted by CADTH, the duration of induction and stabilization differs considerably for methadone. The induction phase alone can take one month, and the stabilization phase could take an additional one to six months. This aligns with provincial guidelines that note that a longer duration is required for methadone, in which the induction phase would take one month and the stabilization phase would be at least six weeks.[17] Furthermore, the duration of OAT was

underestimated. The manufacturer's model allowed patients to successfully complete OAT and become abstinent immediately after the stabilization phase (i.e., a month since initiating OAT). However, according to a clinical expert consulted by CADTH, patients would need to be stable for at least a year on OAT before dose tapering and OAT discontinuation would be considered appropriate. Assuming a shorter OAT duration and earlier achievement of abstinence reduces the associated drug-related costs and increases the proportion of patients achieving abstinence, both favouring BUP-ERs. In CADTH's reanalysis, the induction period for methadone was lengthened to one month and transitions to abstinence were delayed until one year after OAT.

CADTH Common Drug Review Reanalyses

The results of the CADTH reanalyses are presented in Table 4. These reanalyses attempt to address several of the limitations previously noted.

1. To align with the treatment indication, all patients were assumed to be using illicit opioids at baseline. The probability of on top use while on OAT after the induction period was informed by the manufacturer's submitted logistic regression analysis of weekly abstinence data (Table 3). As the reported duration of weekly abstinence data was 24 weeks at most, the probability of on top use after 24 weeks post-induction was assumed to reflect that of 100 mg BUP-ER to limit potential biases from data extrapolation. CADTH also explored other assumptions for on top use extrapolation beyond 24 weeks post-induction, including setting on top use probability for all treatment to reflect the estimates for methadone, setting on top use probability to 40%, and not adjusting on top use probability (Table 12).

Table 3: Coefficients of Weekly On Top Use Logistic Regression Analysis

Parameter	300 mg BUP-ER[a]	100 mg BUP-ER	Methadone	BUP/NAL
Intercept	1.49			
Weeks post-induction minus one week	0.02			
Treatment	–1.63	–1.87	–1.03	Assumed equivalent to 100 mg or 300 mg BUP-ER[b]
Weeks × treatment interaction	–0.05	–0.03	–0.07	

BUP-ER = buprenorphine extended-release injection; BUP/NAL = generic buprenorphine/naloxone.

[a] In a scenario analysis, 300 mg BUP-ER was modelled in lieu of 100 mg BUP-ER (Table 12).

[b] Coefficients for BUP/NAL were based on 100 mg BUP-ER in most reanalyses. The coefficients were based on 300 mg BUP-ER if 300 mg BUP-ER was modelled in lieu of 100 mg BUP-ER in the scenario analysis.

2. Fatal overdose rates were modelled based on the same publication that informed treatment-specific all-cause mortality rates[11] to ensure fatal overdose rates would not exceed all-cause mortality rates.
3. Non-fatal overdose was managed by outpatient care instead of hospitalization.
4. Transition to the abstinence health state was allowed only after a year of OAT.

The CADTH base case consisted of all of the previously described reanalyses (1 to 4).

Furthermore, given limited evidence regarding the relative efficacy between 100 mg and 300 mg BUP-ER, the CADTH reanalysis reflected the dosage schedule reported within the product monograph (i.e., 300 mg injection per month for the first two months followed by

monthly 100 mg injections).[1] A scenario analysis was performed on the 300 mg BUP-ER dose (i.e., monthly BUP-ER 300 mg injections) (Table 12).

Compared with the manufacturer's results, the CADTH base-case analysis reported fewer QALYs for BUP-ER compared with buprenorphine/naloxone and methadone (Table 4). Generic buprenorphine/naloxone remained the least costly drug, and was the dominant option (i.e., less costly and more effective compared with BUP-ER and naloxone). Base-case finding that buprenorphine/naloxone dominated BUP-ER remained robust in most exploratory and scenario analyses.

Table 4: CADTH Reanalysis (Sequential Analysis Results)

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($/QALY)
	Manufacturer's base case	BUP/NAL	23,926	3.40	Reference
		Methadone	24,424	3.38	Dominated
		BUP-ER	***29,602***	***3.49***	***61,165***
1	On top use modelled using weekly abstinence data in first 24 weeks post-induction. On top use reflects 100 mg BUP-ER after 24 weeks post-induction	BUP/NAL	23,873	3.57	Reference
		Methadone	24,409	3.56	Dominated
		BUP-ER	***29,584***	***3.53***	***Dominated***
2	Cost for non-fatal overdose assumed to be managed in outpatient setting	BUP/NAL	23,708	3.39	Reference
		Methadone	24,199	3.37	Dominated
		BUP-ER	***29,442***	***3.48***	***64,327***
3	Fatal overdose does not exceed all-cause mortality	BUP/NAL	23,910	3.39	Reference
		Methadone	24,444	3.38	Dominated
		BUP-ER	***29,593***	***3.49***	***61,682***
4	Abstinence transition after one year of OAT	BUP/NAL	24,005	3.40	Reference
		Methadone	24,510	3.37	Dominated
		BUP-ER	***29,743***	***3.48***	***64,755***
CADTH Base Case					
	Reanalyses 1, 2, 3, and 4	BUP/NAL	23,687	3.56	Reference
		Methadone	24,151	3.54	Dominated
		BUP-ER	***29,358***	***3.52***	***Dominated***

BUP-ER = buprenorphine extended-release injection; BUP/NAL = generic buprenorphine/naloxone; ICUR = incremental cost-utility ratio; OAT = opioid agonist therapy; QALY = quality-adjusted life-year.

As BUP-ER was dominated in the CADTH base case, a price reduction reanalyses (Table 5) found that below a 60% reduction of BUP-ER price, generic buprenorphine/naloxone remained dominant. Above a 60% price reduction, 100 mg BUP-ER became less costly but produced fewer QALYs compared with buprenorphine/naloxone. At a WTP threshold of $50,000 per QALY, buprenorphine/naloxone would be the most likely cost-effective intervention. The price of BUP-ER would need to be reduced by more than 73% for BUP-ER to be cost-effective at a WTP threshold of $50,000 per QALY gained compared with buprenorphine/naloxone.

Table 5: CADTH Reanalysis Price Reduction Scenarios

Incremental Cost-Utility Ratio of Submitted Drug Versus Opioid Agonist Therapies in a Sequential Analysis		
Price	**Base-Case Analysis Submitted by Manufacturer**	**CADTH Reanalysis[a]**
Submitted	• If λ < $61,165 per QALY, BUP/NAL is optimal • If $61,625 ≤ λ < $190,242 per QALY, 100 mg BUP-ER is optimal • If λ ≥ $190,242 per QALY, 300 mg BUP-ER is optimal	• BUP/NAL is optimal
10% reduction	• If λ < $50,318 per QALY, BUP/NAL is optimal • If $50,318 ≤ λ < $171,851 per QALY, 100 mg BUP-ER is optimal • If λ ≥ $171,851 per QALY, 300 mg BUP-ER is optimal	• BUP/NAL is optimal
20% reduction	• If λ < $39,030 per QALY, BUP/NAL is optimal • If $39,030 ≤ λ < $189,875 per QALY, 100 mg BUP-ER is optimal • If λ ≥ $189,875 per QALY, 300 mg BUP-ER is optimal	• BUP/NAL is optimal
30% reduction	• If λ < $27,286 per QALY, BUP/NAL is optimal • If $27,286 ≤ λ < $145,712 per QALY, 100 mg BUP-ER is optimal • If λ ≥ $145,712 per QALY, 300 mg BUP-ER is optimal	• BUP/NAL is optimal
40% reduction	• If λ < $15,755 per QALY, BUP/NAL is optimal • If $15,755 ≤ λ < $131,109 per QALY, 100 mg BUP-ER is optimal • If λ ≥ $131,109 per QALY, 300 mg BUP-ER is optimal	• BUP/NAL is optimal
50% reduction	• If λ < $4,232 per QALY, BUP/NAL is optimal • If $4,232 ≤ λ < $98,407 per QALY, 100 mg BUP-ER is optimal • If λ ≥ $98,407 per QALY, 300 mg BUP-ER is optimal	• BUP/NAL is optimal
60% reduction	• If λ < $81,703 per QALY, 100 mg BUP-ER is optimal • If λ ≥ $81,703 per QALY, 300 mg BUP-ER is optimal	• If λ < $15,474 per QALY, BUP-ER is optimal • If λ ≥ $15,474 per QALY, BUP/NAL is optimal
70% reduction	• If λ < $75,945 per QALY, 100 mg BUP-ER is optimal • If λ ≥ $75,945 per QALY, 300 mg BUP-ER is optimal	• If λ < $41,578 per QALY, BUP-ER is optimal • If λ ≥ $41,578 per QALY, BUP/NAL is optimal
73% reduction	• If λ < $57,081 per QALY, 100 mg BUP-ER is optimal • If λ ≥ $57,081 per QALY, 300 mg BUP-ER is optimal	• If λ < $48,897 per QALY, BUP-ER is optimal • If λ ≥ $48,897 per QALY, BUP/NAL is optimal
74% reduction	• If λ < $50,568 per QALY, 100 mg BUP-ER is optimal • If λ ≥ $50,568 per QALY, 300 mg BUP-ER is optimal	• If λ < $52,586 per QALY, BUP-ER is optimal • If λ ≥ $52,586 per QALY, BUP/NAL is optimal

λ = willingness-to-pay threshold; BUP-ER = buprenorphine extended-release injection; BUP/NAL = generic buprenorphine/naloxone; QALY = quality-adjusted life-year.

[a] In the CADTH reanalysis, BUP-ER reflected the dosage schedule recommended in the product monograph.[1]

Issues for Consideration

- According to the clinical expert contacted by CADTH, sustained-release oral morphine may be used off-label as a treatment for OUD.
- Although monthly injections potentially reduce patient exposure to stigma and dose diversion, this may come at a loss of psychosocial support that would be accompanied by regular monitoring and contact with the health care system. The impact of reduced psychosocial support has not been explicitly captured in the economic model.

- According to a clinical expert contacted by CADTH, monthly injections do not completely eliminate risk for dose diversion as patients may be granted oral buprenorphine medications for use as breakthrough medications.

Patient Input

No patient group input was received for this submission.

Conclusions

In adults with moderate-to-severe OUD, CADTH estimated that BUP-ER would be dominated by generic buprenorphine/naloxone (i.e., produces fewer QALYs at a higher cost). Based on CADTH reanalysis, a price reduction of more than 73% would be required for BUP-ER to be the cost-effective intervention at a willingness-to-pay threshold of $50,000 per QALY gained.

It should be noted that considerable uncertainty remains on the comparative treatment effects between BUP-ER and generic buprenorphine/naloxone and methadone; as such, the interpretation of the economic results warrants careful consideration. The cost-effectiveness of BUP-ERs in less stable patients (i.e., more comorbidities) remains unknown. The average drug cost per month during the maintenance phase is estimated to be $550 for BUP-ER, which is greater than generic buprenorphine/naloxone ($72 to $77).

Appendix 1: Cost Comparison

The comparators presented in the following table 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: CADTH Common Drug Review Cost Comparison Table for Opioid Use Disorder

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Cost per Month ($)	Average Cost per Year ($)
Buprenorphine (Sublocade)	100 mg/0.5 mL 300 mg/1.5 mL	Subcutaneous injection	550.0000[a] 550.0000[a]	300 mg monthly for two months, followed by 100 mg monthly maintenance doses. The maintenance dose can be increased to 300 mg if satisfactory clinical response is not demonstrated	550	6,600
Buprenorphine (Probuphine)	80 mg x 4	Subdermal implant	1,495.0000[b]	4 implants, may be repeated once after six months	249	2,990
Buprenorphine/ Naloxone (generics)	2 mg/0.5 mg 8 mg/2 mg	Sublingual tablet	0.6675 1.1825	12 mg to 16 mg per day	72 to 77	864 to 920
Methadone (Metadol-D)	1 mg 5 mg 10 mg 25 mg 1 mg/mL 10 mg/mL	Tablet Tablet Tablet Tablet Solution Solution	0.1769[b] 0.5896[b] 0.9432[b] 1.7526[b] 0.1106[b] 0.1500	60 mg to 120 mg daily[d]	135 to 271 27 to 55	1,625 to 3,249 329 to 657
Naltrexone (generics)	50 mg	Tablet	2.8075	50 mg daily, 100 mg every other day, or 150 mg every third day	85	1,025

Note: All prices are from the Ontario Drug Benefit Formulary[13] (accessed January 2019) unless otherwise indicated and do not include dispensing fees.

[a] Manufacturer-submitted price.[2]

[b] CADTH Common Drug Review Probuphine pharmacoeconomic review report.[18]

[c] Saskatchewan Drug Plan (accessed January 2019).[19]

[d] Canadian Research initiative on substance misuse national guideline for the clinical management of opioid use disorder.[17]

Appendix 2: Additional Information

Table 7: 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”	There were conflicting statements within the submitted report that required reviewers to consult the model and request addition information from the manufacturer.		
Was the material included (content) sufficient?			X
Comments Reviewer to provide comments if checking “poor”	Manufacturer needed to be contacted to provide a revised economic model that included all relevant sensitivity analyses noted within its economic report. Errors in the calculation of sequential analyses and the incorporation of adverse event disutilities were noted. Sequential analysis results were not provided as part of the conduct of scenario analyses.		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”			

Table 8: 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)

	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 3: Summary of Other HTA Reviews of Drug

The Institute for Clinical and Economic Review in the US included buprenorphine extended-release injection (BUP-ER) in its review of medications for addiction treatment in patients with opioid use disorder. However, BUP-ER was not considered in the base case of the economic analysis.[20]

No other health technology assessment agencies have reviewed BUP-ER for the requested CADTH Common Drug Review indication.

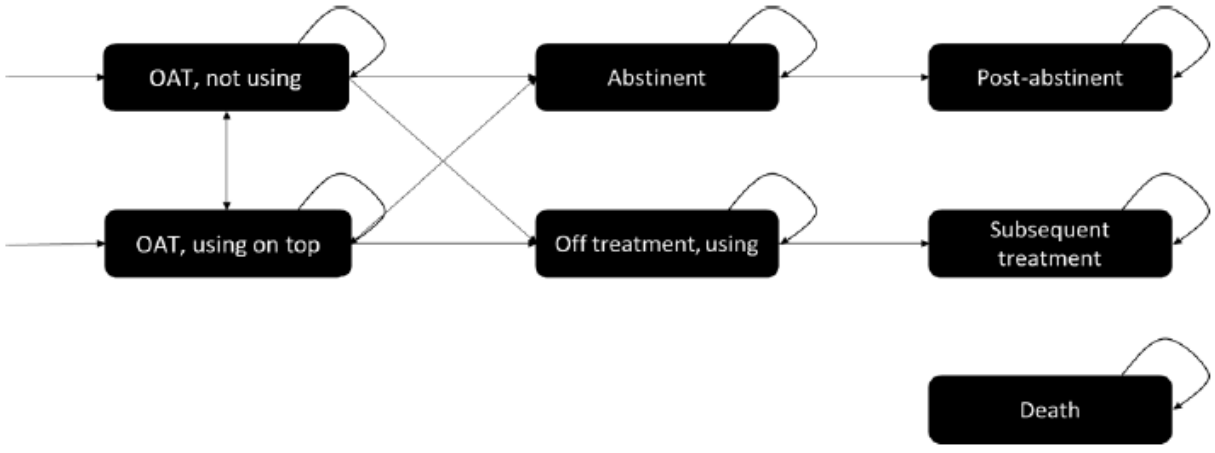
Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a Markov cohort state-transition model with monthly cycles developed in Microsoft Excel.[2] The modelled cohort consisted of patients with moderate-to-severe opioid use disorder who had a mean age of 39.7 years and were 33.8% women based on the manufacturer's Study 13-0001.[8]

The model consisted of seven health states (Figure 1; Table 9) that reflected the status of first-line opioid agonist therapy (OAT) and illicit opioid use (specifically, "OAT, using on top," "OAT, not using," "abstinent" [i.e., not on OAT, not using on top], and "off treatment, using"), long-term relapse health states ("post-abstinent" and "subsequent treatment"), and death. Patients entered the model in either of the two OAT health states (i.e., "OAT, using on top" if concurrently using illicit opioid, and "OAT, not using" otherwise) and were followed over a five-year modelled time horizon. Patients who successfully completed OAT transitioned to the "abstinent" state, while those who dropped out of treatment transitioned to the "off treatment, using" state. Abstinent patients could relapse again after three months in the "post-abstinent" state, and "off treatment, using" patients could be re-treated after two months in the "subsequent treatment" state. Both health states comprised of a weighted average of four states: "OAT, not using," "OAT, using on top," "abstinent," and "off treatment, using." Patients receiving OAT in the "post-abstinent" and "subsequent treatment" states were assumed to have an equal chance of receiving 100 mg buprenorphine extended-release injection (BUP-ER), buprenorphine/naloxone, or methadone regardless of the prior OAT drug they were on. Patients could also transition to death at each cycle in the model, and this transition probability differed by treatment. Although adverse events were not modelled in the base case, fatal and non-fatal overdose were modelled for the OAT and "off treatment, using" health states and were assumed to differ by treatment.

Figure 1: Manufacturer's Model Structure



OAT = opioid agonist therapy.

Source: Manufacturer's submission.[2]

Table 9: Description of Manufacturer's Modelled Health States

Health State	Description
OAT, not using	Receiving treatment for OUD and not using opioids illicitly
OAT, using on top	Receiving treatment for OUD and using opioids illicitly
Abstinent	Not receiving treatment for OUD and not using opioids illicitly
Off treatment, using	Not receiving treatment for OUD and using opioids illicitly
Post-abstinent	A composite health state reflecting the average state of patients who have become abstinent and subsequently relapsed. Comprised of: • 50% OAT, not using • 30% OAT, using on top • 2% abstinent • 18% off treatment, using.
Subsequent treatment	A composite health state reflecting the average state of patients who have relapsed and subsequently sought retreatment. Comprised of: • 50% OAT, not using • 30% OAT, using on top • 2% abstinent • 18% off treatment, using.
Death	Deceased

OAT = opioid agonist therapy; OUD = opioid use disorder.

Source: Manufacturer's submission.[2]

Table 10: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Mean age and gender proportion were based on Study 13-0001.[8] The proportions of patients using illicit opioids at baseline was treatment-specific and were either based on Study 13-0001 and the manufacturer's submitted ITC[3] or a study by Longshore et al.[9]	Appropriate. Inappropriate. The clinical expert consulted by CADTH noted that all patients would be expected to be actively using illicit opioids at baseline.
Clinical outcomes: • **Treatment retention** • **Illicit opioid use (on top use)**	The comparative dropout rates for generic buprenorphine/naloxone and methadone (measured as treatment retention hazard ratios) were based on the manufacturer's ITC[3] that compared time to dropout or study withdrawal. Treatment retention for BUP-ERs was based on data from Study 13-0001. The proportion of patients using illicit opioids while on treatment for the duration of the modelled time horizon was treatment-specific and was identical to the baseline proportion. These proportions were informed by either adjusting odds ratios from the manufacturer's submitted ITC[3] to the overall proportion of positive urinalysis tests reported for the placebo arm of Study 13-0001 for buprenorphine-based regimens, or by the average proportion reported in the methadone arm of a study by Longshore et al.[9]	The comparative efficacy of BUP-ER is uncertain. The CADTH clinical report identified multiple limitations associated with the manufacturer's submitted ITC that informed treatment retention and on top use within the manufacturer's model.[16] The ITCs were conducted with sparsely reported baseline data, without sufficient adjustments to address potential confounders, nor assessment of consistency. Studies informing the ITC may not reflect the Canadian population that is expected to use BUP-ER. In Study 13-0001, informing the treatment effects of BUP-ER may further not be reflective of the Canadian population as it excluded patients with other concurrent substance use disorders or uncontrolled psychiatric comorbidities.[8] The clinical expert consulted by CADTH noted that these comorbidities would be higher in the

Data Input	Description of Data Source	Comment
		Canadian patient population and that the trial recruited more stable patients. Furthermore, there were methodological concerns regarding the application of the ITC data. For treatment retention inputs, the manufacturer used treatment retention curves that were sourced directly from Study 13-0001 for 100 mg BUP-ER instead of adjusting these curves with the indirect comparison information from the ITC. For on top use parameters, the manufacturer incorporated a naive comparison of the calculated on top use proportion against the average proportion reported in single study. This naive comparison is inappropriate. These inputs further reflect a summary measure over the entire study duration, and the data are less robust compared with repeated measures data.
Adverse events	Probabilities of fatal and non-fatal overdose for patients off OAT and using illicit opioids or on OAT were based on a large 10-year retrospective observational study of Australian OUD patients who received buprenorphine or methadone treatments.[4] A scenario analysis considered the impacts of LST in males. Probability of LST while receiving methadone and buprenorphine/naloxone was based on a consultation with experts while the probability for BUP-ER was based on Study 13-0001.[8]	Questionable. CADTH clinical report identified several limitations that added uncertainty to the overdose parameters used in the model.[16] The limitations included lack of accounting for multiple overdoses, prior treatment failures, and place in therapy considerations. These are potential confounders that may account for differences in overdose rates between treatments. There was further a lack of transparent statistical power calculation. Furthermore, as the study is based on an Australian population, this potentially limits the generalizability of the study's findings to the Canadian population. Notably, the fatal overdose rates conflicted with the all-cause mortality rates used in the model; in certain cycles of the model, the number of fatal overdoses were higher than the number of deaths (i.e., all-cause mortality). This is implausible. Uncertain due to the lack of available literature to validate these parameters. A clinical expert consulted by CADTH noted that LST could impact women.
Natural history	Probability of abstinence was not treatment-specific but depended on if patients were using on top during OAT. Probability of abstinence on OAT was based on a proportion of patients (with at least 21 years of OUD history) in treatment who successfully completed OAT during 2012 to 2015, extracted from a 2017 Public Health England report.[10]	The CADTH clinical report noted that the data from PHE were based on a population with declining OUD prevalence; this trend is not observed in Canada where OUD prevalence rates are increasing.[16] It was also considered that patients with a minimum of 21 years of OUD history would not reflect the younger Canadian OUD patient population. The data in the PHE report also appear to be cross-sectional in nature rather than prospective and it is unclear whether the calculated proportion reflects the

Data Input	Description of Data Source	Comment
		probability of abstinence in a person with an exposure to one year of OAT.
	Probability of abstinence for patients who were using on top while on OAT were calculated by adjusting the probability of abstinence on OAT with the relative risk (RR; 7) of abstinence in patients who did not use illicit opioids compared with those who used illicit opioids based on consultation with Canadian experts.	The clinical expert consulted by CADTH confirmed that the relative risk derived from expert opinion appeared reasonable.
	Assumptions pertaining to the long-term relapse health states were based on consultation with experts.	Uncertain due to the lack of available literature to validate these parameters. A clinical expert consulted by CADTH noted that there is limited long-term data on the natural history following relapse.
Utilities	Health state utility weights were based on a UK health state valuation study that directly elicited the utility values using the standard gamble approach.[5]	It is uncertain how well the utility values elicited from 22 UK individuals approximate the utility values for Canadian patients. Furthermore, while the UK study provided a measure of variation for each utility, the manufacturer assumed a standard error equal to 10% of the mean utility value, which would not adequately characterize parameter uncertainty. Alternative utility values from a more recent and larger sample study based on the US population (N = 2,054)[21] were available in the literature. As the application of these utility values require an assumption regarding whether patients who drop out from OAT abuse injection or prescription opioids, each value was separately incorporated into exploratory analyses by CADTH.
	The utility value for the “abstinent” health state was assumed to approximate the general Canadian population.[6]	The clinical expert consulted by CADTH confirmed that this is a reasonable assumption. However, the utility value was derived by the HUI-3 utility measurement, and this may be inconsistent with the remaining utilities values in the model, which were derived from EQ-5D or directly elicited using the standard gamble method.
	The one-time utility decrement for non-fatal overdose was based on a disutility value associated with depressive disorder from a US national population analysis of EQ-5D-3L values associated with chronic conditions and assumed to have a duration of 7 days.[12]	Uncertain. The manufacturer did not provide a clinical rationale for using depressive disorder (a chronic condition) to approximate the quality of life decrement associated with a non-fatal overdose (an acute event). The relationship between these two conditions, and the validity of this approach, are unclear but are unlikely to drive the model’s results.
	The utility decrement for LST used in a scenario analysis was based on a disutility value associated with impotence/erectile dysfunction directly elicited from a small sample (13 men) in	It is uncertain whether this utility value is generalizable to the Canadian moderate-to-severe OUD patient population.

Data Input	Description of Data Source	Comment
	the US with moderate-to-severe benign prostatic hyperplasia symptoms.[15]	
Mortality	Treatment and health state-specific all-cause mortality risk (i.e., "OAT, not using," "OAT, using on top," and "off treatment, using") was based on a 2017 systematic literature review and meta-analysis of observational studies[11] that reported the mortality of patients during and after opioid substitution treatment with methadone or buprenorphine. The mortality risk in "abstinent" health states were derived from Statistics Canada's general population mortality rates.[2]	Uncertain. The CADTH clinical report noted study limitations associated with the generalizability of this study due to the potential heterogeneity of patient populations and the inclusion of patient cohorts that date as far back as 1965.[16] The report also noted that compared with 18 methadone cohorts, only three cohorts were included for buprenorphine. Inappropriate but unlikely to impact the model. According to the clinical expert consulted by CADTH, abstinent patients with a history of OUD may have other risk factors that may increase mortality compared with the general population due to higher comorbidities (e.g., smoking, alcohol consumption, hepatitis C, hypertension, and depression).
Resource Use and Costs		
Drug	Drug costs for BUP-ER was provided by the manufacturer.[2] Drug acquisition costs for all other comparators (and treatment for adverse events in the scenario analyses with LST) were based on the Ontario Drug Benefit Formulary.[13] The number of methadone and buprenorphine/naloxone administrations given during the induction/stabilization phase of OAT and their average dose per administration were based on the manufacturer's review of 219 charts of Canadian patients with OUD from British Columbia, Alberta, Ontario, and Quebec.[7]	Appropriate. Appropriate. Acceptable. The clinical expert consulted by CADTH considered these inputs to be acceptable; however, noted that the mean dose of methadone in the maintenance phase is lower than would be observed in practice. By using this data, this may introduce bias in favour of methadone by underestimating the drug costs during the maintenance phase.
Administration	Injection administration fees for BUP-ER subcutaneous injection (and testosterone intramuscular injection for LST in a scenario analysis), office visit, and laboratory fees were based on the Ontario Schedule of Benefits.[22] Dispensing fees for supervised methadone and buprenorphine/naloxone oral administration, and psychosocial visits were based on the manufacturer's Canadian chart review.[7] The proportion of patients with carry privileges differed by treatment and was based on the manufacturer's Canadian chart review.[7]	Appropriate. Acceptable. Acceptable.
Overdose	The monthly cost of fatal overdose was based on ambulatory costs from OCCI associated with ICD-10 code T40.0 to T40.3.[14]	Appropriate.

Data Input	Description of Data Source	Comment
	The monthly cost of non-fatal overdose was based on in-patient costs from OCCI associated with ICD-10 code T40.0 to T40.3.[14]	Inappropriate. According to the clinical expert consulted by CADTH, hospitalizations are rare for non-fatal overdoses as these are typically cared for in an outpatient setting.
Health State	Off treatment health states (i.e., "abstinent" and "off treatment, using") were assumed to accrue zero OAT resource use based on expert feedback. Treatment-specific resource use while in OAT health states based on manufacturer's Canadian chart review.[7]	Acceptable. Uncertain. It is unclear from the chart review whether the resource use is statistically significantly different. Furthermore, the clinical expert consulted by CADTH noted that most patients in Ontario are treated from standalone clinics with minimal counselling. The frequency of psychosocial visits and blood testing may be lower in such practices. Scenario analysis was conducted to explore an alternative practice setting.

BUP-ER = buprenorphine extended-release injection; EQ-5D = EuroQol 5-Dimensions; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; HUI-3 = Health Utility Index Mark 3; ITC = indirect treatment comparison; LST = low-serum testosterone; OAT = opioid agonist therapy; OCCI = Ontario Case Costing Initiative; OUD = opioid use disorder; PHE = Public Health England.

Table 11: Manufacturer's Key Assumptions

Assumption	Comment
Generic methadone and buprenorphine/naloxone are the most relevant comparators	Buprenorphine subdermal implant and naltrexone are also marketed in Canada. Although not considered in the manufacturer's model, the average cost per year for these two comparators are higher than the comparators included in the model. The clinical expert consulted by CADTH indicated that off-label sustained-release oral morphine may also be used.
Time horizon is 5 years	A five-year time horizon may not be sufficient to capture the chronically relapsing and remitting nature of the condition. Furthermore, this does not adequately consider the long-term patient outcomes given that long-term replacement therapy for opioid dependence is common in practice. Given the duration of the available clinical evidence (24 weeks), it requires extensive extrapolation. The longer time horizon increases the uncertainty in its long-term cost-effectiveness.
Duration of induction and stabilization for buprenorphine/naloxone and methadone was assumed to be identical to the duration of induction and stabilization expected for BUP-ER	Inappropriate. According to a clinical expert consulted by CADTH, methadone induction is expected to last approximately a month, and stabilization could take between 1 to 6 months. Provincial guidelines also recommend longer period for methadone stabilization.[17]
Time to retention and the proportion of patients on top use are assumed to be independent parameters	Uncertain. Treatment withdrawal is likely to be correlated to on top use during OAT.
Treatment retention for sublingual buprenorphine and sublingual buprenorphine/naloxone is equivalent	Acceptable according to the clinical expert consulted by CADTH.

Assumption	Comment
Abstinence assumed possible after one month of initiating OAT	Inappropriate. A PHE report defined abstinence as successfully completing treatment and no longer requiring OAT. According to the clinical expert consulted by CADTH, a minimum of one to two years of stability on maintenance therapy is required before OAT tapering and discontinuation would typically be considered.
Probability of abstinence is independent of treatment drug	According to a clinical expert consulted by CADTH, the validity of this assumption would depend on dose equivalence between interventions.
30% of patients were assumed to achieve long-term abstinence	Acceptable according to the clinical expert consulted by CADTH.
"Subsequent treatment" and "post-abstinent" health states were constructed by weighting several health states ("OAT, using on top," "OAT, not using," "off treatment, using," "abstinent")	Inappropriate. These health states are not sensitive to the chronically relapsing and remitting nature of OUD.
Patients on OAT in the composite health states ("post-abstinent" and "subsequent treatment") were assumed to have an equal chance of receiving 100 mg BUP-ER, buprenorphine/naloxone, and methadone based on consultation with experts	A clinical expert consulted by CADTH considered these to be inappropriate as a subsequent choice of treatment drug may depend on the drug used during the previously failed OAT.
The risk of fatal and non-fatal overdose for oral buprenorphine/naloxone and BUP-ERs were assumed to be equivalent to the risk reported for oral buprenorphine	Acceptable according to the clinical expert consulted by CADTH.
All-cause mortality rates of buprenorphine/naloxone and BUP-ERs are equivalent	Uncertain; however, generally acceptable according to the clinical expert consulted by CADTH.
Adverse events were not modelled in the manufacturer's base-case analysis	The clinical expert consulted by CADTH confirmed that LST is the adverse event with the most likely cost impacts. This adverse event should have ideally been incorporated in the base-case analysis. However, the assumption not to incorporate adverse events is acceptable given the lack of comparative evidence.

BUP-ER = buprenorphine extended-release injection; LST = low-serum testosterone; OAT = opioid agonist therapy; OUD = opioid use disorder; PHE = Public Health England.

CADTH Common Drug Review Reanalyses

CADTH explored the following additional exploratory and scenario analyses that were made to the CADTH base case.

Exploratory Analyses

S1: A shorter time horizon of 14 months was used to minimize the impact of the long-term relapse health states (i.e., "post-abstinence" and "subsequent treatment").

S2: Low-serum testosterone as an adverse event was included. As the manufacturer's submitted model inappropriately applied a quality-adjusted life-year (QALY) decrement corresponding to a year of low-serum testosterone at each monthly cycle, the model was revised to appropriately apply monthly QALY decrement.

S3: Alternative distribution forms to describe treatment retention over time:

S3A: Weibull distribution was assumed for the 300 mg BUP-ER treatment retention curve, upon which the hazard ratios based on the manufacturer's indirect treatment comparison[3] were applied to derive treatment retention curves for methadone and generic buprenorphine/naloxone.

S3B: Gamma distribution was assumed for all treatment retention curves.

S3C: Treatment retention for 100 mg BUP-ER was derived by applying its HR onto the treatment retention curve for 300 mg BUP-ER. This would correctly incorporate indirect comparative evidence for 100 mg BUP-ER.

S4: Alternate utility estimates:

S4A: Use of the "off treatment, using" health state utility value associated with prescription opioid abuse reported in the Wittenberg et al. study.[21]

S4B: Use of the "off treatment, using" health state utility value associated with injection opioid abuse reported in the Wittenberg et al. study.[21]

S5: An alternate estimate for the annual probability of abstinence (16%) was used, reflecting patients with a shorter history of opioid use disorder (three years or less).[10]

S6: Alternate on top use estimates:

S6A: The on top use proportion was based on the manufacturer's logistic regression analysis of weekly abstinence data. After 24 weeks post-induction, on top use was assumed to reflect that of methadone.

S6B: The on top use proportion was based on the manufacturer's logistic regression analysis of weekly abstinence data. After 24 weeks post-induction, on top use was assumed to be 40%, similar to the mean proportion assumed for 100 mg BUP-ER in the manufacturer's submission.

S6C: The on top use proportion was based on the manufacturer's logistic regression analysis of weekly abstinence data. Adjustments were not made after 24 weeks post-induction.

Scenario Analyses

S7: Dispensing fees were removed from the analysis.

S8: Resource use inputs that reflect other Canadian practices outside of a multidisciplinary setting were used. Psychosocial counselling was not billed separately from office visits and blood tests were not conducted.

S9: The 300 mg BUP-ER maintenance dose was used.

The CADTH base case was found to be relatively robust to the majority of the scenario and exploratory analyses conducted (Table 12). CADTH base-case results were sensitive in a minority of the analyses. The use of Weibull parametric distribution to model treatment retention (analysis S3A) resulted in BUP-ER having an incremental cost-utility ratio of $103,218 per QALY gained compared with buprenorphine/naloxone. However, caution is required in interpreting this result as Weibull distribution was not deemed to provide the best fit for the treatment retention data. The model was sensitive to the approach to extrapolate the proportion on top use (analyses S6) and if dispensing fee were excluded (analysis S7).

Table 12: CADTH Exploratory and Scenario Analyses (Sequential Analysis Results)

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($/QALY)
	CADTH base case	BUP/NAL	23,687	3.56	Reference
		Methadone	24,151	3.54	Dominated
		BUP-ER	***29,358***	***3.52***	***Dominated***
S1	Time horizon: 14 months	BUP/NAL	5,949	0.86	Reference
		Methadone	6,133	0.85	Dominated
		BUP-ER	***8,777***	***0.86***	***Dominated***
S2	Low-serum testosterone modelled as an adverse event	BUP/NAL	23,939	3.53	Reference
		Methadone	24,986	3.48	Dominated
		BUP-ER	***29,637***	***3.50***	***Dominated***
S3A	Treatment retention based on Weibull parametric distribution	BUP/NAL	22,770	3.45	Reference
		Methadone	23,078	3.42	Dominated
		BUP-ER	***29,494***	***3.51***	***103,218***
S3B	Treatment retention based on gamma parametric distribution	BUP/NAL	24,426	3.64	Reference
		Methadone	25,033	3.63	Dominated
		BUP-ER	***29,372***	***3.51***	***Dominated***
S3C	Treatment retention of 100 mg BUP-ER based on ITC HR and 300 mg BUP-ER data from Study 13-0001	BUP/NAL	23,725	3.56	Reference
		Methadone	24,233	3.55	Dominated
		BUP-ER	***30,503***	***3.55***	***Dominated***
S4A	"Off treatment, using" health state utility based on Wittenberg et al. study (prescription opioid abuse)[21]	BUP/NAL	23,691	3.66	Reference
		Methadone	24,189	3.63	Dominated
		BUP-ER	***29,459***	***3.64***	***Dominated***
S4B	"Off treatment, using" health state utility based on Wittenberg et al. study (injection drug abuse)[21]	BUP/NAL	23,730	3.54	Reference
		Methadone	24,232	3.53	Dominated
		BUP-ER	***29,461***	***3.50***	***Dominated***
S5	High annual abstinence probability (16%) based on UK patient population with up to 3 years of OUD history[10]	BUP/NAL	23,520	3.57	Reference
		Methadone	23,978	3.57	Dominated
		BUP-ER	***29,355***	***3.54***	***Dominated***
S6A	On top use modelled using weekly abstinence data. On top use reflects methadone after 24 weeks post-induction	BUP/NAL	23,654	3.60	Reference
		Methadone	24,130	3.60	184,342
		BUP-ER	***29,402***	***3.55***	***Dominated***
S6B	On top use modelled using weekly abstinence data. On top use is 40% after 24 weeks post-induction	BUP/NAL	23,720	3.48	Reference
		Methadone	24,219	3.45	Dominated
		BUP-ER	***29,484***	***3.46***	***Dominated***
S6C	On top use modelled using weekly abstinence data. No adjustments after 24 weeks post-induction	BUP/NAL	23,664	3.55	Reference
		Methadone	24,159	3.60	11,257
		BUP-ER	***29,467***	***3.52***	***Dominated***
S7	Removed dispensing fee	Methadone	14,442	3.54	Reference
		BUP/NAL	15,065	3.56	55,862
		BUP-ER	***25,245***	***3.51***	***Dominated***

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($/QALY)
S8	Alternative Canadian practice setting with no billing of psychosocial visits and blood tests	BUP/NAL	19,551	3.55	Reference
		Methadone	19,744	3.54	Dominated
		BUP-ER	***25,366***	***3.51***	***Dominated***
S9	300 mg BUP-ER	BUP/NAL	23,666	3.59	Reference
		Methadone	24,144	3.59	Dominated
		BUP-ER	***30,383***	***3.58***	***Dominated***

BUP-ER = buprenorphine extended-release injection; BUP/NAL= generic buprenorphine/naloxone; HR = hazard ratio; ICUR = incremental cost-utility ratio; ITC = indirect treatment comparison; OUD = opioid use disorder; QALY = quality-adjusted life-year.

References

1. Sublocade: 100 mg / 0.5 mL and 300 mg / 1.5 mL subcutaneous extended-release injection [product monograph]. Slough (UK): Indivior UK Limited 2018 Nov 20.
2. Pharmacoeconomic evaluation. In: CDR submission: Sublocade (buprenorphine) 100 mg / 0.5 mL and 300 mg / 1.5 mL extended-release subcutaneous injection [CONFIDENTIAL manufacturer's submission]. Slough (UK): Indivior UK Limited; 2018.
3. Clinical effectiveness of opioid agonist treatments for opioid dependence: A systematic review and indirect treatment comparison - Full technical report. In: CDR submission: Sublocade (buprenorphine) 100 mg / 0.5 mL and 300 mg / 1.5 mL extended-release subcutaneous injection [CONFIDENTIAL manufacturer's submission]. Richmond (VA): Indivior Inc.; 2018 Oct 12.
4. Kelty E, Hulse G. Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone. *Int J Drug Policy.* 2017;46:54-60.
5. Connock M, Juarez-Garcia A, Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: A systematic review and economic evaluation. *Health Technology Assessment.* 2007;11(9):iii-75.
6. Feeny D, Kaplan MS, Huguet N, McFarland BH. Comparing population health in the United States and Canada. *Popul Health Metr.* 2010;8:8.
7. Cost of care in the Canadian OUD market: Chart audit analysis. In: CDR submission: Sublocade (buprenorphine) 100 mg / 0.5 mL and 300 mg / 1.5 mL extended-release subcutaneous injection [CONFIDENTIAL manufacturer's submission]. Indivior Canada; 2017.
8. Clinical Study Report: Study RB-US-13-0001. A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy, safety, and tolerability of multiple subcutaneous injections of depot buprenorphine (RBP-6000 [100 mg and 300 mg]) over 24 weeks in treatment-seeking subjects with opioid use disorder [CONFIDENTIAL internal manufacturer's report]. Richmond (VA): Indivior, Inc.; 2017 Mar 03.
9. Longshore D, Annon J, Anglin MD, Rawson RA. Levo-alpha-acetylmethadol (LAAM) versus methadone: treatment retention and opiate use. *Addiction.* 2005;100(8):1131-1139.
10. Burkinshaw P, Knight J, Anders P, et al. An evidence review of the outcomes that can be expected of drug misuse treatment in England. London, UK: Public Health England; 2017 Jan: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/586111/PHE_Evidence_review_of_drug_treatment_outcomes.pdf. Accessed 2019 Mar 18.
11. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ (Clinical research ed).* 2017;357:j1550.
12. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making.* 2006;26(4):410-420.
13. Ontario Ministry of Health Long-Term C. Ontario drug benefit formulary/comparative drug index. 2018; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2018 Feb 15.
14. Ontario Case Costing Initiative (OCCI). Toronto: Ontario Health and Long-Term Care; 2018: https://www.ontario.ca/data/ontario-case-costing-initiative-occi. Accessed 1800 Mth Dd.
15. Ackerman SJ, Rein AL, Blute M, et al. Cost effectiveness of microwave thermotherapy in patients with benign prostatic hyperplasia: part I-methods. *Urology.* 2000;56(6):972-980.
16. Buprenorphine extended-release injection (Sublocade): Moderate to severe opioid use disorder *(CDR clinical review report)*. Ottawa (ON): CADTH; 2019. Accessed 2019 Mar 26.
17. Bruneau J, Ahamad K, Goyer M-È, et al. Management of opioid use disorders: a national clinical practice guideline. *Canadian Medical Association Journal.* 2018;190(9):E247-E257.
18. Buprenorphine subdermal implant (Probuphine): Opioid use disorder *(CDR pharmacoecomic review report)*. Ottawa (ON): CADTH; 2018 Sept: https://cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0550_Probuphine_PE_Report.pdf. Accessed 2019 Jan 5.
19. Government of Saskatchewan. Saskatchewan Online Formulary Database. 2019; http://formulary.drugplan.ehealthsask.ca/SearchFormulary. Accessed 2019 Jan 5.
20. Extended-release opioid agonists and antagonist medications for addiction treatment (MAT) in patients with opioid use disorder: Effectiveness and value. Final evidence report. Boston (MA): Institute for Clinical and Economic Review; 2018 https://icer-review.org/wp-content/uploads/2018/04/ICER_OUD_Final_Evidence_Report_120318.pdf. Accessed 2019 Feb 8.
21. Wittenberg E, Bray JW, Aden B, Gebremariam A, Nosyk B, Schackman BR. Measuring benefits of opioid misuse treatment for economic evaluation: health-related quality of life of opioid-dependent individuals and their spouses as assessed by a sample of the US population. *Addiction.* 2016;111(4):675-684.
22. Ontario Ministry of Health Long-Term C. Schedule of benefits for physician services under the Health Insurance Act: effective December 21, 2015. Toronto (ON): The Ministry of Health and Long-Term Care; 2015: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html.