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CADTH COMMON DRUG REVIEW

# Pharmacoeconomic Review Report

## BUPRENORPHINE SUBDERMAL IMPLANT (PROBUPHINE)

(Knight Therapeutics Inc.)

Indication: Opioid use disorder


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| Service Line: | CADTH Common Drug Review |
| Version: | Final |
| Publication Date: | September 2018 |
| Report Length: | 30 Pages |

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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.

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

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## Abbreviations

| | |
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| **AE** | adverse event |
| **BI** | buprenorphine implant |
| **BUP** | buprenorphine |
| **CDR** | CADTH Common Drug Review |
| **HCV** | hepatitis C virus |
| **ICUR** | incremental cost-utility ratio |
| **IVDU** | intravenous drug use |
| **QALY** | quality-adjusted life-year |
| **SL** | sublingual |
| **SL BUP/NLX** | sublingual buprenorphine/naloxone |

## Table 1: Summary of the Manufacturer's Economic Submission

| | |
|---|---|
| **Drug Product** | Buprenorphine hydrochloride subdermal implant (4 × 80 mg) |
| **Study Question** | Not stated. Suggestive of: What is the cost-effectiveness of BI compared with SL BUP/NLX in clinically stable adult patients? |
| **Type of Economic Evaluation** | Cost-utility analysis |
| **Target Population** | Adult clinically stable patients with opioid use disorder |
| **Treatment** | Four 80 mg BIs |
| **Outcome** | QALYs |
| **Comparator** | Low to moderate doses of SL BUP/NLX (≤ 12 mg), considered equivalent to sublingual buprenorphine (≤ 8 mg) |
| **Perspective** | Canadian health care payer |
| **Time Horizon** | 12 months |
| **Results for Base Case** | BI was more effective and less costly (dominant) compared with SL BUP/NLX |
| **Key Limitations** | • Model structure is inflexible and non-transparent, complicating the review and the conduct of reanalyses<br>• The selected clinical efficacy parameter is of uncertain relevance and the model structure does not adequately reflect real-world outcomes<br>• The analysis time horizon is insufficient to capture the potential impact on clinical and harms outcomes<br>• In addition: uncertainty in harms associated with BI has not been explored; competing risks of events were not considered; the cost of the comparator is overestimated; rates and costs of events associated with intravenous drug use bias in favour of BI; costs associated with supplemental SL BUP/NLX not considered; cost of removing second implant not considered for most BI patients |
| **CDR Estimate(s)** | When accounting for the potential overestimation of SL BUP/NLX dosing, the cost and risks associated with the use of supplemental SL BUP/NLX, explantation of all implants, and the cost of chronic infections within the one-year time horizon:<br>• The ICUR was $54,291 per QALY for BI compared with SL BUP/NLX.<br><br>CDR was unable to incorporate a longer time horizon, consider a more patient-relevant and statistically demonstrated efficacy outcome, adjust for competing risks, or alter the model structure to better reflect clinical practice, all of which leads to uncertainty in the ICUR estimate. |

BI = buprenorphine implant; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SL BUP/NLX = sublingual buprenorphine/naloxone.

| | |
|---|---|
| **Drug** | Buprenorphine hydrochloride subdermal implant (Probuphine) |
| **Indication** | The management of opioid dependence in patients clinically stabilized on no more than 8 mg of sublingual buprenorphine in combination with counselling and psychosocial support. |
| **Reimbursement Request** | As per indication |
| **Dosage Form(s)** | 80 mg subdermal implants |
| **NOC Date** | April 18, 2018 |
| **Manufacturer** | Knight Therapeutics Inc. |

# Executive Summary

## Background

Buprenorphine implant (BI, Probuphine) is a partial mu-opioid receptor agonist with a proposed indication for the management of opioid dependence in patients clinically stabilized on no more than 8 mg of sublingual buprenorphine (SL BUP) in combination with counselling and psychosocial support.[1] BI is available in kits containing four individually packaged 80 mg implants at a submitted price of $1,495 per kit, with a recommended dose of four implants (320 mg total) inserted subdermally in the inner side of the upper arm for up to six months, removed by the end of the sixth month. Implantation may be repeated in the other arm at the time of removal. There is no experience at the current time with inserting additional implants after two six-month periods.

The manufacturer submitted a cost-utility analysis comparing BI to buprenorphine/naloxone sublingual tablets (SL BUP/NLX) in adult patients with opioid drug dependence previously stabilized on SL BUP/NLX therapy (up to 8 mg/day of SL BUP, stated as equivalent to up to 12 mg/day of SL BUP/NLX).[2] The base case was a deterministic Markov state–transition model consisting of 1,000 hypothetical patients per treatment arm from the perspective of a Canadian public health care payer with a time horizon of one year with monthly cycles. As the time horizon was not longer than one year, costs and benefits were not discounted. The model consisted of four health states: on treatment without relapse (state A), on treatment with relapse (state B), off treatment with relapse (state C), and death (state D). States B and C were further divided, with 21% of patients assumed to relapse to intravenous heroin use, while the remainder of patients relapsed to prescription opioids. Comparative treatment effect was based on the PRO-814 randomized controlled trial (RCT),[3,4] with time to first evidence of opioid use by urine sampling as the parameter of interest. Transitions from state B to C and/or D were derived from observation studies.[5,6] Utilities for non-death health states were obtained from a UK panel.[7,8] Patients who relapsed in either treatment group were at risk of adverse events related to overdose and the consequences of intravenous drug use (IVDU), while 16.3% those in the SL BUP/NLX group were assumed to misuse their medication intravenously. These events were associated with costs in the model but did not impact quality of life.

In its deterministic base case, the manufacturer estimated that the use of BI in patients stabilized on doses of less than 8 mg of SL BUP was associated with an additional 0.023 quality-adjusted life-year (QALY) and a savings of $201 per patient over the one-year time horizon, concluding that BI was dominant over SL BUP/NLX.

### Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) identified a number of limitations in the model submitted by the manufacturer. The model was not transparent and lacked flexibility, making critical appraisal, methods assessment, and the exploration of alternative assumptions difficult. The model structure did not adequately reflect likely clinical pathways and outcomes, as patients could not return to a state of remission after a relapse, nor was quality of life affected by adverse events. The one-year time horizon was insufficient to assess the long-term costs, risks, and benefits of BI therapy for patients with opioid drug dependence, and specifically excluded the cost of removal of the second implant in patients who do not discontinue therapy. In addition, to capture chronic infections such as hepatitis C virus (HCV), as intended in the manufacturer's model, would require a longer time frame to realistically diagnose and treat patients, which would involve incorporating discounting. These assumptions and the over-simplification of the model bias the results in favour of BI.

The clinical efficacy parameter was of uncertain relevance, as time to first evidence of illicit opioid use was considered less important to patient outcomes than time in remission, time to remission, or quality of life. In the PRO-814 trial, BI was noninferior to SL BUP/NLX at doses of 8 mg/day or less in terms of the proportion of patients responding, defined as those with at least four of six months without evidence of illicit opioid use, and met superiority for this outcome in the primary but not sensitivity analyses. Although data were reported on symptoms of withdrawal and cravings to use opioids, the trial was not powered to detect differences between groups for these outcomes.

The manufacturer assumed that SL BUP/NLX would be used at higher doses than the SL BUP/NLX as described in the pivotal trial, which does not appear to be clinically based and increases the cost of the comparator. Limited clinical experience with BI increases uncertainty with respect to potential harms, none of which were included or explored in the model. Additionally, assumptions around the use of IVDU leading to increased cases of cellulitis in patients using SL BUP/NLX were not observed in the pivotal trial. Finally, competing risks were not considered, i.e., patients who overdosed and accrued three months of rehabilitation as a result of overdose were as likely to experience the same event the following cycle as those who did not.

CDR attempted to address some of the identified limitations by: assuming that SL BUP/NLX would be used at the same doses as SL BUP/NLX as described in the pivotal trial; including the costs and risks associated with supplemental SL BUP/NLX as used in the pivotal trial; including the cost of explanting all BI implants; removing the cost of chronic infections such as HIV and HCV; and removing the markup on drug products. Based on these revisions, in patients with opioid drug dependence stabilized on SL BUP/NLX doses of up to 8 mg/day, the ICUR was $54,291 per QALY for BI compared with SL BUP/NLX. The difference in incremental cost relative to the manufacturer's base case was driven primarily by the consideration of alternative dosing of SL BUP/NLX.

## Conclusions

In adults with clinically stable opioid drug dependence adequately managed on low doses of SL BUP, BI (320 mg total dose) was noninferior to SL BUP/NLX at doses of up to 8 mg per day based on the proportion of responders, defined as those with at least four of six months with no evidence of illicit opioid use. The economic evaluation was based on a secondary outcome from the PRO-814 trial, time to first evidence of illicit use, which is of uncertain

clinical relevance and which was not part of the fixed statistical testing procedure; thus, it should be interpreted as inconclusive. In addition, limitations with the manufacturer's model did not permit a full examination of the uncertainty in all parameters of interest.

The annual acquisition cost of BI ($2,990 per patient per year) is greater than that of SL BUP/NLX ($487 to $1,462 per patient per year for doses of between 2 mg and 8 mg per day). As there is no current experience with BI beyond two implants, it is also unknown how long patients will continue to use BI, and what the impact of switching to another therapy thereafter might be.

# Information on the Pharmacoeconomic Submission

## Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis comparing buprenorphine implant (BI) with sublingual buprenorphine/naloxone (SL BUP/NLX) in adult patients with opioid drug dependence previously stabilized on SL BUP/NLX therapy. The base case was a deterministic Markov state–transition model consisting of 1,000 hypothetical patients per treatment arm from the perspective of a Canadian public health care payer with a time horizon of one year with monthly cycles. As the time horizon was not longer than one year, costs and benefits were not discounted. No half-cycle correction was incorporated. The manufacturer also provided a probabilistic analysis of 1,000 simulations.

The model consisted of four health states: on treatment without relapse (state A), on treatment with relapse (state B), off treatment with relapse (state C), and death (state D). All patients entered the model in state A and could transition to state B at the end of the first cycle; once in state B, patients could transition to state C. Mortality was only a possibility for patients in states B or C, and fewer than 1 in 1,000 patients died over the duration of the model. Utilities for non-death health states were obtained from a UK panel of 22 members of the general population using the standard gamble technique.[7,8] States B and C were further divided, with 21% of patients assumed to relapse to intravenous heroin use, while the remainder relapsed to prescription opioids; these sub-states were associated with different utilities and risks of adverse events (Table 8). It was not possible for patients in the model to return to the non-relapsed state, to remain not relapsed if off therapy, or to return to therapy once discontinued (Figure 1).

The transition probabilities from state A to state B were derived from the PRO-814 trial, a 26-week, double-blind RCT of 177 patients randomized to receive BI or SL BUP/NLX,[3] with relapse rates (defined as first evidence of opioid use by urine sampling or self-report) observed in the six-month trial extrapolated out to 12 months, using the exponential function as best fit. The transition probability in the BI group was based on the longer time to first evidence of opioid use reported in the PRO-814 trial, leading to a hazard ratio of 0.49 (95% C, 0.25 to 0.97).[3] The confidence interval (CI) around the hazard ratio was used to calculate standard deviation to inform the distribution used in the manufacturer's probabilistic analysis around the relative efficacy parameter. A range of ± 25% was used to vary all other transitions within the probabilistic analysis, with the exception of the transition from state A to B in the SL BUP/NLX group, which was held static instead. Transitions from state B to C and/or D were derived from observation studies to offset the artificial nature of clinical trials in terms of discontinuation and mortality.[5,6] Mortality within the model incorporated only fatal overdose; all-cause mortality was not included (Table 8).

Patients who relapsed in either treatment group were at risk of adverse events such as non-fatal overdose, use of emergency and rehabilitation services, acute infections from intravenous drug use (IVDU), and chronic infections such as HIV or hepatitis C virus (HCV) from IVDU. These events were associated with costs in the model but not decrements to quality of life. Additionally, 16.3% of patients in the SL BUP/NLX group were assumed to misuse their treatment intravenously, which did not count as a relapse for the sake of state

transition or quality-of-life adjustment, but was incorporated into the risk of overdose, the use of health care services due to overdose, and the risk of infections due to IVDU.

Costs were derived from the Ontario Drug Benefit Formulary for SL BUP/NLX and pharmacy fees, from the manufacturer for BI costs, and from the Ontario Schedule of Benefits for Physicians Services for implant insertion and removal as well as for patient counselling and urine testing. Costs for emergency services and detoxification in hospital were derived from the Ontario Case Costing Initiative and expert opinion, while costs for adverse events were sourced from other published economic analyses and converted to 2017 Canadian dollars, if applicable, using the Statistics Canada Consumer Price Index for health care.[2]

## Manufacturer's Base Case

The manufacturer presented a deterministic analysis as the base case. The use of BI rather than SL BUP/NLX was associated with an additional 0.023 QALY per patient over the one-year time horizon, and a reduction in costs of $201 (Table 2).

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

| Treatment | Total Costs ($) | Incremental Cost of BI ($) | Total QALYs | Incremental QALYs of BI | Incremental Cost per QALY |
|---|---|---|---|---|---|
| BI | 4,515 | −201 | 0.841 | 0.023 | |
| SL buprenorphine/naloxone | 4,716 | | 0.818 | | Dominant |

BI = buprenorphine implant; QALY = quality-adjusted life-year; SL BUP/NLX = sublingual buprenorphine/naloxone.

Source: Adapted from the manufacturer's pharmacoeconomic submission, Table 1.[2]

While the drug acquisition cost of BI was more expensive than SL BUP/NLX ($3,199 per patient compared with $1,900), BI was associated with lower administration costs (weekly pharmacy fees for SL BUP/NLX compared with semi-annual implantation for BI), lower urine testing and patient counselling costs, and lower downstream costs due to overdose, rehabilitation services, and adverse events (Table 13).

The manufacturer reported a median incremental cost savings of $219 with BI compared with SL BUP/NLX and a median incremental QALY gain of 0.0239 in their probabilistic analysis. At a willingness to pay of $100,000, the manufacturer reported that BI was cost-effective in 100% of simulations. The average incremental cost savings with BI was $234, with a mean incremental QALY gain of 0.0239.

## Summary of Manufacturer's Sensitivity Analyses

BI remained dominant over SL BUP/NLX for the majority of the manufacturer's sensitivity analyses. Exceptions included the reduction of the cost of BUP/NLX acquisition, reducing the misuse of BUP/NLX to zero, reducing the referral to outpatient rehabilitation following emergency room services to 0%, assuming patients receive no in-patient or outpatient rehabilitation following overdose, and excluding the cost of all infections resulting from IVDU. The ICUR did not exceed $17,500 per QALY in any of the manufacturer's sensitivity analyses.

## Limitations of Manufacturer's Submission

**Model structure inflexible and non-transparent**: The model contained a variety of inputs that were hard-coded without adequate explanation for how they were derived from their source data, and some assumptions were unspecified and unsourced. For example, it was unclear how the monthly transition probability of relapse from state A to state B for patients using SL BUP/NLX was calculated from the time to event data provided in PRO-814; varying this input had substantial impact on incremental costs and QALYs. Nor was it possible to explore alternative assumptions around imputed data. Additionally, the submitted pharmacoeconomic report was insufficiently detailed and was often inconsistent with methods used within the model itself, particularly regarding the probabilistic analysis. As such, the model did not allow for sufficient exploration of clinical uncertainty or alternative assumptions.

**Clinical efficacy parameter of uncertain relevance**: Clinical effectiveness in the manufacturer's model is based on a single efficacy outcome from the PRO-814 trial: time to first evidence of illicit opioid use.[2] Given that occasional illicit opioid use (a lapse) is not unexpected, even among stable patients, the clinical expert consulted by CDR considered time to illicit use to be a less important clinical outcome than time spent in remission, time to remission, or patient quality of life / functioning in a harm-reduction treatment paradigm. Additionally, time to first evidence of illicit use was a secondary outcome in PRO-814, as no adjustments for multiplicity were performed for secondary outcomes and, thus, all secondary outcomes should be interpreted as inconclusive. In terms of the primary outcome, BI was noninferior to SL BUP at doses of up to 8 mg/day for the proportion of patients responding, defined as those with at least four of six months without evidence of illicit opioid use. Superiority of BI versus SL BUP was met for the primary analysis for this outcome, but not for sensitivity analyses, which tested key assumptions (see CDR Clinical Report, Critical Appraisal).

**Model structure does not adequately reflect real-world outcomes**: The model structure does not allow patients to re-enter the remission state after early or one-time illicit or opioid drug use, to go off treatment without relapse, or to restart treatment after discontinuation. Adverse events are not associated with disutilities which, while favouring the comparator in the manufacturer's base case, also precludes the ability to test the impact of alternate assumptions on quality of life. Additionally, while the potential abuse of sublingual tablets is incorporated into the risk and cost of adverse events, it is not considered a relapse, nor is it associated with increased risk of relapse to opioids or heroin due to treatment non-compliance.

**Time horizon**: A time horizon of 12 months is insufficient to quantify the relative long-term costs, risks, and benefits for patients with opioid drug dependence, or to justify the inclusion of costs associated with chronic infections such as HCV and HIV, given the unlikelihood that new cases would be diagnosed within a short period. The choice of a 12-month time horizon also excludes the cost of removing a second implant for patients who do not discontinue therapy, which the manufacturer assumes would occur at month 13. The manufacturer should have considered a longer model time frame to fully capture the clinical effects of BI, such as IVDU, if that was of interest.

**Uncertainty in harms associated with BI**: There is greater clinical experience with SL BUP/NLX, allowing for a greater understanding of its associated adverse events. There is substantially more uncertainty in the potential harms associated with BI, given its different mode of administration and signals within the pivotal trial, which do not appear in the

manufacturer's model. For example, more patients in PRO-814 experienced gastrointestinal adverse events in the BI group compared with the SL BUP group, and there were potentially higher rates of common infections. Additionally, the trial did not have sufficient numbers to evaluate device-related adverse events, such as migration of the implant or nerve damage, as have been observed with similar contraceptive devices.[9]

**Competing risks not considered**: Patients who experience an adverse event appear to have an equal chance of experiencing the same adverse event in each subsequent month. For example, patients accruing the cost of three months of intensive outpatient rehabilitation due to overdose appear to continue to have the same risks and costs as all other patients in their health state, including the risk of overdosing again and starting concurrent intensive rehabilitation. This biases the result in favour of BI; in the absence of data to populate more advanced statistical methods to adjust for competing events, additional health states could be added to account for patients experiencing adverse events with durations longer than a cycle length, reducing the impact of such double counting.

**Cost of comparator overestimated**: The manufacturer asserted in its pharmacoeconomic submission that 12 mg of SL BUP/NLX was equivalent to 8 mg of SL BUP alone, as used at baseline by the majority of patients in trial PRO-814, citing the SL BUP/NLX product monograph. CDR was unable to find any mention of differential dosing of buprenorphine with and without naloxone in the product monograph. While SL BUP alone is not available in Canada, the recommended BUP target dose of both products is identical in the US.[10,11] Additionally, a retrospective cohort study found that the vast majority of patients who were switched from SL BUP to SL BUP/NLX remained on the same dose of BUP and, of those who changed dose, most reduced it.[12] The clinical expert consulted by CDR also did not find this assumption valid. Aligning the dosing of BUP/NLX in the model with the doses described in the SL BUP/NLX arm of PRO-814 increases the ICUR of BI compared with SL BUP/NLX from dominant to $48,832 per QALY.

**Rates and costs of events associated with IVDU bias in favour of BI**: The assumptions regarding the consequences of IVDU bias results in favour of BI. For example, the model estimates that cellulitis will cost an average of $237 more per patient using SL BUP/NLX than those using BI over one year; however, there was only a single incident of cellulitis observed in each arm of the six-month PRO-814 trial.[3] Additionally, given the one-year time horizon, it is unlikely that patients would be screened, diagnosed, and treated for HCV or HIV immediately upon relapsing to IVDU; in reality, most cases would be diagnosed and treated in future years, which would be discounted in a model with a longer time horizon. HCV was associated with an additional $167 per SL BUP/NLX patient, biasing the results in favour of BI.

**Costs associated with supplemental SL BUP/NLX not considered**: 17.9% of BI and 14.6% of SL BUP/NLX patients received supplemental BUP/NLX in addition to their assigned treatments, with a higher number of supplemental sublingual tablets not returned in the BI arm. These costs and the risk of abuse in the BI arm were not considered by the manufacturer, despite substantial risks and downstream costs being associated with the use of SL BUP/NLX tablets in the model.

**Cost of removing second implant not considered for most BI patients**: The manufacturer excluded the cost of explanting the second set of implants for all BI patients who did not discontinue treatment during the model, artificially reducing the cost of BI administration. As the monograph states that the implant should be removed by the end of

the sixth month, and removal would be required within close proximity to the end of the time horizon regardless, the exclusion of the cost of explantation was inappropriate.

## CADTH Common Drug Review Reanalyses

The inflexibility and lack of transparency within the manufacturer's model limited the ability of CDR to conduct reanalyses. Of the limitations described previously, CDR was able to conduct reanalyses:

- correcting the dose of SL BUP/NLX used
- incorporating the cost of all BI explantations (the manufacturer excluded the cost of explanting the second dose of BI for all patients who did not discontinue treatment)
- incorporating the costs and risk of IVDU abuse associated with supplemental SL BUP/NLX as used in the PRO-814 trial. In order to incorporate the use of supplemental SL BUP/NLX, a monthly average number of an additional 2 mg of SL BUP as dispensed in the PRO-814 trial was calculated for the 17.9% and 14.6% of BI and SL BUP patients who were given them in the trial. Dispensing fees were included based on the number of dispensing episodes reported.[4] Of the 17.9% of BI patients receiving supplemental SL BUP/NLX, 16.3% were assumed to abuse it intravenously, consistent with the 16.3% of SL BUP/NLX patients assumed to do so by the manufacturer
- removing the costs associated with diagnosing and treating HIV and HCV given the short time horizon. The downstream costs associated with risks due to IVDU were thus also incorporated for this proportion of the BI group. This reanalysis impacted incremental costs but not QALYs, as IVDU-related adverse events were not associated with an impact on quality of life in the model.

Additionally, CDR excluded the 8% markup incorporated into the cost of both SL BUP/NLX and BI.

### Table 3: CDR Reanalyses Exploring Limitations of the Manufacturer's Model

| | Description | Manufacturer's Base-Case Value | CDR Value | Incremental Cost ($) | Incremental QALYs | ICUR ($) |
|---|---|---|---|---|---|---|
| | **Manufacturer's base case** | Reference | | −201 | 0.023 | Dominant |
| | **ODB markup removed** | 8% markup applied to drug acquisition costs | No markup applied | −292 | 0.023 | Dominant |
| 1 | **SL BUP/NLX dose consistent with SL BUP arm of PRO-814** | BUP/NLX dose assumed to be BUP + 2 mg or 4 mg<br>4 mg/day: 3.4%<br>6 mg/day :16.9%<br>8 mg/day: 4.5%<br>12 mg/day: 75.3% | BUP/NLX dose assumed equivalent to BUP<br>2 mg/day: 3.4%<br>4 mg/day :16.9%<br>6 mg/day: 4.5%<br>8 mg/day: 75.3% | 1,110 | 0.023 | 48,832 |
| 2 | **All explant costs included** | Explant of second BI dose not included, unless patient discontinued therapy | Cost of explanting all remaining BI added to last cycle | −177 | 0.023 | Dominant |

| | Description | Manufacturer's Base-Case Value | CDR Value | Incremental Cost ($) | Incremental QALYs | ICUR ($) |
|---|---|---|---|---|---|---|
| 3 | **Include cost and risk of abuse of supplemental SL BUP/NLX** | Supplemental BUP/NLX not included | BI group: 17.9% of patients, average monthly cost $26.05<br>SL BUP/NLX group: 14.6% of patients. Average monthly cost: $17.14 | −55 | 0.023 | Dominant |
| 4 | **Remove costs of chronic infection** | Cost of HCV and HIV infection included immediately upon seroconversion | Cost of HCV and HIV not included due to time horizon | −31 | 0.023 | Dominant |
| **1 to 4** | **CDR reanalysis** | | | 1,234 | 0.023 | 54,291 |

BI = buprenorphine implant; BUP = buprenorphine; BUP/NLX = buprenorphine/naloxone; CDR = CADTH Common Drug Review; HCV = hepatitis C virus; ICUR = incremental cost-utility ratio; ODB = Ontario Drug Benefit; QALY = quality-adjusted life-year; SL = sublingual.

Of these reanalyses, the adjustment of SL BUP/NLX dosing to be consistent with the doses of SL BUP/NLX described in PRO-814 had the largest impact on the ICUR. Incorporating all four reanalyses together into a CDR reanalysis and removing the 8% markup resulted in an ICUR of $54,291 per QALY (Table 3).

When a scenario was considered where patients who were stabilized on low doses of SL BUP/NLX therapy received supplies of SL BUP/NLX monthly rather than weekly, the ICUR increased to $61,266 per QALY (Table 14). Additionally, the publicly posted list prices of SL BUP/NLX vary between jurisdictions; incorporating the Alberta public list prices for SL BUP/NLX resulted in an ICUR of $30,534 per QALY for BI, while those of New Brunswick resulted in an ICUR of $66,303 per QALY (Table 15). Finally, the ICUR was sensitive to varying either the underlying monthly risk of a patient relapsing to illicit opioid use when using SL BUP/NLX, or the hazard ratio associated with using BI instead. For example, adjusting the hazard ratio of monthly relapse for patients using BI relative to those using SL BUP/NLX to either 0.25 or 0.97 (the limits of the 95% CI for time to first evidence of illicit opioid use), resulted in ICURs of $27,363 per QALY and $1,405,583 per QALY, respectively (Table 16).

Under the assumptions of CDR's main reanalysis (Table 3), the price of BI would need to be reduced by 4% to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY, and by 23% at a willingness to pay of $25,000 per QALY.

## Issues for Consideration

- Continuous, long-acting treatment may be beneficial in remote communities or for patients who lack secure housing.
- As BI is implanted at six-month intervals rather than taken orally on a daily basis, it may increase adherence in some patients, although no studies have been done to capture this outcome.
- Patients not having to take or have medication dispensed over short regular intervals may find this helps them to avoid facing stigma for their opioid dependence.
- Although the long duration and infrequent administration of BI is likely to be of benefit to some patients, the clinical expert consulted by CDR for this review expressed concern that it may lead to a reduction in patients attending regular appointments with health care

providers and/or attending opioid dependence counselling sessions, as it will no longer be necessary for them to regularly see their physician for prescription renewals.

- The cost of training physicians in the administration and removal of BI is unknown.

## Patient Input

No input from patient groups was received for this submission.

## Conclusions

In adults with clinically stable opioid dependence adequately managed on low doses of SL BUP, BI (320 mg total dose) was noninferior to SL BUP at doses of up to 8 mg per day based on the proportion of responders, defined as those with no evidence of illicit opioid use for at least four out of six months. The economic evaluation was based on a secondary outcome from the PRO-814 trial, time to first evidence of illicit use, which is of uncertain clinical relevance and which was not part of the fixed statistical testing procedure and, thus, should be interpreted as inconclusive. In addition, limitations within the manufacturer's model did not permit a full examination of the uncertainty in all parameters of interest.

The annual acquisition cost of BI ($2,990 per patient per year) is more expensive than that of SL BUP/NLX ($487 to $1,462 per patient per year for doses of between 2 mg and 8 mg per day). As there is no current experience with BI beyond two implants, it is also unknown how long patients will continue to use BI and what the impact of switching to another therapy thereafter might be.

# Appendix 1: Cost Comparison

The comparators presented in Table 4 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 4: CDR Cost Comparison Table for Opioid Dependence Disorder

| Drug/ Comparator | Strength | Dosage Form | Price ($) | Recommended Dosage | Average Cost per Month ($) | Average Cost per Year ($) |
|---|---|---|---|---|---|---|
| **Buprenorphine hydrochloride (Probuphine)** | **80 mg × 4** | **Subdermal implant** | **1,495.0000[a]** | **4 implants; may be repeated once after six months** | **249** | **2,990** |
| Buprenorphine/ naloxone (generics) | 2 mg/0.5 mg<br>8 mg/2 mg | Sublingual tablet | 1.3350<br>2.3650 | 12 mg to 16 mg per day<br>2 mg to 8 mg per day considered as BI is not indicated in patients taking more than 8 mg buprenorphine | 40 to 120 | 487 to 1,462 |
| Methadone (Metadol-D) | 1 mg<br>5 mg<br>10 mg<br>25 mg<br>1 mg/mL<br>10 mg/mL | Tablet<br>Tablet<br>Tablet<br>Tablet<br>Solution<br>Solution | 0.1733[b]<br>0.5775[b]<br>0.9238[b]<br>1.7166[b]<br>0.1084[b]<br>0.1500 | 15 to 40 mg daily for up to 180 days[c] | 46 to 98<br><br><br><br>7 to 18 | 546 to 1,171<br><br><br><br>82 to 218 |
| Naltrexone (generics) | 50 mg | Tablet | 7.3025 | 50 mg daily | 222 | 2,658 |

CDR = CADTH Common Drug Review.

[a] Manufacturer's submitted price.[2]

[b] DeltaPA database, IQVIA (March 2018).[14]

[c] Maximum dose is 120 mg per day. Maintenance may continue beyond 180 days.

Source: Ontario Drug Benefit (March 2018),[13] unless otherwise noted; annual period assumes 52 weeks, 365 days.

# Appendix 2: Summary of Key Outcomes

## Table 5: When Considering Only Costs, Outcomes and Quality of Life, How Attractive is Buprenorphine Implant Relative to Sublingual Buprenorphine/Naloxone?

| Buprenorphine Implant Versus Sublingual Buprenorphine/ Naloxone | Attractive | Slightly Attractive | Equally Attractive | Slightly Unattractive | Unattractive | N/A |
|---|---|---|---|---|---|---|
| **Costs (total)** | | | | X | | |
| **Drug treatment costs alone** | | | | X | | |
| **Clinical outcomes** | | X | | | | |
| **Quality of life** | | X | | | | |
| **Incremental CE ratio** | $54,291 per QALY based on CDR reanalysis over a one-year time horizon.<br><br>This result is considered uncertain, as clinical uncertainty and limitations with the manufacturer's evaluation could not be fully addressed. | | | | | |

CDR = CADTH Common Drug Review; CE = cost-effectiveness; N/A = not applicable; QALY = quality-adjusted life-year.

# Appendix 3: Additional Information

## Table 6: Submission Quality

| | Yes/ Good | Somewhat/ Average | No/ Poor |
|---|---|---|---|
| Are the methods and analysis clear and transparent? | | | X |
| Comments<br>Reviewer to provide comments if checking “no” | Model is not laid out in a standard manner, many inputs are hard-coded and poorly or not referenced, and the submitted report is insufficiently thorough in explaining methodology. | | |
| Was the material included (content) sufficient? | | X | |
| Comments<br>Reviewer to provide comments if checking “poor” | None | | |
| Was the submission well organized and was information easy to locate? | | | X |
| Comments<br>Reviewer to provide comments if checking “poor” | See above | | |

## Table 7: 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 | | |

# Appendix 4: Reviewer Worksheets

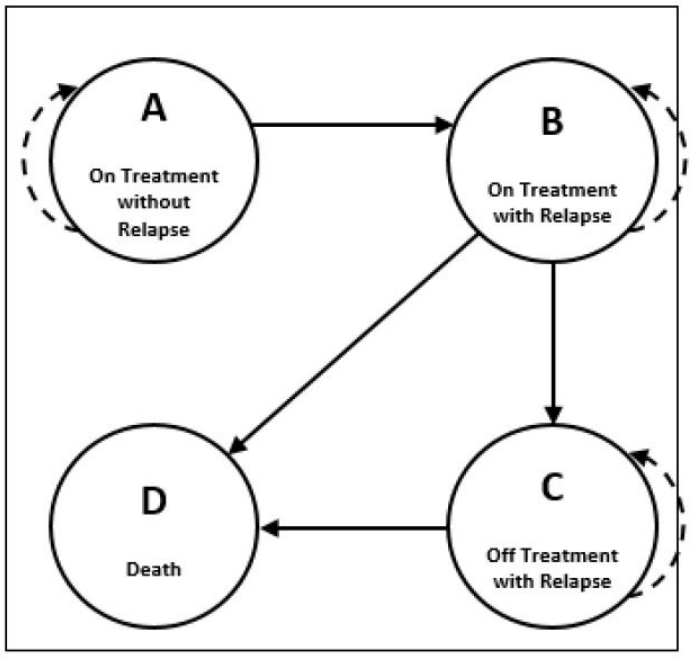
## Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis comparing buprenorphine implant (BI) with sublingual buprenorphine/naloxone (SL BUP/NLX) in adult patients with opioid drug dependence previously stabilized on SL BUP/NLX therapy. The base case was a deterministic Markov state–transition model consisting of 1,000 hypothetical patients per treatment arm from the perspective of a Canadian public health care payer with a time horizon of one year with monthly cycles. As the time horizon was not longer than one year, costs and benefits were not discounted. No half-cycle correction was incorporated. The manufacturer also provided a probabilistic analysis incorporating 1,000 simulations.

The model consisted of four health states: on treatment without relapse (state A), on treatment with relapse (state B), off treatment with relapse (state C), and death (state D). All patients entered the model in state A and could transition to state B at the end of the first cycle; once in state B, patients could transition to state C. Mortality was only a possibility for patients in states B or C, and fewer than 1 in 1,000 patients died over the duration of the model. States B and C were further divided, with 21% of patients assumed to relapse to intravenous heroin use, while the remainder relapsed to prescription opioids. These sub-states were associated with different utilities and risks of adverse events.

It was not possible for patients in the model to return to the non-relapsed state, to remain not relapsed if off therapy, or to return to therapy once discontinued (Figure 1**).**

### Figure 1: Manufacturer's State Transition Model Structure




Source: Manufacturer's pharmacoeconomic submission, Figure 1, page 14.[2]
Originally published by Carter et al.[15]

The transition probabilities from state A to state B were derived from the PRO-814 trial, a 26-week, double-blind randomized controlled trial of 177 patients randomized to receive BI or SL BUP/NLX,[3] with relapse rates (defined as first evidence of opioid use by urine sampling) observed in the six-month trial extrapolated out to 12 months, using the exponential function as best fit. The transition probability in the BI group was based on the longer time to first evidence of opioid use reported in the PRO-814 trial, leading to a hazard ratio of 0.49 (95% CI: 0.25 to 0.97).[3] The confidence interval around the hazard ratio was used to calculate standard deviation to inform the distribution used in the manufacturer's probabilistic analysis around the relative efficacy parameter. A range of plus or minus 25% was used to vary all other transitions within the probabilistic analysis, with the exception of the transition from state A to B in the SL BUP/NLX group, which was held static instead. Transitions from state B to C and/or D were derived from observation studies to offset the artificial nature of clinical trials in terms of discontinuation and mortality.[5,6] Mortality within the model incorporated only fatal overdose; all-cause mortality was not included (Table 8).

## Table 8: Health State Transition Probabilities Within Manufacturer's Model

| Health State | BI | SL BUP/NLX | Cited Source |
|---|---|---|---|
| State A to B | 0.0260[a] | 0.0535[b] | Rosenthal[3] |
| State B to C | 0.0530 | | Campbell[5] |
| State B to D | 0.0001 | | Sordo[6] |
| State C to D | 0.0004 | | Sordo[6] |

BI = buprenorphine implant; SL BUP/NLX = sublingual buprenorphine/naloxone.

[a] Based on a hazard ratio of 0.49 (0.28 to 0.97; *P* = 0.37) from the PRO-814 trial.[3]
[b] Calculation method from the data provided in the PRO-814 trial[3,4] not specified.

Source: manufacturer's pharmacoeconomic submission, Excel model.[2]

Utilities for non-death health states were obtained from a UK panel of 22 members of the general population using the standard gamble technique (Table 9).[7,8]

## Table 9: Health State Utility Weights in Manufacturer's Model

| Health State | Utility | Proportion of Patients Within State | SD From Utility Source[8] | SD Used in Model[2] |
|---|---|---|---|---|
| State A: On treatment without relapse | 0.867 | 100% | 0.152 | 0.111 |
| State B: On treatment with relapse to heroin | 0.633 | 21% | 0.208 | 0.081 |
| State B: On treatment with relapse to prescription opioids | 0.683 | 79% | 0.204 | 0.087 |
| State C: Off treatment with relapse to heroin | 0.588 | 21% | 0.202 | 0.075 |
| State C: Off treatment with relapse to prescription opioids | 0.678 | 79% | 0.217 | 0.086 |
| State D: Death | 0.000 | 100% | NA | NA |

NA = not applicable; SD = standard deviation of utilities.

Source: Based on manufacturer's pharmacoeconomic submission, Appendix 1 and Excel model.[2] Originally from Connock et al.[8]

Patients who relapsed to states B and C in either treatment group were at risk of adverse events such as non-fatal overdose, use of emergency and rehab services, acute infections from intravenous drug use (IVDU), and chronic infections such as HIV or hepatitis C virus (HCV) from IVDU. These events were associated with costs in the model but not decrements to quality of life. Additionally, 16.3% of patients in the SL BUP/NLX group were

assumed to misuse their treatment intravenously, which did not count as a relapse for the sake of state transition and quality-adjusted life-year (QALY) calculation, but was incorporated into the risk of overdose, the use of emergency services due to overdose, and the risk of infections due to IVDU. Adverse events potentially specific to BI were not explored (Table 10).

## Table 10: Probabilities and Costs Associated With Adverse Events in Manufacturer's Model

| Adverse Event | Probability of Event | Cost of Event |
|---|---|---|
| Misuse of SL BUP/NLX | 0.163 | NA |
| **Associated with IVDU (applied to patients using heroin in States B and C, and patients misusing SL BUP/NLX)** | | |
| Cellulitis | 0.027 | 4,047 |
| Endocarditis | 0.001 | 8,599 |
| Phlebitis | 0.004 | 1,377 |
| Skin infection/abscess | 0.010 | 4,499 |
| Hepatitis C virus | 0.013 | 18,158 (divided by 12 per cycle) |
| HIV | 0.001 | 68,950 (divided by 12 per cycle) |
| **Associated with relapse and misuse (applied to patients in states B and C, and patients misusing SL BUP/NLX)** | | |
| Non-fatal overdose in treatment (state B and patients in state A misusing SL BUP/NLX) | 0.017 | 0 |
| Non-fatal overdose out of treatment (state C) | 0.038 | 0 |
| Use of emergency services assuming overdose | 0.600 | 537 |
| Hospital admittance assuming emergency services (3 days) | 0.528 | 3,630 |
| Intensive outpatient rehab assuming hospital admittance (90 days) | 0.200 | 54,000 |
| In-patient rehab assuming hospital admittance (28 days) | 0.150 | 15,400 |
| Intensive outpatient rehab assuming emergency services (90 days) | 0.300 | 54,000 |
| In-patient rehab assuming emergency services (28 days) | 0.100 | 15,400 |

IVDU = intravenous drug use; NA = not applicable; SL BUP/NLX = sublingual buprenorphine/naloxone.

Costs were derived from the Ontario Drug Benefit Formulary (2017) for SL BUP/NLX and pharmacy fees, the manufacturer for BI, and the Ontario Schedule of Benefits for Physicians Services for implant insertion and removal as well as for patient counselling and urine testing. Costs for emergency services and detoxification in hospital were derived from the Ontario Case Costing Initiative and expert opinion, while costs for adverse events were sourced from several Canadian economic analyses (Table 11). All costs were converted to 2017 Canadian dollars when required using the Statistics Canada Consumer Price Index for health care.

## Table 11: Data Sources

| Data Input | Description of Data Source | Comment |
|---|---|---|
| **Efficacy** | Based on the hazard ratio of time to first evidence of illicit opioid use over 24 weeks reported in PRO-814; assumes a 20% penalty on imputation of missing urine results. | Incorporates 95% confidence interval reported in Rosenthal,[3] however, no scenario analyses were conducted, such as assuming all or a higher proportion of missing urine samples were positive. |
| **Natural history** | There is no untreated group. The rate of transition from state A to state B in the SL BUP/NLX group was reported as the cumulative percentage in the SL BUP group in PRO-814, with evidence of opioid use at six months. | Does not appear to be directly reported in Rosenthal[3] or the CSR.[4] Referenced in the economic submission as "after several; extrapolations […] exponential function was chosen over other parameter models." Actual method of approximation and calculations is unclear. This parameter remained static within the submitted PSA; however, manually varying it had a large impact on the ICUR. |
| **Utilities** | Taken from a previous US cost-effectiveness study of long-term SL BUP/NLX versus no treatment[7] that used utilities derived from a UK study of 22 members of the general public using the standard gamble method.[8] | While the UK study provided the standard deviation for each utility, the manufacturer calculated standard deviation within the model based on a plus or minus 25% range. |
| **Adverse events** | SL BUP/NLX misuse; non-fatal overdose; infections, including cellulitis, endocarditis, phlebitis, skin infections, and HCV and HIV, all with IVDU; were considered and cited from Lofwall, White, and Villano.[16-18] | Manufacturer states that monthly risk of acute infections due to IVDU is derived from annual incidence rates reported in White;[17] however, White appears to report only prevalence rates. Method of calculation is unclear. While Villano 1997[18] does report incidence rates for HCV and HIV in IVDU, the manufacturer's extraction of this data is also unclear and the age of the publication may limit its generalizability to the current clinical situation. |
| **Mortality** | Derived through an unspecified method from a systematic review and meta-analysis of mortality risk during opioid substitution treatment, based on death due to overdose in patients using buprenorphine in and out of opioid dependence treatment.[6] | Does not account for all-cause mortality; patients can die only once they have relapsed and only due to overdose. All-cause mortality rates reported in Sordo[6] are substantially higher than overdose mortality rates in all categories. |
| **Resource Use and Costs** | | |
| **Drug** | The cost of BI was supplied by the manufacturer. The cost of BUP/NLX was based on the ODB Formulary list price. | Drug prices were adequately sourced; however, the manufacturer did not incorporate the cost of supplemental BUP/NLX, as used in the PRO-814 trial into either group. Additionally, there is substantial variation in publicaly posted list prices for SL BUP/NLX across jurisdictions.[14] |
| **Administration** | Patients using SL BUP/NLX were assumed to incur an $8.83 dispensing fee (ODB) every seven days they were on treatment.<br><br>BI patients were assumed to incur a $31.05 (unspecified but presumably assumed equal to G342 implantation of hormone pellets) and $25.25 explant (presumably Z1114 foreign body removal under local anesthetic) every six months they were on treatment (Ontario Schedule of Benefits for Physician Services). However, the manufacturer did not include the cost of the second explantation in patients who did not | The manufacturer assumed that patients would receive SL BUP/NLX in one-week supplies, incurring a dispensing fee every seven days. CDR's clinical expert believed many patients who had been stabilized for some time (such as those in the PRO-814 trial) would receive monthly supplies, reducing administration costs for tablets.<br><br>The manufacturer did not consider that approximately 5% of patients in PRO-814[3] (9 cases in 176 patients: 4 with active implant, 5 with placebo implant) required ultrasound to locate non-palpable implants for removal, which would slightly increase administration costs for BI. |

| Data Input | Description of Data Source | Comment |
|---|---|---|
| | discontinue therapy before the end of the time horizon. | This fee would likely be of similar value to J149: Ultrasonic guidance of biopsy, aspiration, amniocentesis or drainage procedures ($36.85).<br><br>Dispensing fees and drug costs for the proportion of BI patients receiving supplemental SL BUP/NLX in PRO-814 were also not considered. |
| **AEs** | Costs associated with adverse events are drawn from a variety of economic sources, with emergency services and hospitalization from the Ontario Case Costing Initiative, rehabilitation from Bellwood Health Services (Toronto), cellulitis, chronic HCV and HIV from Canadian analyses,[19-21] endocarditis from a UK analysis,[22], and phlebitis, skin abscess/infection, and pediatric overdose from American sources.[17,23] Non-Canadian sources were converted to Canadian dollars and all sources were inflated to 2017 figures using the Statistics Canada Consumer Price Index for health care.[2] | Sources are Canadian where available. Costs from the US are less likely to be transferable; however, given the very small number of patients affected by HIV, this is unlikely to have much impact on the model.<br><br>Contrary to the manufacturer's submitted report, costs for pediatric poisoning were not included in the submitted model; costs were listed, but no risk was incorporated. |
| **Health state** | Time spent in on-treatment health states (states A and B) were associated with drug acquisition and administration costs, as well as costs for regular urine testing and counselling. The cost of urine tests and counselling were doubled in state B (relapsed, on treatment) compared with state A (not relapsed, on treatment). State C was not associated with any underlying costs, outside of the consequences of adverse events. | No description or source was referenced for the doubling of counselling and urine test costs, although CDR's clinical expert did not find the assumption unreasonable. |

AE = adverse event; BI = buprenorphine implant; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; HCV = hepatitis C virus; ICUR = incremental cost-utility ratio; IVDU = intravenous drug use; ODB = Ontario Drug Benefit; PSA = probabilistic sensitivity analysis; SL BUP/NLX = sublingual buprenorphine/naloxone.

## Table 12: Manufacturer's Key Assumptions

| Assumption | Comment |
|---|---|
| Patients cannot revert to non-relapsed state | • In clinical practice, patients can experience short-term relapses and subsequently return to a state of remission. The model relegates these patients to a lower utility value for the remaining duration of the time horizon.<br>• The expert consulted by CDR considered the primary outcome of the PRO-814 trial (proportion without evidence of opioid use for 4 out of 6 months) or unmeasured outcomes such as patient quality of life or functioning to be more relevant to clinical practice than time to first evidence of opioid use, as short-term relapse is less relevant than long-term remission. |
| No half-cycle correction applied | • Unlikely to introduce significant bias, given cycle length is one month. |
| 26-week trial results extrapolated to one year | • Manufacturer attempted several extrapolations and found the exponential function to have the best fit, although a Weibull distribution was also included as an option. This is acceptable if done correctly; however, calculations and excluded results were not been provided for assessment, nor was the ability to examine alternative assumptions around imputed data made possible within the model. |
| Time horizon | • A one-year time horizon (technically, 11 one-month cycles) was not considered sufficient to capture long-term patient outcomes by CDR, given that long-term replacement therapy for opioid dependence is common in practice.<br>• BI has not currently been tested for use after two six-month cycles. No data were presented |

| Assumption | Comment |
|---|---|
| | to assess the outcomes for patients who switch back to SL tablets, nor of patients who continue BI therapy beyond one insertion in each arm. Treatment paradigms and clinical outcomes for BI patients after 12 months are unknown, increasing uncertainty in its long-term cost-effectiveness.<br>• The 12-month time horizon allowed the manufacturer to avoid considering the cost of explanting the second set of implants all BI patients who did not discontinue treatment during the model received, artificially reducing the cost of BI administration. As the monograph states, the implant should be removed by the end of the sixth month; therefore, this was inappropriate.<br>• Incorporating the cost of chronic infections such as HIV and HCV within a one-year time horizon assumes all patients will be diagnosed and treated immediately upon seroconversion, which biases the results in favour of BI. In reality, most patients would likely be diagnosed after the one-year time horizon; costs and effects associated with HCV and/or HIV infection in future years would be discounted in a longer model. |
| Utilities modelled using log-normal distribution with 25% variability | • The manufacturer states in its submission (Appendix 1) that health state utilities are modelled using beta distributions based on utilities and standard deviations in Connock et al.,[8] however, the model itself incorporates log-normal distributions and the ± 25% range used for parameters with unknown variation. This is inappropriate. |
| Supplemental use of SL BUP/NLX not considered in BI group | • In PRO-814, 17.9% of patients receiving BI and 14.6% of SL BUP/NLX patients also received supplemental SL BUP/NLX tablets. It is inappropriate for the manufacturer to not consider the drug and acquisition costs as well as the risk of intravenous SL BUP/NLX misuse for these patients. |
| Disutilities for AEs not incorporated | • While modelled patients accrued costs when they experienced AEs ranging from cellulitis to non-fatal overdose to HCV seroconversion, these events were not associated with a detriment to quality of life in the model. This assumption likely biases the results in favour of SL BUP/NLX in the base case, but also negates the ability to test the full impact of alternative scenarios, such as the incorporation of supplemental SL tablets for both treatment groups into the model. |
| Mortality due to overdose only | • Not appropriate; however, over a one-year horizon, incorporating all-cause mortality is unlikely to have significant impact on the model. |
| Relapse to prescription opioid or intravenous heroin use | • The model assumes patients will relapse to either prescription opioids (79%) or heroin (21%) in a proportion equivalent to the primary substance of abuse at baseline in the PRO-814 trial. It is reasonable to assume that patients would be most likely to revert to their previous mode of substance abuse. |
| Methadone was not considered a comparator | • While the clinical expert consulted by CDR considered methadone to still be in common use for patients with opioid drug dependence in Canada, given that the indication for BI is for patients who have been stabilized on low doses of SL buprenorphine, it is unlikely that BI therapy will directly displace the use of methadone. |

AE = adverse event; BI = buprenorphine implant; CDR = CADTH Common Drug Review; HCV = hepatitis C virus; SL = sublingual; SL BUP/NLX = sublingual buprenorphine/naloxone.

## Manufacturer's Results

The key results as presented by the manufacturer have been reported in the main body of this report. The manufacturer presented a deterministic analysis as the base case. The use of BI rather than SL BUP/NLX was associated with an additional 0.023 QALYs per patient over the one-year time horizon, and a reduction in costs of $201 (Table 2).

While the drug acquisition cost of BI was more expensive than SL BUP/NLX ($3,199 per patient compared with $1,900), BI was associated with lower administration costs (weekly pharmacy fees for SL BUP/NLX compared with semi-annual implantation for BI), lower urine

testing and patient counselling costs, and lower downstream costs due to overdose, rehabilitation services, and adverse events (Table 13).

### Table 13: Breakdown of Manufacturer's Deterministic Base-Case Costs

| Component | BI ($) | SL BUP/NLX ($) | Difference ($) |
|---|---|---|---|
| **Treatment costs** | | | |
| Drug acquisition | 3,199 | 1,900 | 1,181 |
| Administration[a] | 88 | 406 | −319 |
| Urine testing and counselling | 614 | 656 | −43 |
| **Cost of relapse and overdose** | | | |
| Emergency services and hospitalization | 47 | 127 | −80 |
| Rehabilitation services | 478 | 1,002 | −524 |
| IVDU-related infections | 81 | 610 | −529 |
| Fatal overdose | 8 | 15 | −7 |
| **Total costs** | **4,515** | **4,716** | **−201** |

BI = buprenorphine implant; IVDU = intravenous drug use; SL BUP/NLX = sublingual buprenorphine/naloxone.

[a] Administration includes implantation and some explantation for the BI group, and weekly dispensing fees for the SL BUP/NLX group.

Source: Adapted from the manufacturer's pharmacoeconomic submission, Table 1.[2]

The manufacturer also provided probabilistic results based on 1,000 iterations; however, the CADTH Common Drug Review (CDR) was not confident enough in the methods used, particularly in the distributions chosen for health state utility values, to consider the results appropriate.

## CADTH Common Drug Review Reanalyses

### Scenario Analyses

The manufacturer assumed that all patients receiving SL BUP/NLX would receive their medications in weekly supplies, accruing a dispensing fee ($8.83, based on Ontario Drug Benefit Formulary) four times monthly, based on unspecified claims data and expert opinion. Given that the indication for BI is for patients stabilized on sublingual buprenorphine (BUP) therapy, and the average length of BUP therapy for patients in PRO-814 was 3.5 years at baseline, the expert consulted by CDR believed that many patients would instead receive monthly supplies of SL BUP/NLX.

## Table 14: Impact of Monthly Sublingual Buprenorphine/Naloxone Prescriptions

| Description | Incremental Cost ($) | Incremental QALYs | ICUR ($) |
|---|---|---|---|
| Manufacturer's analysis<br>7-day SL BUP/NLX prescriptions | −201 | 0.023 | Dominant |
| Manufacturer's analysis<br>30-day SL BUP/NLX prescriptions | 104 | 0.023 | 4,558 |
| CDR's analysis<br>7-day SL BUP/NLX prescriptions | 1,234 | 0.023 | 54,291 |
| CDR's analysis<br>30-day SL BUP/NLX prescriptions | 1,539 | 0.023 | 67,703 |

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SL BUP/NLX = sublingual buprenorphine/naloxone.

Additionally, list prices for SL BUP/NLX vary substantially across jurisdictions and may not reflect actual costs paid by drug plans. While the Ontario Drug Benefit Formulary reports a list price of $1.34 and $2.37 for the 2 mg/0.5 mg and 8 mg/2 mg SL BUP/NLX tablets respectively, Alberta's list prices are $2.67 and $4.73, while New Brunswick's are $0.67 and $1.18.[14] This variation may substantially impact the estimated incremental cost-utility ratio (ICUR), depending on jurisdiction (Table 15).

## Table 15: Impact of Sublingual Buprenorphine/Naloxone List Price Variation Across Jurisdictions

| Description | Incremental Cost ($) | Incremental QALYs | ICUR ($) |
|---|---|---|---|
| Manufacturer's analysis, Ontario list prices | −201 | 0.023 | Dominant |
| Manufacturer's analysis, Alberta list prices | −2,088 | 0.023 | Dominant |
| Manufacturer's analysis, New Brunswick list prices | 752 | 0.023 | 33,080 |
| CDR's analysis, Ontario list prices | 1,234 | 0.023 | 54.291 |
| CDR's analysis, Alberta list prices | 694 | 0.023 | 30,534 |
| CDR's analysis, New Brunswick list prices | 1,507 | 0.023 | 66,303 |

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

While the manufacturer attempted to incorporate uncertainty in the risk of relapse for patients using SL BUP/NLX, as well as the hazard ratio modelling the relative treatment effect of BI in their probabilistic analysis, CDR's lack of confidence in the methods used for the probabilistic analysis precluded its use in all reanalyses conducted by CDR. Instead, CDR conducted a series of scenario analyses, varying the rate of relapse in the SL BUP/NLX group as well as the relative effect of using BI instead, using the manufacturer's deterministic model. The relative effect of BI was varied by incorporating the 95% confidence interval reported in PRO-814,[3] as well as by assuming that BI was clinically equivalent to SL BUP/NLX (i.e., hazard ratio = 1.00). As the manufacturer did not provide sufficient information on how the monthly relapse probability for the SL BUP/NLX group was calculated from time to first evidence of illicit opioid use, nor the ability to incorporate alternative methods of imputing missing data, CDR explored probabilities that were higher and lower than that assumed in the base-case analysis. Varying either the underlying probability of relapse in the control arm or the hazard ratio for BI has a large impact on ICUR (Table 16), increasing uncertainty in the cost-effectiveness of BI compared with SL BUP/NLX. When BI and SL BUP/NLX are assumed to be equally efficacious, BI is more costly.

## Table 16: Impact of Variation of Sublingual Buprenorphine/Naloxone Transition Probability From State A to State B and Hazard Ratio for Buprenorphine Implant Transition

| Hazard Ratio, Transition From State A to B BI Relative to SL BUP/NLX | Monthly Transition Probability From State A to B for SL BUP/NLX | | |
|---|---|---|---|
| | Probability 0.040 | Probability 0.053[a] | Probability 0.060 |
| **HR: 0.25**[b] | 40,642 per QALY | 27,363 per QALY | 23,135 per QALY |
| **HR: 0.49**[b] | 73,597 per QALY | 54,291[c] per QALY | 48,185 per QALY |
| **HR: 0.75** | 180,854 per QALY | 142,029 per QALY | 129,855 per QALY |
| **HR: 0.97**[b] | 1,724,732 per QALY | 1,405,583 per QALY | 1,306,352 per QALY |
| **HR: 1.00** | BI more costly, equally effective | BI more costly, equally effective | BI more costly, equally effective |

BI = buprenorphine implant; CDR = CADTH Common Drug Review; CI = confidence interval; HR = hazard ratio; QALY = quality-adjusted life-year; SL BUP/NLX = sublingual buprenorphine/naloxone.

[a] Monthly transition probability from state A to B in SL BUP/NLX reported in manufacturer's in economic model.[2]
[b] Hazard ratio (0.49; 95% CI, 0.25 to 0.97) of time to first evidence of opioid use for BI implants relative to SL BUP/NLX from PRO-814.[3]
[c] CDR base-case analysis.

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