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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

BUPRENORPHINE SUBDERMAL IMPLANT (PROBUPHINE — KNIGHT THERAPEUTICS INC.)
Indication: Opioid use disorder

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that buprenorphine subdermal implant be reimbursed for the management of opioid dependence in patients clinically stabilized on no more than 8 mg of sublingual (SL) buprenorphine in combination with counseling and psychosocial support, if the following criteria and conditions are met:

Criteria
- Stabilized on a dose of no more than 8 mg per day of SL buprenorphine for the preceding 90 days.

Conditions
- Patient under the care of a health care provider with experience in the diagnosis and management of opioid use disorder and has been trained to implant the buprenorphine subdermal implant.
- The total cost of buprenorphine subdermal implant should not exceed the total drug plan cost of SL buprenorphine at a dose not higher than 8 mg per day.

Service Line:	CADTH Drug Reimbursement Recommendation
Version:	Final
Publication Date:	August 2018
Report Length:	7 Pages

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

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Reasons for the Recommendation:

1. One double-blind, randomized controlled trial (RCT) (Study 814; N = 177) that enrolled clinically stable adults with opioid dependence who received SL buprenorphine (≤ 8 mg per day) for the preceding 90 days, found that buprenorphine subdermal implants (320 mg total dose) were non-inferior to SL buprenorphine/naloxone (BUP/NLX) at maintaining the proportion of responders at 24 weeks based on a –0.20 non-inferiority margin (per-protocol population; proportion difference, 0.053; 95% confidence interval [CI], –0.022 to 0.129). However, Study 814 did not provide evidence for the effects of buprenorphine subdermal implants as compared with SL BUP/NLX on health-related quality of life or social functioning, or on comparative longer-term efficacy and safety beyond six months of treatment with buprenorphine subdermal implants.
2. The frequency of adverse events associated with buprenorphine subdermal implants was similar to those with SL BUP/NLX in Study 814. However, given the small sample sizes and relatively short duration of exposure, there is uncertainty about the longer-term comparative clinically important adverse effects associated with buprenorphine subdermal implants.
3. At the manufacturer-submitted price of $1,495 per kit, the cost of one year of buprenorphine subdermal implants per patient ($2,990) is more costly than SL BUP/NLX (range: $487 to $1,462 per patient per year for doses between 2 mg to 8 mg per day). A CADTH Common Drug Review (CDR) assessment of the manufacturer-provided cost-utility analysis found several important limitations that could not be addressed by CDR. Hence, it is uncertain whether buprenorphine subdermal implants are cost-effective at the submitted price.

Of Note:

- There is uncertainty regarding the comparative efficacy, safety, and cost-effectiveness of continuing treatment with buprenorphine subdermal implant beyond two six-month cycles due to a lack of evidence. A clinical expert suggested that the duration of treatment depends on the underlying social or medical issues that may have contributed to a patient's opioid use disorder. Some patients remain on therapy indefinitely.
- The product monograph for buprenorphine subdermal implant suggests a treatment duration of one year (i.e., the initial set of implants removed after six months and a new set inserted into the opposite arm for an additional six months), and any patient who requires treatment after one year may be transitioned back to the SL buprenorphine dose they were receiving prior to initiating treatment with buprenorphine subdermal implant. If treatment with buprenorphine subdermal implants is continued beyond one year, the product monograph states that dosing beyond two years cannot be recommended at this

time because of limited experience with inserting additional implants into other sites of the arm, sites other than the upper arm, or re-insertion into previously used sites.

Discussion Points:

- Clinical evidence in support of the indicated population for buprenorphine subdermal implants is limited to a single double-blind, non-inferiority RCT (Study 814) with a relatively small sample size (less than 90 patients per treatment group), short duration of follow-up (24 weeks), and limited data on clinically important outcomes. The long-term efficacy and safety of buprenorphine subdermal implants is uncertain.
- CDEC heard from a clinical expert with experience in the diagnosis and management of opioid use disorder that buprenorphine subdermal implants are likely suited for those people with an opioid use disorder, especially secondary to prescription opioids, who are stable for at least 90 days on SL BUP/NLX 8 mg or less per day. This reflects the patient population included in Study 814.
- CDEC noted a lack of evidence whether the plasma levels of buprenorphine from buprenorphine subdermal implants are high enough to act as an antagonist should a patient relapse to highly potent opioids, such as fentanyl and or hydromorphone. The clinical expert concurred that this may be a remaining concern for patients who receive buprenorphine subdermal implants; however, the expert suggested that this may be a small issue for the population of patients most likely to receive buprenorphine subdermal implants (i.e., patients stabilized on buprenorphine therapy and who are less likely to engage in high-risk behaviours).
- CDEC noted that the annual administration costs for two rounds of buprenorphine subdermal implant were estimated at $113, while annual pharmacy fees for SL BUP/NLX may range from $106 to $459 depending on the frequency of dispensing (every 30 or every 7 days, respectively). Physicians are likely to require training to administer buprenorphine subdermal implant, the cost of which, and whether public payers will bear that cost, is unknown.

Background:

Buprenorphine implants have a Health Canada indication for for 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. The product is a rod-shaped implant (26 mm by 2.5 mm), which contains 80 mg of buprenorphine hydrochloride (a partial mu-opioid receptor agonist) embedded in ethylene vinyl acetate. The recommended dose is four implants (320 mg) inserted subdermally in the upper arm by trained health care professionals, for six months.

Summary of CDEC Considerations:

CEDAC considered the following information prepared by the CADTH CDR: a systematic review of RCTs of buprenorphine implants and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with opioid use disorder.

No patient groups submitted information about outcomes and issues important to patients.

Clinical Trials

The systematic review included one pivotal double-blind randomized placebo-controlled trial of clinically stable adult patients with opioid dependence, who had received treatment with SL buprenorphine for at least six months and were on doses ≤ 8 mg per day for the past 90 days (Study 814). Patients (N = 177) were randomized to receive 24 weeks of treatment with buprenorphine implants (4 implants) plus placebo SL tablets, or SL BUP/NLX (at the buprenorphine dose they were on prior to study entry; ≤ 8 mg/day) plus four placebo implants (double-dummy). Overall, 6% of patients withdrew from the trial.

Two other placebo-controlled double-blind randomized trials provided supporting evidence for the use of buprenorphine implants in patients with opioid dependence, who had not received treatment for their substance use disorder in the past 90 days. In these trials, patients underwent induction therapy with SL BUP/NLX and those whose withdrawal symptoms and cravings were controlled on 12 mg to 16 mg of buprenorphine daily, were eligible for randomization (Study 806 N = 287; Study 805 N = 163). Patients were randomized to receive four buprenorphine or placebo implants (blinded). Study 806 also randomized patients to open-label SL

BUP/NLX at a dose of 12 mg to 16 mg buprenorphine daily. Both studies were 24 weeks in duration. The frequency of withdrawals was 69% to 74% among patients randomized to placebo implants compared with 34% to 36% in those who received buprenorphine implant or SL buprenorphine.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CEDAC discussed the following: illicit opioid use; retention in treatment; opioid withdrawal symptoms and cravings; need for supplemental treatment; and harms. The primary outcome in Study 814 was the proportion of responders, and for Study 805 and 806, was the cumulative distribution function of the percentage of urine samples that were negative for illicit opioids.

- The proportion of responders was defined as patients with no more than two of six months with any evidence of illicit opioid use. Evidence of illicit opioid use was defined as a positive opioid urine toxicology result or self-reported illicit opioid use.
- The intensity of withdrawal symptoms was evaluated using two instruments. The Subjective Opioid Withdrawal Scale (SOWS) (self-reported) includes 16 questions for subjective symptoms of withdrawal with each item scored from 0 (not at all) to 4 (extremely) for a total ranging from 0 to 64. Higher scores indicate more intense withdrawal symptoms. The Clinical Opioid Withdrawal Scale (COWS) (observer-reported) includes 11 objective opiate withdrawal signs and symptoms which are rated on a numeric scale (0 to 4 or 5 points with higher numbers indicating worse withdrawal symptoms) and based on a timed period of observation of the patient by the rater (total score 47). No data on the minimum clinically important difference (MCID) was found in the literature for either instrument.
- For the assessment of cravings, need to use, or desire to use visual analogue scale (VAS), patients were asked to mark the degree of craving, need, or desire to use since the last visit on a 100 mm VAS, where 0 represents no cravings, desire or need to use, and 100 represents the strongest craving, desire or need. No MCID was identified.
- No data were available on health-related quality of life or social functioning.

Efficacy

In the pivotal trial, more patients in the buprenorphine implant group met the criteria for a responder (96.4%) than in the SL BUP/NLX group (87.6%), with a between-group difference in proportions of 0.088; 95% CI, 0.009 to 0.167 (modified intention-to-treat [mITT] population). The buprenorphine implant was non-inferior to SL buprenorphine as the lower bound of the 95% CI was greater than the –0.20 non-inferiority margin. Buprenorphine implant also demonstrated superiority to SL BUP/NLX ($P = 0.034$) in the primary analysis. Non-inferiority was met in the analysis based on the per-protocol population (proportion difference 0.053; 95% CI, –0.022 to 0.129), but not superiority ($P = 0.18$). Non-inferiority was consistently met based on the other sensitivity analyses conducted by the manufacturer, as well as more conservative post hoc analyses reported by the FDA that used the intention-to-treat population and assumed all missing urine samples were positive. Most sensitivity analyses, however, did not support a superiority claim, and superiority testing was not pre-specified in the study's protocol.

Overall, the proportion of patients who remained in the study was high (94%) and was similar between groups. Participants received a stipend for attending study visits (average of $40/visit). Fifteen patients (18%) in the buprenorphine implant group and 13 patients (15%) in the SL buprenorphine group were dispensed supplemental SL buprenorphine on one or more occasion.

In Study 814, the mean COWS, SOWS, and desire or need to use VAS scores in both treatment groups were generally low at baseline as well as at week 24 (mean COWS ≤ 1.0; SOWS ≤ 2.7; desire or need to use ≤ 6.8), and no statistically significant differences were detected between groups in the change from baseline to week 24 for any of these outcome measures, which were outside the fixed statistical testing procedure.

In the supporting trials (Studies 805 and 806), statistically significant differences were detected between the buprenorphine implant and placebo implant groups in the cumulative distributions function of the percentage of urine samples negative for illicit opioids. The buprenorphine implant was non-inferior to SL buprenorphine based on the proportion of negative urine tests, as the lower bound of the 95% CI for the between-group difference (–10.7%) was higher than the –15% non-inferiority margin.

Harms (Safety and Tolerability)

- Adverse events were reported by most patients. Frequency varied between studies, ranging from 56% to 58% in Study 814, from 67% to 72% in Study 806, and from 82% to 86% in Study 805.
- Among patients who received buprenorphine implants, 2% to 5% experienced a serious adverse event, compared with 6% and 7% of those in the placebo implant group and 3% to 6% in the SL BUP/NLX groups. The proportion of patients who stopped treatment due to adverse events was generally low and ranged from 0% to 4%.
- The frequency of implant-site adverse events was high in Study 805 (46% to 57%) and its extension study, and consequently the manufacturer modified the applicator, insertion and removal procedures, and the training materials for Studies 806 and 814. Implant-site adverse events were reported in 14% to 27% of patients in these two trials and no patients stopped treatment or had a serious adverse event related to the implant site.
- There was one patient per group who experienced an overdose in Study 806, and one incident of accidental pediatric overdose in SL BUP/NKX group in Study 814.
- The available data are limited to treatment durations of up to one year (one set of implants per arm), and the product monograph states there is no experience with inserting additional implants into other sites of the arm, sites other than the upper arm or re-insertion into previously-used sites.

Cost and Cost-Effectiveness

Buprenorphine implant is available in kits containing four individually packaged 80 mg implants at a submitted price of $1,495 per kit. Recommended dose is four implants (320 mg total) inserted subdermally in the inner side of the upper arm for up to six months and 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 buprenorphine implant to SL BUP/NLX tablets in adult patients with opioid drug dependence previously stabilized on SL BUP/NLX therapy (up to 8 mg/day of sublingual buprenorphine, stated as equivalent to up to 12 mg/day of SL BUP/NLX). 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 Study 814, with time to first evidence of opioid use by urine sampling or self-report as the parameter of interest. Transitions from State B to C and/or D were derived from observation studies. Utilities for non-death health states were obtained from a UK panel. 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.

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

- The model structure was inflexible and non-transparent, complicating the review and the conduct of reanalyses.
- The selected clinical efficacy parameter was of uncertain relevance and the model structure did not adequately reflect clinically meaningful outcomes.
- The analysis time horizon was insufficient to capture the potential impact on clinical and harms outcomes of the included treatments.
- In addition: uncertainty in harms associated with buprenorphine implant was not explored; competing risks of events were not considered; the dosing and thus the cost of the comparator was overestimated; rates and costs of events associated with IVDU were biased in favour of buprenorphine subdermal implant; supplemental use of SL BUP/NLX-associated costs were not considered; and the cost of removing the second implant was not considered for most buprenorphine implant patients.

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 buprenorphine implants; removing the cost of chronic infections such as HIV and hepatitis C virus, given the time horizon; 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 quality-adjusted life-year for buprenorphine implant compared to 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. However, as CDR was unable to address many of the limitations, there is considerable uncertainty associated with the ICUR. As there is no current experience with buprenorphine implant beyond two courses, it is also unknown how long patients will continue to use buprenorphine implant, and what the impact of switching to another therapy thereafter might be.

When considering drug acquisition costs alone, the annual cost of buprenorphine implant ($2,990 per patient per year, four implants every six months) is greater than that of SL BUP/NLX ($487 to $1,462 per patient per year for doses between 2 mg/day and 8 mg/day).

CDEC Members:

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

May 16, 2018 Meeting

Regrets:

Two CDEC members.

Conflicts of Interest:

None