

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

BUPRENORPHINE (SUBLOCADE — INDIVIOR CANADA LTD.)

Indication: Opioid use disorder

RECOMMENDATION

The CADTH Canadian Drug Expert Committee recommends that buprenorphine extended-release injection be reimbursed for the management of moderate to severe opioid use disorder in adult patients who have been induced and clinically stabilized on a transmucosal buprenorphine-containing product, if the following conditions are met:

Conditions for Reimbursement

Initiation criteria

1. Patients must be induced and stabilized on an equivalent of 8 mg to 24 mg per day of transmucosal buprenorphine for a minimum of seven days.

Administration conditions

1. Patients are under the care of a health care provider with experience in the diagnosis and management of opioid use disorder.
2. As stated in the Health Canada indication, buprenorphine extended-release injection should be used as part of a complete treatment plan that includes counselling and psychosocial support.
3. As stated in the Health Canada indication, buprenorphine extended-release injection must be administered subcutaneously in the abdominal region by a healthcare provider.

Pricing conditions

1. A reduction in price.

Service Line: CADTH Drug Reimbursement Recommendation

Version: 1.0

Publication Date: June 2019

Report Length: 8 Pages

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

BUPRENORPHINE EXTENDED-RELEASE INJECTION (SUBLOCADE — INDIVIOR CANADA, LTD.)

Indication: Opioid use disorder

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that buprenorphine extended-release injection (BUP-ER) be reimbursed 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, if the following conditions are met:

Conditions for Reimbursement

Initiation criteria

1. Patients must be inducted and stabilized on an equivalent of 8 mg to 24 mg per day of transmucosal buprenorphine for a minimum of seven days.

Administration conditions

1. Patients are under the care of a health care provider with experience in the diagnosis and management of opioid use disorder.
2. As stated in the Health Canada indication, BUP-ER should be used as part of a complete treatment plan that includes counselling and psychosocial support.
3. As stated in the Health Canada indication, BUP-ER must be administered subcutaneously in the abdominal region by a health care provider.

Pricing conditions

1. A reduction in price.

Reasons for the Recommendation

1. In one phase III, double-blind, randomized controlled trial (RCT) (Study 13-0001 [N = 504]) in adults with moderate or severe opioid use disorder who were clinically stabilized on 8 mg to 24 mg of sublingual buprenorphine/naloxone, the percentage abstinence (defined as the cumulative distribution function of the percentage of urine samples negative for opioids combined with negative self-reports of illicit opioid use) was significantly higher in the BUP-ER treatment groups (100 mg and 300 mg) than those in the placebo group at week 24 (41% and 43% compared with 5%; $P < 0.0001$). Treatment success (defined as $\geq 80\%$ of urine drug samples negative for opioids combined with negative self-report of illicit opioid use) was also significantly higher in both BUP-ER groups (29% and 28%) than in the placebo group (2%; $P < 0.0001$).
2. BUP-ER is not considered to be cost-effective at the manufacturer-submitted price for treating adult patients with opioid use disorder. BUP-ER was dominated by generic sublingual buprenorphine/naloxone (i.e., produces fewer quality-adjusted life-years [QALYs] at a higher cost).

Discussion Points

- CDEC recognized the significant public health burden associated with opioid use disorder, particularly harms from injection drug use related to the spread of bloodborne infections, and the significant loss of life associated with rising rates of opioid overdose poisoning. While Study 13-0001 evaluated benefits and harms to individuals, CDEC recognized that there may be additional public health benefits associated with decreased use of illicit drugs. These important potential benefits were not enumerated in either the clinical or pharmacoeconomic analyses that CDEC considered.
- Study 13-0001 had a relatively short duration of follow-up (24 weeks), and limited data on clinically important outcomes. CDEC considered longer-term data from an open-label extension study, Study 13-0003 (N = 669), and a longitudinal observational study, RECOVER (N = 826), but limitations in the methods prevented drawing concrete conclusions on the results of these studies. The long-term efficacy and safety of buprenorphine subcutaneous injection is uncertain.
- Study 13-0001 was a placebo-controlled trial; there is no evidence directly comparing BUP-ER with other treatments for opioid use disorder, including transmucosal buprenorphine/naloxone. A manufacturer-provided indirect comparison was limited by

sparingly populated networks and important methodological issues. Therefore, there is uncertainty with respect to the comparative treatment effects between BUP-ER and other treatments for opioid use disorder.

- The use of a placebo control group makes interpretation of the results from Study 13-0001 more difficult and risks overestimating the treatment effect of the BUP-ER groups relative to currently available opioid agonist therapies. In the original protocol for Study 13-0001, patients in the placebo group were initiated on sublingual buprenorphine/naloxone and then administered placebo injections over a period of 24 weeks, with no access to any form of opioid agonist therapy or rescue therapy for withdrawal. The protocol was amended at the request of the FDA to include a five-day taper in order to preserve blinding in the placebo group of the trial; however, this was only administered to 32% of the study population. Treatment in the placebo group of the trial is not consistent with current guidelines for treating patients with opioid use disorder.
- The generalizability of the results from Study 13-0001 may be limited because certain subpopulations of patients of interest were not eligible for trial enrolment, such as those with a positive urine drug sample result at screening for cocaine or cannabis and those who met DSM-V criteria for concurrent moderate or severe alcohol, cocaine, or cannabis use.
- BUP-ER contains a solvent that is a known teratogenic compound causing developmental toxicity in animals. High exposure of this solvent has also been linked to abnormal sperm parameters in animals. Study 13-0001 required that women of childbearing potential provide a negative pregnancy test prior to enrolment, and that all men and women of childbearing potential agree to contraceptive use throughout treatment. The product monograph states that “Sublocade should not be used in women of childbearing potential who are not using an effective and reliable method of contraception. Sublocade should not be administered to pregnant women unless in the judgment of the physician, the potential benefit to the mother outweighs the risk to the fetus.” Jurisdictions may wish to review access to contraceptive medications and services for people with opioid use disorder who are likely to be administered BUP-ER.
- 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.

Background

Sublocade has a Health Canada 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 in combination with counselling and psychosocial support. BUP-ER is a non-aqueous solution dissolved in a polymeric (non-gelatin containing) delivery system (Atrigel) in a pre-filled syringe containing 100 mg (0.5 mL) or 300 mg (1.5 mL) of buprenorphine hydrochloride, a partial mu-opioid receptor agonist. It is indicated for administration through abdominal subcutaneous injections by a health care practitioner. The Health Canada-recommended starting dose is 300 mg monthly for two months, followed by a maintenance dose of 100 mg monthly. The maintenance dose can be increased to 300 mg monthly in the case of an unsatisfactory clinical response and demonstrated ability to tolerate the 100 mg dose. There is no suggested treatment duration provided for this product.

Summary of Evidence Considered by CDEC Considerations

CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of phase III and phase IV RCTs of BUP-ER subcutaneous injection, a summary and critique of a manufacturer-provided indirect comparison, and a critique of the manufacturer’s pharmacoeconomic evaluation. CDEC also considered input from clinical experts with experience in treating patients with opioid use disorder.

Summary of Patient Input

No submissions were received from patient groups.

Clinical Trials

The CDR review included one double-blind RCT of patients with moderate or severe opioid use disorder (Study 13-0001). Patients entered an open-label induction phase and received buprenorphine/naloxone sublingual film for three days, followed by a dose-adjustment period of four to 11 days to achieve a daily dose between 8 mg and 24 mg buprenorphine. Patients were then randomized 4:4:1:1 to receive either: BUP-ER 300 mg subcutaneously every four weeks for six doses (300 mg/300 mg, N = 201), BUP-ER 300 mg subcutaneously every four weeks for two doses followed by BUP-ER 100 mg subcutaneously every four weeks for

four doses (300 mg/100 mg, N = 203), placebo volume-matched to the 300 mg/300 mg regimen, or placebo volume-matched to the 300 mg/100 mg regimen (combined placebo comparison group N = 100). Randomized patients in this study received once weekly individualized behavioural counselling as well as individualized drug counselling to accompany pharmacotherapy. Key limitations of Study 13-0001 were the percentage of premature withdrawals in the placebo group (66%) compared with the BUP-ER groups (38% in the 300 mg/100 mg group and 36% in the 300 mg/300 mg group), placebo comparator, and uncertain generalizability of the results to patients with opioid use disorder in Canada.

Outcomes

Outcomes were pre-specified in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Urine samples negative for opioids intended to detect the presence of codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Negative self-reports of illicit opioid use via a timeline follow-back interview that was conducted to assess recent drug use, including opioids, methadone, buprenorphine, cocaine, barbiturates, ethanol, benzodiazepines, amphetamines or methamphetamines, and phencyclidine. The interview instrument was administered electronically by an interviewer and asked patients to estimate their own drug use in the 30 days before screening, at the screening visit, and since the last visit at all subsequent visits. Patients were to only report whether there was use or no use, not the frequency or amount used.
- Opioid withdrawal symptoms assessed using the following: Subjective Opiate Withdrawal Scale (SOWS), Clinical Opiate Withdrawal Scale (COWS), and Visual Analogue Scale (VAS) for Cravings. The SOWS was completed weekly by patients in order to assess their perception of opiate withdrawal symptoms throughout the double-blind treatment period, in the form of a 16-item scale. The COWS was recorded throughout this study by clinicians to assess signs and symptoms of opiate withdrawal.

The primary outcome in the pivotal trial was percentage abstinence. This was a composite outcome defined as a combination of the cumulative distribution function of the percentage of urine samples negative for opioids combined with negative self-reports of illicit opioid use collected from week 5 to week 24 in the full analysis set of the patient population. The key secondary outcome was treatment success, which was defined as any patient with $\geq 80\%$ of urine samples negative for opioids combined with self-reports negative for illicit opioid use from week 5 to week 24. The first four weeks were intended as a “grace period” for patients to achieve better treatment stabilization as well as adequate plasma levels of buprenorphine.

Efficacy

Both the BUP-ER 300 mg/100 mg and 300 mg/300 mg treatment regimen groups were found to be superior to placebo from week 5 to week 24 for the primary outcome in Study 13-0001, with a mean percentage abstinence of 42.7% and 41.3% in the 300 mg/100 mg and 300 mg/300 mg arms, respectively, compared with 5.0% in the placebo arm ($P < 0.0001$ for each regimen compared with placebo). In each of the BUP-ER treatment groups, 12% to 13% of patients had no positive or missing urine drug samples or self-reports of illicit opioid use over this period of time, compared with 1% in the placebo group. Treatment success was statistically significantly higher in BUP-ER 300 mg/100 mg (28%) and 300 mg/300 mg (29%) groups, compared with 2% in placebo ($P < 0.0001$). Also, the percentage of patients abstinent at any week from week 5 to week 24 was numerically higher in both the BUP-ER 300 mg/100 mg and 300 mg/300 mg groups compared with the placebo group in the full analysis set, ranging from 35.1% to 48.5% in the 300 mg/300 mg group and 38.5% to 45.4% in the 300 mg/100 mg group versus 2.0% to 11.1% in the placebo group.

In Study 13-0001, the mean COWS and SOWS were numerically low at baseline and at week 24 in all treatment groups (mean COWS ≤ 1.9 ; SOWS ≤ 4.9). Regarding the desire or need to use VAS scores, mean scores in the placebo group were slightly higher at baseline (9.5) compared with active treatment groups (5.5 in the 300 mg/100 mg group and 7.1 in the 300 mg/300 mg group). There was an increase in the placebo group noted at week 2 (26.9), and values remained high until week 24, indicating a higher desire to use. Final mean scores in the placebo group for the desire or need to use VAS scores at week 24 (17.1) were significantly higher than in active treatment groups (6.8 in the 300 mg/100 mg group and 3.2 in the 300 mg/300 mg group). Analyses for these outcomes were not adjusted for multiplicity, and therefore should be interpreted with consideration of the risk of type 1 errors.

There were no data on social function outcomes, health-related quality of life, or other patient-focused outcomes from Study 13-0001. The manufacturer-provided data related to patient-reported outcomes collected in Study 13-0001 at the time of providing comments on a draft version of the CDR review report. The data suggested that BUP-ER improved health-related quality of

life (measured using the EQ-5D-5L index and EQ-5D-5L VAS), and the proportion of patients with employment and health insurance as compared with placebo. However, there was insufficient information reported to assess the validity of these results.

Harms (Safety)

Adverse events were reported by most patients treated with BUP-ER in Study 13-0001, ranging from 66.7% to 76.4% of patients (56% in the placebo group). Among patients who received BUP-ER in Study 13-0001, 2% to 4% experienced a serious adverse event versus 5% in the placebo group. The proportion of patients who stopped treatment due to adverse events was approximately 4% in both BUP-ER treatment groups and 2% in the placebo group.

No overdoses (fatal or non-fatal) were reported in either of the active treatment groups, compared with one non-fatal overdose reported in the placebo arm. No patients in Study 13-0001 reported any adverse events potentially related to respiratory depression. There appeared to be numerically similar proportions of patients with a shift from normal (at baseline) to low levels of testosterone between the active and placebo groups at any time during the trial.

The frequency of injection site adverse events was high in Study 13-0001, but most were reported as mild or moderate severity, resulting in pain, tenderness and induration.

In study 13-0001, the frequency of adverse events associated with liver disorders was found to be 7.1% in the BUP-ER arms compared with 1% in the placebo arm. Three patients in the 300 mg/300 mg arm withdrew due to adverse events related to liver injury.

BUP-ER is dissolved in a polymeric (non-gelatin containing) solvent (Atrigel) that may be teratogenic. As well, high exposure of this solvent has also been associated with abnormal sperm parameters. As a result, the BUP-ER studies required that women of childbearing potential provide a negative pregnancy test prior to enrolment, and that all men and women of childbearing potential agree to contraceptive use throughout treatment. Currently, the product monograph recommends that the use of BUP-ER in women of childbearing potential who are not using effective contraception be avoided, unless the potential benefit to the mother outweighs the risk to the fetus.

Indirect Treatment Comparisons

The manufacturer-provided indirect comparison, based on network meta-analyses (NMAs), compared BUP-ER (300 mg/100 mg, BUP-ER 300 mg/300 mg) with methadone (variable dose), sublingual buprenorphine (variable dose), buprenorphine implants, and a different buprenorphine depot injection (CAM2038) for the outcomes of opioid test positivity and treatment retention. BUP-ER 300 mg/100 mg was associated with a decreased likelihood of opioid test positivity compared with placebo (odds ratio [OR]: 0.12, 95% confidence interval [CI], 0.06 to 0.24), sublingual buprenorphine (OR: 0.34, 95% CI, 0.12 to 0.90) and buprenorphine implants (OR: 0.32, 95% CI, 0.12 to 0.78). Similar results were observed in the BUP-ER 300 mg/ 300 mg arm. Both BUP-ER doses appeared to be similar to sublingual buprenorphine, buprenorphine implants, and CAM2038 with respect to study dropout. Using the same model, treatment with methadone was associated with a lower rate of study dropout than both the BUP-ER 300 mg/ 100 mg and BUP-ER 300 mg/ 300 mg arms. Key limitations included the lack of transparency in systematic review methods, limited heterogeneity analyses performed, and the inclusion of studies with sparse baseline data.

Other Studies

CDEC considered evidence from two additional studies that were summarized and critiqued in the CDR systematic review. The extension study, Study 13-0003 (N = 669), was an open-label study designed to evaluate the safety and tolerability of BUP-ER over 48 weeks, and included a combination of patients who had completed Study 13-0001 with six doses of BUP-ER treatment or placebo, as well as newly initiated patients (de novo patients). The mean percentage abstinence after 48 weeks of BUP-ER treatment was 46% in newly initiated patients and 57% for the roll-over patients from Study 13-0001. No formal statistical tests were outlined a priori for this analysis, and therefore interpretation of the results is limited. Other important limitations of this study included the open-label and non-comparative design.

RECOVER (N = 826) was a longitudinal observational study that enrolled patients who had participated in Study 13-0001 and 13-0003 and who had received at least one study injection. Data were collected up to 12 months before patients were treated with BUP-ER and up to 24 months after treatment initiation, to examine differences in criminal activity, opioid abstinence and withdrawal, depression and psychological stress, work attendance and performance over time. Changes in criminal activity from the 12 months leading up to study enrolment until up to 12 months after initiation of BUP-ER treatment found a numerically lower number of total arrests; however, the proportion of patients receiving felony charges remained the same. Patients receiving placebo as well as those receiving BUP-ER treatment for 13 months or longer had a lower proportion of missed work days compared with patients receiving BUP-ER treatment for one to two months, three to eight months and nine to 12 months. Results from this study should be interpreted with caution as this data were primarily self-reported and potentially limited by recall bias and truthfulness of responses. Results were also subject to bias in the differential length of follow-up between treatment groups, and relatively high proportion of losses to follow-up. Criminal data were obtained from public records, for which only 65% of patient records were found.

Cost and Cost-Effectiveness

BUP-ER is available as 100 mg and 300 mg single-use pre-filled syringe at a submitted price of \$550 for either dose. At the manufacturer's submitted price, the annual cost of treatment with BUP-ER is \$6,600.

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) with oral methadone and generic buprenorphine/naloxone in adults with moderate to severe opioid use disorder. The analysis was conducted from the Canadian publicly funded health care payer perspective during 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" 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 while patients who dropped out of OAT were assumed to continue using opioids illicitly. To model relapse and return to OAT, after a fixed period in the off treatment health states, patients could transition to long-term relapse health states that reflected a composite of health states defined by illicit opioid use and OAT status. 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 NMA or from an observational study. Treatment-specific mortality and treatment-specific overdose (which could be fatal or non-fatal) were further incorporated. Health state utilities, except abstinence, were based on a UK study while health care resource use and cost inputs were primarily informed by the manufacturer's commissioned chart review of Canadian opioid use disorder practices and from public pricing databases.

CADTH identified the following key limitations with the manufacturer's economic submission:

- Uncertain comparative clinical evidence informed by the manufacturer's indirect treatment comparison and through naive comparisons from observational studies. The indirect treatment comparison involved studies with sparse baseline data without assessment of inconsistency or sufficient adjustment for potential confounders. The patient population in the trials may not be consistent with the Canadian population.
- 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 long-term cost-effectiveness.
- Estimation of model parameters did not reflect real-world clinical management with opioid use disorder. This included applying treatment-specific proportion of patients using opioids at baseline; assuming 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 OAT. Combined, these biases generally favoured BUP-ER.

CADTH considered BUP-ER (300 mg injection per month for the first two months followed by monthly 100 mg injection) as a single treatment comparator rather than considering the 100 mg and 300 mg doses as separate treatments. CADTH further undertook

reanalyses by revising parameters and assumptions associated with on top use, overdose, and abstinence to better reflect the clinical pathway of opioid use disorder in Canada.

In the CADTH base case, BUP-ER was dominated by generic buprenorphine/naloxone (associated with greater expected costs and fewer expected QALYs). Based on the CADTH reanalysis, 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. However, there is significant uncertainty associated with the comparative treatment effects between BUP-ER, generic buprenorphine/naloxone, and methadone; and the cost-effectiveness of BUP-ER in less stable patients (i.e., more comorbidities) remains unknown.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Ms. Heather Neville, Mr. Allen Lefebvre, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

May 15, 2019 Meeting

Regrets

Two CDEC members did not attend.

Conflicts of Interest

None