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MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

2.6 Recommendations for Sublocade® & Considerations for Informed Consent

GENERAL CONSIDERATIONS

Buprenorphine extended-release injection (Sublocade®) is a partial opioid agonist for the management of moderate to severe opioid use disorder (OUD). As a subcutaneous monthly depot injection, it is an alternative treatment option that essentially replaces daily dosing with sublingual buprenorphine/naloxone.

It is important to note that thus far in clinical trials Sublocade® has only been evaluated for clinical effectiveness in the treatment of OUD against placebo. The effectiveness of Sublocade® has yet to be definitively compared to sublingual buprenorphine/naloxone[1]. Results of a true non-inferiority study are not yet available. The intent of this chapter is *not* to promote Sublocade® use over daily buprenorphine/naloxone treatment, but to discuss considerations for its use and associated recommendations.

To be considered for Sublocade® a patient must tolerate a sublingual buprenorphine/naloxone dose of 8 to 24 mg daily. Presently, there is no injectable dose equivalency for patients requiring less than 8 mg of buprenorphine. While patients treated with 26 to 32 mg of buprenorphine/naloxone daily may be considered for Sublocade®, this option may be less effective at adequately treating withdrawal than buprenorphine/naloxone in this population.

Sublocade® must be administered by subcutaneous injection in the abdominal region by a trained physician, nurse, or pharmacist. For effective treatment, it is administered once per month. This may reduce the patient burden of treatment when compared to daily administration of buprenorphine/naloxone[1]. Sublocade® can be helpful for patients who wish to simplify treatment, who have barriers to regular pharmacy attendance, and/or who have no practical pharmacy access due to geographic limitations. Monthly administration can offer patients more flexibility with treatment, particularly when clinical instability does not warrant take-home dosing of sublingual buprenorphine.

Other potential benefits may include more predictable steady-state concentrations and lower peak-to-trough fluctuations than with daily dosing[2], potentially providing superior overdose protection, especially in patients who frequently miss doses on a daily regimen. Sublocade® may also be associated with reduced stigma (associated with regular pharmacy visits) and reduced risk for theft/diversion of sublingual tablets. The monthly administration can also support extended travel and employment opportunities without the added effort of arranging daily medication availability.

Importantly, Sublocade® has created treatment access for northern/remote patients who do not have pharmacy access in their home communities and where daily witnessed self-administration of OAT medications (under the direct supervision of a pharmacist, approved prescriber, or a nurse) cannot be feasibly arranged.

SPECIFIC CONSIDERATIONS

Sublocade® can be explored with both clinically stable patients and those struggling with instability and/or regular pharmacy attendance. As above, it can enhance convenience for some patients who may find less frequent medication administration preferrable. It can also enhance medication adherence, particularly when patients are frequently missing doses of sublingual buprenorphine/naloxone.

Sublocade® for Patients Missing Doses

Missed doses of OAT (due to patients not attending the pharmacy for witnessed self-administration and possible take-home doses) can indicate a variety of problems that warrant exploration. The prescriber should review reasons for missed doses and make every effort to problem solve with the patient (see Ongoing Care for details, specifically MISSED OAT DOSES).

If the patient is on buprenorphine/naloxone and sufficiently stable, but struggling to attend the pharmacy due to work or family responsibilities, consider accelerating the provision of take-home doses as outlined in Buprenorphine Take-home Dosing Recommendations.

Alternatively, if the patient is not a candidate for accelerated take-home doses, consider switching to Sublocade® to facilitate fewer pharmacy visits. An open-label randomized clinical trial in Australia found that treatment satisfaction was higher in patients receiving depot buprenorphine (a different formulation, brand name Brixadi®) compared to sublingual buprenorphine/naloxone, after 24 weeks[3]. Providers should assess and discuss with the patient if switching to Sublocade® would be suitable and preferable, based on their patient-specific circumstances.

Sublocade® therapy can be considered in patients stabilized on 8 to 24 mg sublingual buprenorphine/naloxone daily, for at least 3 (based on local experience) to 7 days. The depot injection does not require abstinence from other opioids before initiation, but it is preferable.

Importantly, if a patient switches to depot buprenorphine therapy, the prescriber must also consider the overall medication management plan for patients on other sedating/psychoactive medications to determine a safe and reasonable dispensing schedule for these medications.

Training Requirements

To prescribe other formulations of buprenorphine, including Sublocade® or Probuphine® (subdermal implant), prescribers must hold a buprenorphine/naloxone prescribing approval/authorization from their respective regulatory body and pursue additional training as required by Health Canada and outlined in the box below. Additionally, see A NOTE ON PROBUPHINE® at the end of this chapter.

Prescribers must also ensure they have the requisite knowledge, skills, and clinical competence to administer Sublocade®, and for the proper insertion and removal of the Probuphine® implant, before prescribing.

Pharmacists should review the joint Guidance on the Administration of Sublocade by a Pharmacist and contact the College of Pharmacists of Manitoba (CPhM) for more information on training requirements for dispensing the buprenorphine injectable depot and subdermal implant formulations.

INFORMATION ON SUBLOCADE® TRAINING

More information on Sublocade® use and administration is available **for prescribers and pharmacists** in this document: Joint Guidance on Sublocade® Administration.

- Prescribers must hold a current, active buprenorphine/naloxone prescribing approval/authorization from CPSM/CRNM to prescribe Sublocade®.
- Currently, approved/authorized prescribers wanting to prescribe Sublocade® must complete the non-accredited certification program, **a Health Canada requirement**, available at www.sublocadecertification.ca. The completed program certificate must be faxed to the pharmacy along with the M3P prescription when prescribers first order Sublocade® from a particular pharmacy.

INFORMATION ON PROBUPHINE® TRAINING

More information on Probuphine® (buprenorphine implant) is available **for prescribers and pharmacists** by contacting the CPSM's Prescribing Practices Program directly.

- Please note that prescribers must hold a current, active buprenorphine/naloxone prescribing approval/authorization from CPSM/CRNM to prescribe/implant Probuphine®.
- Because of the risks associated with insertion and removal, Probuphine® must be prescribed, implanted, and removed only by trained prescribers who have successfully completed a training program on the insertion and removal of Probuphine®.

Medication Coverage

Sublocade® is covered for patients whose medications are covered by Non-Insured Health Benefits (NIHB) for First Nations and Inuit. Additionally, to qualify for coverage, patients are **no longer required** to be on a stable dose of buprenorphine/naloxone for a minimum of 7 days prior to starting Sublocade®. Prior approval for Sublocade® is also no longer required.

Otherwise, Sublocade® is an eligible benefit under Part 2 of the Manitoba Drug Benefits Formulary for the management of moderate to severe OUD, in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product, if the following criteria and conditions are met:

Criteria:

- Patients must be induced and stabilized on an equivalent of 8 to 24 mg per day of transmucosal buprenorphine for a minimum of 7 days.

Conditions:

- Patients are under the care of a healthcare provider with experience in the diagnosis and management of OUD and who has been trained to administer the buprenorphine extended-release injection.
- Buprenorphine extended-release injection should be used as part of a complete treatment plan that includes counselling and psychosocial support.
- Buprenorphine extended-release injection must be administered subcutaneously in the abdominal region by a healthcare provider.

CONSIDERATIONS FOR INFORMED CONSENT

When starting any OAT medication, prescribers must counsel patients about the benefits and risks of treatment to obtain informed consent. Starting Sublocade® is no different. The Centre for Addiction and Mental Health (CAMH) guideline, *Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder*, notes that there is not yet evidence about the long-term safety and effectiveness of depot (or implant) buprenorphine therapy and encourages prescribers to review the existing evidence to counsel patients accordingly for informed consent[4]. Other considerations include the patient's comfort with an invasive procedure and available medication coverage options.

Patients of Reproductive Age & Informed Consent

Unique considerations for informed consent with Sublocade® include discussion about pregnancy and reliable contraception. **Presently, it is not known if Sublocade is safe in pregnancy**.

While there is limited evidence surrounding its use in pregnancy, providers must weigh the risks and benefits of treatment with Sublocade® collaboratively with the patient and be frank about what is not yet known from a medical perspective. (see *Sublocade® In Pregnancy* below).

Prescribers must ensure that female patients of reproductive age are counselled to use a reliable form of birth control (such as an intrauterine device (IUD) or Depo Provera) prior to receiving a Sublocade® injection, and for the duration of treatment with Sublocade®. Two forms of less reliable birth control (such as an oral contraceptive pill combined with a barrier method) may be an alternative.

Due diligence is also needed to ensure patients understand the potential implications of not using reliable birth control. While medicine is not aware of any teratogenicity with Sublocade® use in pregnant women to date, it is not yet known if Sublocade® is safe in pregnancy as one of its excipients, *N*-methyl-pyrrolidone (NMP), has been identified as potentially teratogenic in animal studies.

If a patient who understands this information indicates that they do not require birth control for some reason or indicates that they find the use of birth control unacceptable, OAT providers are to use their clinical judgement in **weighing the potential benefits of treatment with Sublocade® (including treatment access and retention) against the risks of an unplanned pregnancy while on Sublocade®**. This conversation and any decisions made, should be carefully documented in the patient record.

Regardless of the patient's choice around the use of reliable birth control, if the provider and patient agree to proceed with Sublocade® treatment, the use of a **written consent form is strongly recommended** to facilitate further documentation of the patient's informed consent to treatment with Sublocade® (see **Appendix W** and **X** for an example).

In addition to the above, in patients of reproductive age, an in-office pregnancy test is strongly recommended before every injection and regardless of the contraceptive option selected by the patient.

When Sublocade® is administered in pharmacy and a pregnancy test is not available, periodic pregnancy tests in clinic are recommended when the patient presents for follow-up care and other reasons.

Other Considerations for Consent

Another important aspect of informed consent is ensuring that patients understand the implications of missing their monthly Sublocade® injection. If patients are more than two weeks late for a scheduled administration, this may necessitate restarting on daily witnessed buprenorphine/naloxone at a pharmacy, for a period, before transitioning to Sublocade® again. See *Approach to Missed Injections* for details.

CARING FOR PATIENTS ON SUBLOCADE®

OAT treatment teams are encouraged to actively track the intervals between Sublocade® injection appointments. If a patient misses an injection appointment, a member of the team should contact the patient to remind them their injection is due and to proactively reschedule the appointment or offer drop-in times when they could be accommodated, considering prescriber/nurse and patient availability, and travel/transportation issues. Missed monthly administration can have a substantial negative impact on patients' lives and responsibilities, and carries a risk of relapse, especially if the patient is prone to breakthrough withdrawal if the injection is delayed (see *Breakthrough Withdrawal* and other considerations below).

Approach to Missed Injections

A patient who misses a Sublocade® injection should receive the dose as soon as possible, with the following dose given no less than 26 days later. Unavoidable occasional delays in dosing up to two weeks are not expected to have a clinically significant impact on treatment effect for patients stable on Sublocade®.

Occasionally patients may present for the next Sublocade® injection past the six-week mark. The following is recommended in these situations:

- The prescriber, or a member of the treatment team, should assess the patient in-person or, if not possible, virtually (ideally on-camera) to inform the next steps.
- During assessment, ask about recent opioid use including the pattern of use and when the patient last used opioids.
- Assess the patient for opioid withdrawal. A Clinical Opiate Withdrawal Scale (COWS) score may be useful.
- Conduct a urine drug test (UDT) to verify the patient history. A point-of-care UDT is preferred, if available, due to immediate availability of results.
    - **Consider Sublocade® injection** if the patient has not used opioids and this is confirmed by UDT, and they look well or are experiencing mild opioid withdrawal. Clinical discretion can be used at this point to determine if the Sublocade® injection is advisable. The patient must be made aware of the limited risk of precipitated withdrawal in this scenario.
    - **A restart on buprenorphine/naloxone with transition to Sublocade®** is indicated if the patient confirms opioid use and/or this is confirmed on UDT, and/or if the patient is in moderate to severe opioid withdrawal, and/or if the patient presents well past the six-week mark. The patient should also be educated about the increased risk of precipitated withdrawal under these circumstances.

If point-of-care UDT is not readily available and lab results will be delayed, and the patient report is deemed reliable, the absence of UDT results *should not* significantly impact clinical decision making.

Sublocade® Dosing Intervals

According to the product monograph, Sublocade® is to be administered monthly only by subcutaneous injection in the abdominal region, and the recommended dose is 300 mg monthly for the first two months followed by a maintenance dose of 100 mg monthly. The maintenance dose may be increased to 300 mg monthly for patients who tolerate the 100 mg dose, but do not demonstrate a satisfactory clinical response, and where the benefits outweigh the risks[5].

Breakthrough Withdrawal

With the conventional monthly dosing regimen, practical experience indicates that about two-thirds of patients treated with Sublocade® achieve clinical stability early on, with elimination of opioid withdrawal for 24 hours. In one-third of patients, opioid withdrawal often returns several days before the second injection of 300 mg is due. In select patients, withdrawal may return as soon as two weeks before the second dose is due and intensify until the second dose is administered. OAT treatment teams are encouraged to make patients aware of this possibility from the first discussion about transitioning to Sublocade®. Reassure patients that they will not be left to suffer if they report breakthrough withdrawal symptoms before the next injection is due.

The experience of breakthrough withdrawal will gradually improve and eventually resolve in a subset of patients, as Sublocade® accumulates and reaches steady state after multiple monthly injections (it can take 4-6 months to achieve steady state[5]). While this happens, it is important to support the patient by treating breakthrough withdrawal, as this promotes adherence and treatment retention over time. This is especially important in patients who do not have practical pharmacy access and who cannot to return to daily buprenorphine/naloxone dosing.

Top-Up Dosing

Top-up dosing with sublingual buprenorphine/naloxone can address breakthrough withdrawal on Sublocade®. This is typically done by prescribing a low dose of buprenorphine/naloxone for daily use, in addition to scheduled Sublocade® injections. The buprenorphine/naloxone dose may be titrated to effect. As the Sublocade® serum level accumulates over time, top-up dosing should be tapered accordingly and eventually discontinued.

In communities with no pharmacy access, top-up dosing often implies take-home (carry) doses, and the benefits of this approach must be weighed against the potential patient and community risks associated with buprenorphine take-home dosing. A low dose of

buprenorphine/naloxone prescribed as a top-up is often reasonable in communities without pharmacy access, provided the patient has a lockbox and can store the medication safely.

Adjusted Dosing Intervals

A second potential strategy to address breakthrough withdrawal on Sublocade® is to schedule injections closer together. The product monograph states that Sublocade® injections should not be administered less than 26 days apart. However, practical experience dictates that patients who experience *significant* breakthrough withdrawal can benefit from administering Sublocade® within a shorter interval.

OAT prescribers/treatment teams must assess the patient frequently and use their clinical discretion in scheduling Sublocade® injections less than 26 days apart. This strategy can be particularly useful when sublingual buprenorphine/naloxone is not a practical/safe option. As the Sublocade® serum level accumulates, injections may be scheduled further apart, and providers should rely on regular clinical assessment to guide adjustments in the dosing schedule.

Concurrent Chronic Pain & OUD

Occasionally, a patient with an active chronic pain condition and OUD may require Sublocade® to facilitate engagement in OAT care. If the chronic pain condition is not adequately addressed with the traditional Sublocade® dosing regimen, and with adjunctive pharmacological and non-pharmacological pain therapies, consideration may be given to continuing with the 300 mg Sublocade® dosage beyond two months and potentially long-term. Once again, the patient should be assessed regularly to ensure that they are tolerating the sustained higher dose and that the burden of treatment (side effects) does not outweigh the benefits of the adjusted dosing regimen.

Patients with Severe & Persistent Breakthrough Withdrawal

OAT providers may occasionally encounter a patient who experiences *early* and *persistent* severe withdrawal with a traditional Sublocade® dosing regimen, that does not resolve in time and is not associated with chronic pain. While top-up dosing may be utilized in early treatment, this is not always a desirable or practical long-term option. Patient safety and stability, community safety, and potential diversion of top-up doses, may dictate that alternatives must explored when breakthrough withdrawal does not resolve after 4-6 months on Sublocade®.

In such rare cases, consideration may be given to continuing with 300 mg doses indefinitely AND scheduling these doses closer together on an ongoing basis. **Inexperienced prescribers are encouraged to reach out for advice/mentorship support from prescribers with robust Sublocade® experience to navigate these complex patients**.

Extended Intervals Between Injections

A subset of patients who are transitioned to Sublocade® may report that their withdrawal is immediately and effectively addressed for more than one month following their first injection. If Sublocade® injections are adequately controlling withdrawal for more than 30 days and this pattern persists, such patients may elect to present for their injections at extended intervals. Prescribers/treatment teams are encouraged to accommodate these requests based on the absence of withdrawal throughout the dosing interval and to further reduce the burden of treatment. These patients should be encouraged to present for Sublocade® injections no more than six weeks apart, even if they are not experiencing breakthrough withdrawal.

Opaskwayak Health Authority (OHA) OAT Program

The OHA OAT Program is a northern remote program serving individuals with OUD from Opaskwayak Cree Nation, The Pas, Moose Lake, Easterville, Grand Rapids, and surrounding areas. Many patients from these areas do not have pharmacy access in their home communities, making daily dispensing of OAT especially challenging.

The availability of Sublocade® has created treatment access for many patients in this region who previously did not have practical access to OAT. The program's clinical experience with Sublocade® has highlighted key aspects of patient care and consent that require careful navigation. The program has developed consent forms to manage these special considerations in clinic and offered to share their forms as a resource for other programs. See **Appendix W** and **X** for the following templates:

- Treatment with Sublocade® Consent Form: General Version
- Treatment with Sublocade® Consent Form: Reproductive Age Version

Respectfully, please retain the acknowledgment that this work is the intellectual property of the OHA OAT program staff when adapting them for clinical use. Prescribers/nurses from this program are also available to provide advice/guidance to other prescribers regarding the use of Sublocade® as challenges or clinical questions arise.

Sublocade® In Pregnancy

As outlined in Treatment of OUD in Pregnancy, there is limited evidence surrounding the use of Sublocade® in pregnancy. As data emerges, these recommendations will be revised accordingly, however, reliable data is not expected to be imminently available:

- **Consideration of RISK**: In general, pregnancy and breastfeeding have been viewed as relative contraindications to Sublocade®, as one of its excipients, *N*-methyl-pyrrolidone (NMP), has been identified as potentially teratogenic in animal studies. Human data is extremely limited: two cases of undiagnosed pregnancy treated with Sublocade®, up to 18 weeks gestation, had normal obstetrical and pediatric outcomes[6].

- **Anticipation of BENEFIT**: The motivation to explore Sublocade® in pregnancy is not only for the perceived benefits that apply to non-pregnant patients (more stable steady-state than daily dosing, fewer pharmacy visits and associated stigma, and reduced risk for theft/diversion of sublingual tablets)[7]. The pharmacokinetics are also theorized to result in decreased neonatal withdrawal severity. Clinical trials of a novel formulation without NMP are underway at the time of writing. CAM2038 has a weekly depot formulation that replaces NMP with ethanol at a clinically irrelevant concentration; the maximum fetal exposure over 9 months gestation is one tablespoon[8]. This is being studied in a randomized control trial compared with daily sublingual buprenorphine/naloxone.
- As above, it is not uncommon to have breakthrough withdrawal during the first month of Sublocade® treatment, requiring supplementation with sublingual buprenorphine/naloxone[9]. For some patients, breakthrough withdrawal may even last longer than the first month of treatment. This may obviate some of the improved convenience of Sublocade® during pregnancy.

STRONG RECOMMENDATION: USE OF SUBLOCADE® IN PREGNANCY

Given the paucity of data for antepartum efficacy, maternal tolerance, and fetal safety, introduction to Sublocade® during pregnancy should be deferred to the postpartum interval.

Continuation of Sublocade® may be considered when pregnancy is identified after treatment is well-established with Sublocade®, if alternative therapy is not available, and gestation is already greater than 12 weeks (beyond embryogenesis). Patients who are breastfeeding are encouraged to further defer until 6 months postpartum when breastfeeding is no longer exclusive nutrition.

PRESCRIBING, DISPENSING, & ADMINISTRATION OF SUBLOCADE®

As above, Sublocade® can only be prescribed by an approved/authorized prescriber who has completed the Health Canada required Sublocade® Certification. The certificate generated by this program must be faxed to the pharmacy along with the M3P prescription when the prescriber first orders Sublocade® from a particular pharmacy.

Of note, Sublocade® must be ordered by a pharmacist via a closed-distribution system. Prescribers should contact pharmacists prior to sending a prescription to ensure the patient can access Sublocade® in a timely manner, to account for expected shipping times, as well as delivery of the product to the healthcare professional for administration. Pharmacists who need to set up an account with the manufacturer for the first time will require additional time. Pharmacists and prescribers/treatment teams who need further information about this process may contact CPhM or the Prescribing Practices Program at CPSM.

The following requirements must also be met:

- Ideally, the first two Sublocade® injections should be administered by the approved prescriber or a nurse who works in the clinic the patient attends for OAT care.
- The subcutaneous injection of Sublocade® must be within the scope of practice of the nurse or physician doing the injection. Additionally, if a patient that a physician or nurse cares for requires access to Sublocade® injections, they are encouraged to seek the appropriate training to become competent in performing this procedure.
- Sublocade® must only be injected by a trained physician or nurse **with the knowledge and authorization of the approved prescriber** (i.e., if a physician who is not an approved buprenorphine prescriber wishes to inject Sublocade® they require authorization from the prescriber who wrote the Sublocade® prescription).
- A pharmacist can administer further doses if they meet the requirements outlined in Guidance on the Administration of Sublocade by a Pharmacist and are authorized to do so by the Sublocade® prescriber. A pharmacist should only administer the first dose of Sublocade® if the prescriber or a nurse is not able to administer the medication in a timely manner and the pharmacist is comfortable and competent in doing so. Prescriber obligations in terms of counselling, ruling out pregnancy, discussing/offering reliable fertility control, informed consent, and all standards of care would still apply.
- Communication and collaboration between the pharmacist and prescriber, throughout the patient's treatment, are of utmost importance to ensure that the patient receives safe and optimal care:
    - Prescribers must actively collaborate and communicate with pharmacists when circumstances indicate that Sublocade® administration by a pharmacist would facilitate access to care for the patient and support the patient's ability to participate in their care plan.
    - A pharmacist must receive authorization from the prescriber to administer the medication, to ensure that the patient has been assessed and will receive the appropriate follow up from the prescriber. **The pharmacist must also notify the prescriber when the medication has been administered or if a patient misses their injection**.
- Pharmacy managers must ensure that all pharmacists, including new or casual staff, are aware of the requirements around the administration of Sublocade®. Information must be included in the pharmacy policy and procedures manual.
- It is recommended that Sublocade® be administered to patients in the supine position, in both clinic and pharmacy settings. To ensure appropriate administration, a prescriber, nurse, or pharmacist should administer the injection where the patient is able to lie

down, face up. **A private area with an exam table is required**. Occasionally, in patients who are very slim with minimal subcutaneous fat, it may be beneficial for the patient to sit in a chair during administration, as this may help to manipulate the site to gather enough subcutaneous fat for appropriate injection. This must still occur in a private area.

Other Practical Considerations for Sublocade®

- Patients are not permitted to pick up their Sublocade® injection from the pharmacy or self-administer (inject) their dose. Therefore, the logistics of this treatment option warrant discussion and collaborative planning between the pharmacy team and the prescriber/clinic team.
- Once the pharmacy notifies the clinic team that a Sublocade® dose is ready, a member of the clinic team will need to pick up the dose from the pharmacy. Alternatively, if practically possible, the prescriber may request that the Sublocade® dose be delivered to the clinic by the pharmacy.
- Specific federal and provincial narcotic transport, delivery, storage, and record-keeping requirements must be adhered to by the pharmacy and clinic teams for pick-up and delivery procedures. Templates for record keeping can be helpful for quality control.
- Importantly, the cold chain must be preserved. In clinic, Sublocade® doses must be stored in a locked temperature-controlled fridge with an alarm to alert staff if the temperature fluctuates outside of the recommended range.
- In clinic, two nurses/physicians are required to sign the medication log when adding or removing Sublocade® doses to/from the locked storage fridge. The use of a separate medication administration record (MAR) is also strongly recommended when administering Sublocade® doses in clinic.
- Once the patient has arrived in clinic for their Sublocade® injection appointment, the package containing the Sublocade® pre-filled syringe should be removed from the fridge 15-20 minutes prior to administration to warm to room temperature.
- A private room with exam table is required for the administration, as above.
- Offering the patient an ice pack during administration is a useful strategy to address the burning sensation that may occur with the injection. This burning sensation is often more intense with the 300 mg dose due to the larger volume injected. It usually improves after 3-5 minutes. Some patients may also prefer to apply the ice pack to the abdominal skin for a few minutes prior to the prescriber/nurse disinfecting the area and injecting the dose.

- It is important to remind patients not to manipulate the injection site for the first couple of days after injection and to watch for injection site reactions that may need to be assessed by clinic staff.
- Some patients report feeling "high" (e.g., dizzy, nauseous) following the first 300 mg Sublocade® injection. It is important to remind patients not to drive or operate heavy machinery during this brief period. Reassure them that this feeling usually subsides after a few hours, and in rare cases it may persist up to two days.

A NOTE ON PROBUPHINE®

Probuphine® is a buprenorphine subdermal implant used for the treatment of OUD that allows for continuous blood levels of buprenorphine for up to six months following implantation[1].

The ability of this subdermal implant to release continuous, non-fluctuating levels of buprenorphine may also enhance medication adherence and convenience for some patients and can be explored with both clinically stable patients and those struggling with stability and/or regular pharmacy attendance. Probuphine® can be considered in patients stabilized on ≤ 8 mg of sublingual buprenorphine/naloxone daily, noting the implant requires a period of abstinence from opioids before initiation[4].

The subdermal implant is currently not recommended for use beyond two treatment cycles of six months[1].

Additional Information & Recommendations for Probuphine®

- The Probuphine® subdermal implant must be inserted and removed by a prescriber who have successfully completed a live training program, the PROBUPHINE Education Program.
- Ongoingly, prescribers must also ensure they have the requisite knowledge, skills, and clinical competence for the proper insertion and removal of the Probuphine® implant. Support, including in-person procedural support, is available to new and existing prescribers from the manufacturer.
- Patients must be adequately counselled regarding the potential risks and benefits of transitioning to Probuphine®, including what is not known at this time. It is important that patients are adequately informed regarding the potential risks of the implant and explant procedures, as these are invasive in nature.
- Each Probuphine® is a sterile, single, off-white, soft, flexible, rod-shaped ethylene vinyl acetate (EVA) implant, 26 mm in length and 2.5 mm in diameter, containing 74.2 mg of buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride)[10].

- Each dose consists of four Probuphine® implants inserted subdermally in the inner side of the upper arm[10].
- The implant must be removed by the end of the six-month period[10].

Practical Considerations for Probuphine®

Given that local practical experience with Probuphine® is still growing, the following recommendations rely predominantly on the product monograph:

- Once prescribers have completed the training program, the manufacturer will provide prescribers with the forms that essentially act as the prescription and order form for the implant kit. The manufacturer will work collaboratively with the patient and insurance plans/agencies to facilitate coverage.
- Once coverage is confirmed, the manufacturer will ship one dose (four rods) of Probuphine®, along with the sterile implant kit directly to the prescriber's office address ahead of the insertion date. Probuphine® can only be acquired through this closed distribution system (one pharmacy only).
- Prescribers should arrange to have a second healthcare professional present during the implant procedure. This individual can assist in the sterile procedure and serve as an emotional support person for the patient. The procedure is usually completed with local anaesthetic only. Before going home, patients must be educated about appropriate wound care and to watch for any symptoms or signs of an insertion site infection.
- After completing an implant, the provider must notify the manufacturer and confirm the implant date. The manufacturer will then ship the explant kit to the prescriber's office six months after the implant date.
- Should the patient elect to continue with Probuphine® treatment, the explant procedure of the existing Probuphine® and the implant of the new Probuphine® can be completed during the same office visit. The second device is implanted in the other arm to allow the first site to heal[10].
- If new implants are not inserted on the same day as the removal, patients should be switched back to their previous dose of transmucosal buprenorphine (i.e., the dose from which they were transferred to Probuphine® treatment) prior to additional Probuphine® treatment, if so desired by the patient[10].
- After one insertion in each arm, most patients should be transitioned back to their previous sublingual buprenorphine dose (i.e., the dose from which they were transferred to Probuphine® treatment) for continued treatment. At this time, there is no experience with inserting new implants into a previously-used site or using another site of a previously used arm[10].

- The following procedures should only be considered if the potential benefits of continuing Probuphine® outweigh the potential risks of additional insertion and removal procedures and the clinical need of the patient for ongoing treatment with subdermal medication. If continued treatment is desired at the completion of two six-month treatment periods, new Probuphine® implants may be inserted into a previously unused area of the opposite arm. It is important to avoid previously-implanted sites because the effect of scarring and fibrosis in previously-used insertion sites on either the effectiveness of Probuphine®, or the safety of insertion, have not been evaluated. Dosing beyond 24 months (fifth implantation) cannot be recommended at this time[10].
- Finally, although some patients may require occasional supplemental dosing with buprenorphine/naloxone, patients should not be provided with ongoing prescriptions for transmucosal buprenorphine-containing products for as-needed use. Patients who feel the need for supplemental dosing should be seen and evaluated promptly. Ongoing use of supplemental dosing with transmucosal buprenorphine indicates that the amount of buprenorphine delivered by Probuphine® is not adequate for patient stability. Consider use of alternate buprenorphine products for continuing treatment[10].

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Appendix W

TREATMENT WITH SUBLOCADE® CONSENT FORM: GENERAL VERSION

Used with permission & acknowledgment of original author **Opaskwayak Health Authority OAT Program** (2021)

OAT PROGRAM

Address
Phone **Fax**

I hereby acknowledge that I am a client of the _____ Opioid Agonist Therapy (OAT) Program. I have had an opportunity to discuss the next phase of my treatment with the clinic team and I have agreed to proceed with treatment with Sublocade. The common side-effects and potential for injection site reactions have been reviewed with me. I have had an opportunity to have my questions regarding this injectable treatment answered.

I understand that I must receive a Sublocade injection from an OAT program nurse or physician once per month, for treatment to be effective. I also understand that if I am more than two weeks late for my scheduled injection, I may have to restart on daily witnessed buprenorphine/naloxone (Suboxone) at my pharmacy, for a period, before I can be transitioned to Sublocade again. Having to restart on Suboxone may require an in-person assessment, which may result in a delay in returning to treatment. This delay carries a risk of relapse.

I acknowledge that Sublocade injections have NOT been studied in pregnant women. Therefore, it is NOT KNOWN if Sublocade is safe in pregnancy. The drug manufacturer states, in the written product information insert (product monograph): “Do NOT use Sublocade if you are:

- Pregnant. Your doctor will decide whether the benefit of giving you Sublocade outweighs the risk to your unborn baby.
- Or if you are of reproductive age and not using an effective and reliable method of birth control.
- Are pregnant or planning to become pregnant.”

By signing below, I acknowledge that this form has been reviewed with me and I have had an opportunity to have my questions answered.

Client’s Name: _____

Signature: _____ **Date**: _____

OAT Program RN or MD (name): _____

Signature: _____ **Date**: _____

Appendix X

TREATMENT WITH SUBLOCADE® CONSENT FORM: REPRODUCTIVE AGE VERSION

Used with permission & acknowledgment of original author **Opaskwayak Health Authority OAT Program** (2021)

OAT PROGRAM

Address

Phone **Fax**

I hereby acknowledge that I am a client of the _____ Opioid Agonist Therapy (OAT) Program. I have had an opportunity to discuss the next phase of my treatment with the clinic team and I have agreed to proceed with treatment with Sublocade. The common side-effects and potential for injection site reactions have been reviewed with me. I have had an opportunity to have my questions regarding this injectable treatment answered.

I understand that I must receive a Sublocade injection from an OAT program nurse or physician once per month, for treatment to be effective. I also understand that if I am more than two weeks late for my scheduled injection, I may have to restart on daily witnessed buprenorphine/naloxone (Suboxone) at my pharmacy, for a period, before I can be transitioned to Sublocade again. Having to restart on Suboxone may require an in-person assessment, which may result in a delay in returning to treatment. This delay carries a risk of relapse.

I acknowledge that Sublocade injections have NOT been studied in pregnant women. Therefore, it is NOT KNOWN if Sublocade is safe in pregnancy. The drug manufacturer states, in the written product information insert (product monograph): “Do NOT use Sublocade if you are:

- Pregnant. Your doctor will decide whether the benefit of giving you Sublocade outweighs the risk to your unborn baby.
- Or if you are of reproductive age and not using an effective and reliable method of birth control.
- Are pregnant or planning to become pregnant.”

Being of reproductive age, I understand that it is important for me to use a reliable and effective birth control method while being treated with Sublocade. I have had an opportunity to discuss options for reliable birth control with my treatment team. **Both Depo Provera and an intra-uterine device were discussed with me as the two most reliable and effective forms of fertility control**.

Other methods such as the oral contraceptive pill, the pull-out method, and barrier methods such as male and female condoms or sex dams, are less effective at preventing pregnancy, especially in the context of a substance use disorder (addiction).

Therefore, if I choose to use one of these less reliable methods, I understand that it is strongly recommended that I use two different birth control methods at the same time, every time I have intercourse (e.g., an oral contraceptive pill plus condoms). **If I choose not to receive Depo Provera and I do not have an IUD in place, that also means that I will require a urine pregnancy test before every injection. This applies even if I use two less reliable methods of birth control.**

By signing below, I acknowledge that this form has been reviewed with me and I have had an opportunity to have my questions answered.

Client's Name: _____

Signature: _____ **Date**: _____

OAT Program RN or MD (name): _____

Signature: _____ **Date**: _____