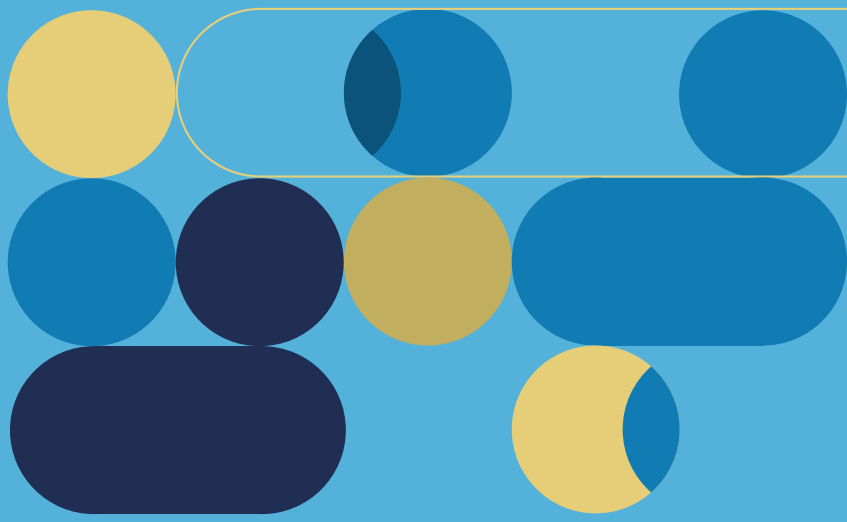
**L'Équipe de soutien clinique et organisationnel**
en dépendance et itinérance

# A Guide to Using Extended-Release Buprenorphine (Sublocade®) in Opioid Agonist Therapy (OAT)

MARCH 2023



Québec

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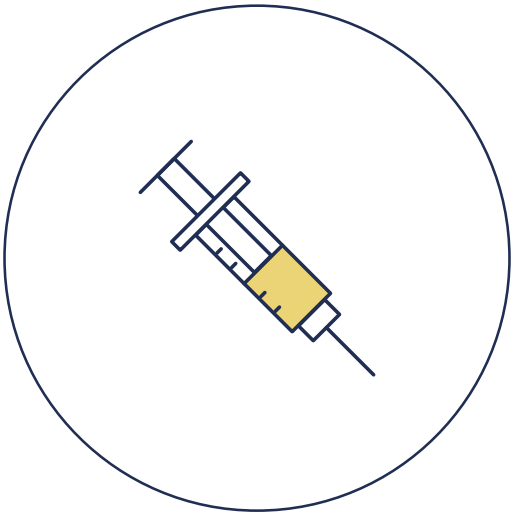

Québec

***A Guide to Using Extended-Release Buprenorphine (Sublocade®) in Opioid Agonist Therapy (OAT)*** is a publication of the Équipe de soutien clinique et organisationnel en dépendance et itinérance at the CIUSSS du Centre-Sud-de-l'Île-de-Montréal.

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Two members of the Committee of Québec Experts, who reviewed the guide, disclosed conflicts of interest. However, the Research Ethics Committee did not deem any of these conflicts significant enough to warrant exclusion.


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## DISCLAIMER

The content of this guide is based on scientific data and clinical guidelines and is the result of discussions and debate by a committee of Québec-based expert practitioners. In addition, the content of the document was verified by competent experts to ensure that it was as accurate as possible in a context where there is a still a paucity of quality literature.

However, it should be noted that the guide is not prescriptive in nature, and its authors **cannot be held accountable** for the clinical practices of professionals. Clinicians are expected to assume responsibility for being appropriately qualified and trained. They must exercise clinical judgment when providing care and services, in compliance with the professional standards and codes of ethics to which they are subject. Should there be any doubt about whether or how the molecule should be used, consulting an expert is recommended.



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# NOTES

The advice given in this guide may come from case reports in the scientific literature or from Québec-based clinical expertise – the text makes this distinction.

Although this document only addresses the use of Sublocade® because it is available in Canada, the literature review for this guide also includes data from outside Canada based on other formulations of extended-release buprenorphine, which are marketed under different names and are used in different doses than Sublocade®.

Where reference is made to buprenorphine-naloxone (Suboxone®), it should be understood that this refers to sublingual tablet and/or sublingual/oral soluble film formulations.

Literature review available upon request.

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# Guide to Using Extended-Release Buprenorphine (Sublocade®) in Opioid Agonist Therapy (OAT)

## 1. GENERAL PRINCIPLES

- Extended-release buprenorphine (BUP-XR) is a partial agonist of the mu (μ) and ORL-1 receptors.[1] It is also an agonist at the kappa and delta opioid receptors.[1]
- Sublocade®, the only formulation of BUP-XR currently available in Québec, is covered by the Québec public drug plan as an exception drug. This drug uses the Atrigel® polymer as a drug delivery system. It is injected as a liquid and creates a solid mass (a "depot") upon contact with body fluids. The buprenorphine is released by diffusion and biodegradation of this depot.
- BUP-XR is approved and covered by Health Canada as an OAT under the Non-Insured Health Benefits (NIHB) program for First Nations and Inuit people.
- BUP-XR is administered subcutaneously every 28 days (the interval may be from 26 to 42 days).
- BUP-XR's maximum plasma concentration is reached 24 hours after injection. Its plasma half-life is 43 to 60 days.[1]
- BUP-XR reaches a steady state after 4 to 6 months, after 4 to 6 injections.
- In general, the buprenorphine molecule shows less negative impact on QTc than methadone.[2-4] However, as with any buprenorphine product, BUP-XR may be associated with QTc prolongation in some people.[1,5] (See the Treatment Principles section for more information.)
- BUP-XR eliminates the need for supervised oral doses of OAT and reduces the number of clinic or pharmacy visits. This greater flexibility in treatment helps achieve treatment goals and results in high satisfaction levels among patients, a lower treatment burden, and a generally improved quality of life.[6–11]
- Because BUP-XR is injected subcutaneously by a health professional, it has a low risk of diversion.

**For the partner care team:**

According to clinical experts, the interval between injections can be extended once a steady state has been achieved and depending on the comfort level of the person receiving treatment. The current evidence indicates that the injections should be given in an interval of 26 to 42 days.[1,12]

It should be noted that the depot formed following the administration of BUP-XR remains visible or palpable for several weeks and usually disappears within two months of injection.

## 2. ELIGIBILITY

### To be eligible for the treatment, a patient must:

- Be between the ages of 18 and 65 (with some exceptions);
- Have a diagnosis of opioid use disorder (OUD) as described in the DSM-5.

**Note:**

The safety of BUP-XR has not been studied in people under 18 years of age. Exceptionally, subject to compliance with the rules regarding the consent of minors to treatment (in French only), a person under the age of 18 may be eligible for OAT with BUP-XR, based on the clinical judgment of an experienced prescriber.

There is currently no data available on the use of BUP-XR in a geriatric population (≥ 65 years). If the partner care team chooses to start using this molecule anyway, special care should be taken in monitoring the person (see Appendix 3 for more information).



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## 3. CONTRAINDICATIONS

### Main contraindications

- Hypersensitivity to the drug or to any of the non-medicinal ingredients, including any component of the Atrigel® delivery system.
- Severe respiratory failure.
- Acute hepatic failure. (See Appendix 3: Dosage Adjustments.)
- Moderate to severe chronic hepatic failure (Child class B and C cirrhosis). (See Appendix 3: Dosage Adjustments.)
- Gastrointestinal obstruction (including paralytic ileus).
- Severe central nervous system depression, such as a significant acute intoxication with a central nervous system depressant (an opioid, alcohol, benzodiazepine, etc.).
- Concomitant use, or use within the last 14 days, of a monoamine oxidase inhibitor (MAOI).

For a full list of the contraindications, see Appendix 1 and the monograph.

**For the partner care team:**

In the presence of relative contraindications, a longer induction period may be recommended for buprenorphine-naloxone to ensure the person's safety before the first BUP-XR injection.

## 4. TREATMENT PRINCIPLES

### Pre-treatment assessment

- Check for drug interactions and consider the risk of interactions with other substances that the patient may be consuming.
- Perform a pregnancy test on anyone who may become pregnant.
  - It is not recommended to induce BUP-XR during pregnancy. Therefore, a pregnancy test and contraception should be offered prior to initiating treatment. (See the section Precautions – Pregnancy and Breastfeeding.)
- Obtain free and informed consent from the person before each treatment. (See Appendix 5).
- Perform a physical examination, especially of the intended BUP-XR injection sites, and look for stigmata indicating liver disease.
- Assess liver function
  - Evaluate the risk of liver damage (hepatitis, alcohol use disorders, hepatic cirrhosis, etc.).
  - Perform a hepatic workup to determine the person's baseline values.
  - Inform the person of the signs and symptoms of liver damage to watch for following initiation of treatment.
- Assess the risk of cardiac arrhythmia
  - Enquire about a history of QTc anomalies.
  - Assess for concomitant medications that may increase QTc.
  - Perform an ECG if there is a significant history, medical conditions (electrolyte disorders) and/or medication that may increase QTc.
- Discuss the use of motor vehicles and machinery
  - Like any opioid, BUP-XR can cause drowsiness, dizziness, and weakness.[1] Usually, these effects occur within the first few days of the injection and at the beginning of treatment, as peak plasma levels are reached within the first 24 hours.

For more information on the initial assessment required of a person before prescribing an OAT, see the guidelines published by the CMQ, OIIQ and OPQ (in French only).



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## Assessments during treatment

- Before each new injection:
  - Reassess the risk of drug interactions and interactions with the substances used.
  - Offer the person a pregnancy test, if appropriate.
  - Validate the time since the last injection (usually 28 days, with a potential interval of 26-42 days).
  - Examine injection sites for signs of infection or changes.
- Monitor liver function:
  - For people without significant liver conditions, continue to pay attention to liver function and perform additional investigations based on clinical judgment.
  - For people with significant liver disease, perform a physical examination and liver function tests every 2 to 4 weeks at the start of treatment and every 3 to 6 months thereafter, once treatment has stabilized.[12] (For more information, see Appendix 3: Dosage Adjustments.)
- Monitor the risk of cardiac arrhythmia:
  - Reassess whether the addition of concomitant medication may increase QTc.
  - Perform a follow-up ECG, based on clinical judgment.

## Administration

- Health Canada requires prescribers to be certified, by Indivior, to prescribe BUP-XR. Although the training on administering the molecule is not mandatory, it is strongly recommended.
- BUP-XR comes as a sterile, clear, viscous solution that can be colourless or yellow to amber in colour and is intended solely for subcutaneous injection.[1] It is available in pre-filled sterile syringes, supplied with a single-use 16 mm 19G needle, and in doses of 100 mg/0.5 mL or 300 mg/1.5 mL.
- BUP-XR is administered subcutaneously to the abdomen.
- BUP-XR must be stored in a refrigerator (between 2°C and 8°C) and removed at least 15 minutes prior to injection to ensure that the product is administered at room temperature. Discard any product that has been at room temperature for more than 7 days.
- If the person is intoxicated when presenting for the injection, ensure that he or she is able to give free and informed consent and that it is safe to proceed with the injection. Since peak plasma concentration is reached 24 hours after injection, there is minimal clinical indication for delaying the injection.

For more information on administration, see the monograph.

**For the partner care team:**

To reduce the pain associated with the injection, some experts recommend applying ice to the intended injection area 15 minutes prior to the injection and injecting the product slowly. It should be noted that a 300 mg dose of BUP-XR takes longer and is more painful to receive than a 100 mg dose.

It is important to tell the person not to massage or touch the depot for 1-2 hours after the injection.

The person does not need to be lying down to receive the injection. Sitting or standing is possible, depending on the person's comfort level.

The use of a 20G needle can also be considered as one way to reduce the pain associated with the injection, although it is not indicated.

The molecule may be injected in a clinic by a physician or nurse, and also in a pharmacy by a nurse who is authorized to do so (additional costs per injection are to be expected, depending on the pharmacy). Currently, Québec pharmacists are not authorized to inject BUP-XR.



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## Prescription

- For a starter kit containing a tracking tool and a sample BUP-XR order, see Appendix 2.
- The prescriber must send a copy of his or her certification to the pharmacy after completing the training.
- As BUP-XR is an exception drug, the RAMQ form must be completed online.

**For the partner care team:**

Prior to the first injection, communication is required between the clinician and the community pharmacy because of the lead time required to order the molecule (up to 3 weeks for the first dose). This is also to ensure that the pharmacy has a sufficient supply of buprenorphine-naloxone for seven days of stabilization before the first injection.

Schedule prescriptions for subsequent injections to ensure that the medication is available at the pharmacy, and enter the information in the pharmacy record.

Indicate on the prescription the expected date of the next injection. Remember that the scheduled date of injection and the actual date may differ.

For a summary of the induction steps for extended-release buprenorphine, see Appendix 6.

## Induction, dosage, and stabilization of treatment

- Typically, before initiating BUP-XR treatment, the person needs to be stabilized beforehand, for at least 7 days, on a dose of between 8 and 24 mg/day of buprenorphine-naloxone.[1]
- The first injection of BUP-XR is usually administered 24 hours after the last dose of buprenorphine-naloxone.[1,12] However, since peak plasma levels are reached 24 hours after injection, there is no need to delay the injection if the last dose of buprenorphine-naloxone was given the same day.[12]
- Once the person is stabilized on buprenorphine-naloxone, he or she begins BUP-XR treatment with a dose of 300 mg/month for two months (two injections). Then, he or she typically continues treatment with a maintenance dose of 100 mg/month.[1] However, a person who is stable on buprenorphine-naloxone OAT at a dose of 8 to 18 mg may receive a maintenance dose of 100 mg on the second injection.[1]
- If the person experiences withdrawal symptoms, cravings, or signs of illicit opioid use when receiving 100 mg/month, then the recommended maintenance dose is 300 mg/month.[1,12]
- If there are any concerns over the person's safety (e.g., severe liver disease) or over drug interactions, treatment can be initiated with administration of 100 mg of BUP-XR.[12]
- If the person has withdrawal symptoms or cravings, buprenorphine-naloxone can be used as an adjunct until his or her next dose of BUP-XR.[12] A maximum dose of 8 mg per day is recommended.
- At the first assessment and at each subsequent follow-up appointment, you should offer a naloxone kit, provide instructions on how to use it, and provide essential harm reduction supplies.




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**For prescribers:**

Based on clinical expertise, it is possible to initiate BUP-XR treatment at the recommended doses if the person is stabilized at a dose of buprenorphine-naloxone greater than 24 mg.

It is also possible to initiate BUP-XR treatment when the person is stabilized at a dose of buprenorphine-naloxone lower than 8 mg as recommended. It is then recommended to initiate BUP-XR treatment at a dose of 100 mg rather than 300 mg.

**Off-label induction methods:**

There is currently a lack of data on off-label induction methods for BUP-XR that do not require a 7-day stabilization period with the same buprenorphine-naloxone dosage. However, alternative induction methods could be used, based on the clinical expertise as well as anecdotal evidence in the literature.[13–15] This includes:

- Buprenorphine-naloxone microdose induction (the Bernese method): this involves introducing low doses of buprenorphine-naloxone (e.g., a starting dose of 0.5 mg DIE at BID) together with the previously used substance (usually a pure opioid agonist), and then gradually increasing the doses until a comfort dose of buprenorphine-naloxone is reached that would allow for discontinuation of the initial opioid. Once the comfort dose has been reached, the first injection of BUP-XR can be given the next day. Refer to the *Guide to Using Buprenorphine-naloxone Microdosing as an Induction Method* for more information on this topic (forthcoming).
- Macrodose induction of buprenorphine-naloxone: this involves introducing consecutive high doses of buprenorphine-naloxone during transfer from a pure opioid agonist (e.g., a starting dose of 8 mg, subsequent doses of 8-16 mg and a maximum dose of 32 mg).[16] Once the person is sufficiently stabilized on buprenorphine-naloxone, BUP-XR injections can be initiated.[17]

These alternative induction methods are particularly useful in alleviating sudden withdrawal symptoms during a transfer from a pure opioid agonist. They may be considered for persons for whom the goal of stabilization for at least 7 days at the same buprenorphine-naloxone dosage appears unattainable. As these induction methods are off-label, the prescriber is advised to document the person's clinical history and consult an expert, if necessary.

**For the partner care team:**

At the start of treatment, offer the person regular follow-up appointments, either in the clinic or by teleconsultation, including at least one follow-up appointment within one week of the injection to ensure that there are no side effects or withdrawal symptoms.

Monitor the person for withdrawal symptoms until he or she is stabilized.

For purposes of harm reduction, a safer supply* can be prescribed to supplement BUP-XR. However, it is possible that the effect of a safer supply may be reduced or masked by the presence of buprenorphine at mu (μ) receptors. For more information on safer supply, see the document Substance Replacement Therapy in the Context of the COVID-19 Pandemic in Québec: Clinical Guidance for Prescribers.

According to clinical practice (and even though this has not been subject to a scientific study), an injection of 100 mg of BUP-XR would have some protective effect against an overdose, while leaving the person free to use psychoactive substances. A concurrent prescription of safer supply could then be considered.

*The term "safer supply" refers to replacing psychoactive substances purchased on the illicit market with pharmaceutical substances of known and stable content.[18]

## Missed or late doses

- The administration of doses is scheduled every 28 days, but may be advanced by 2 days and delayed by up to 14 days (for a minimum interval of 26 days and a maximum interval of 42 days).[1,12]
- Once steady state has been reached (after 4 to 6 injections):
  - An occasional delay in administration of up to 4 weeks after the scheduled injection date (e.g., ≤ 8 weeks after the last injection) is not expected to have a significant impact on treatment effectiveness. Plasma buprenorphine levels are generally maintained during this period.[12] BUP-XR dosing can then be resumed as before, with no changes.
  - On the other hand, a delay of more than 4 weeks after the scheduled injection date (e.g., ≥ 8 weeks after the last injection) may result in reduced buprenorphine plasma levels, thereby lowering the person's opioid tolerance threshold.[12] In such cases, it may be advisable to administer a dose of buprenorphine-naloxone (e.g., 8 mg) to test the person's tolerance, and resume regular BUP-XR therapy the following day.[12]
  - If an opioid other than a buprenorphine formulation has been taken regularly since the last injection, it is recommended that treatment be re-initiated according to the original protocol in order to avoid provoking sudden withdrawal symptoms.[12]



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## Stopping and transferring treatment

- Voluntary cessation of treatment:
  - Discontinuation of OAT is generally not recommended due to the risks associated with opioid withdrawal (risk of relapse and overdose).[19]
  - The decision to discontinue BUP-XR should be made only after considering the benefits and risks associated with the treatment and after evaluating the possibility of continuing on an alternative OAT. For more information on opioid withdrawal, see Appendix 4 of the *Québec Guide to Improving Practices in the Management of Opioid Use Disorder (OUD)*.
  - For someone who is stable on a dose of 300 mg, it is recommended to reduce the dose to 100 mg before discontinuing treatment.[12]
  - Plasma concentrations of buprenorphine due to injections gradually decrease after the last injection and remain at therapeutic levels for several weeks to months.[1,12] This feature of BUP-XR may make it difficult to predict the timing of withdrawal symptoms, adverse events, and drug interactions, and may affect the transition to other opioids.[12] It may also have a protective effect against overdose, should opioid use be resumed.[12]
  - After treatment is discontinued, it is recommended to monitor the person for several months for signs of withdrawal and provide appropriate treatment. The person should be able to restart OAT at any time.
  - Provide the person with a naloxone kit, and teach them how to use it.
- Forced termination of treatment and withdrawal of the depot:
  - If there are signs of intolerance or severe injection site reactions, the BUP-XR depot can be surgically removed under local anesthesia within 14 days of injection.[1]
  - As with voluntary cessation, if termination is forced by removing the depot, the person should be followed for several months to monitor for signs of withdrawal and provided appropriate treatment. It should be noted that withdrawal symptoms may appear more quickly following a premature withdrawal than would occur in a normal discontinuation of treatment.
- Transfer of treatment:
  - To transfer a patient from BUP-XR to a buprenorphine-naloxone formulation, it is recommended to administer a low dose (typically 8 mg) of buprenorphine-naloxone at the time of the next planned BUP-XR injection, i.e. approximately 4 weeks after the last injection, and then increase the dosage if necessary in the following days or weeks.[12]
  - In the absence of data on transfers from BUP-XR to methadone or another opioid, it is recommended to transfer the person to a buprenorphine-naloxone formulation for at least 4 weeks for a subsequent induction to another OAT, as per the standard recommendations.[12]

**For the partner care team:**

A 2020 case report mentions the successful use of a single injection of 100 mg of BUP-XR to discontinue buprenorphine-naloxone OAT after several unsuccessful attempts to stop this medication.[20]



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## 5. PRECAUTIONS

### Adverse effects

- The adverse effects associated with BUP-XR are similar to those for buprenorphine-naloxone, with the exception of injection-related adverse effects.[6–8,11,20]
- The major (relatively rare) adverse effects of BUP-XR are the same as those caused by opioids, and include respiratory depression up to and including death, particularly when BUP-XR is combined with benzodiazepines and other CNS depressants, such as other opioids or alcohol.[1]
- The most common adverse effects (≥ 5%) are constipation, nausea, vomiting, headache, fatigue, insomnia, increased liver enzymes (very often asymptomatic), injection site pain and pruritus, and peripheral edema.[1,6–8,20]
- Less common adverse effects (approximately 1%) are upper abdominal pain, injection site abnormalities (including erythema, ecchymosis, induration, and edema), drowsiness, sedation, dizziness, and lethargy.[1]
- Less common (<1%) adverse effects include blurred vision, injection site abnormalities or infections including ulcers or cellulitis, hypotension with or without orthostatic hypotension, fainting, euphoria, erectile dysfunction and decreased libido, and urinary retention.[1]
- Chronic use of BUP-XR, much like chronic use of other opioids, may also be associated with endocrine disorders such as adrenal insufficiency and hypogonadism.[1]

### Metabolism and elimination

- Buprenorphine is metabolized to its main metabolite, norbuprenorphine, primarily by an oxidation reaction (phase I reaction) at cytochrome P450. The primary substrate for buprenorphine is CYP3A4 and, to a lesser extent, CYP2C8.[1] In the case of BUP-XR, since administration is subcutaneous, the first hepatic passage is avoided (phase I reaction), so the plasma concentrations of norbuprenorphine are significantly lower than those observed with buprenorphine-naloxone. The ratio of the area under the norbuprenorphine/buprenorphine curve is 0.2 to 0.4 with BUP-XR, compared to 0.7 to 2.11 with buprenorphine-naloxone. The cytochrome transformation of buprenorphine is therefore approximately one quarter of that when using the injectable product.[1] Consequently, the effect of CYP3A4 and CYP2C8 on metabolism and their clinical impact are significantly less.[1]
- Biotransformation of buprenorphine also involves glucuronic conjugation reactions (phase II reactions) through the isoenzymes UGT1A1, UGT1A3 and UGT2B7.
- Buprenorphine has a mild inhibitory effect on CYP1A2, CYP2A6, CYP2C19, and CYP2D6.
- Buprenorphine is eliminated through the urine (30%) and feces (69%). Buprenorphine and norbuprenorphine have been found in a predominantly conjugated form in urine and in a predominantly free unchanged form in feces.

### Drug interactions

- Prior to the introduction of BUP-XR, it is important to consider certain drug interactions (see Appendix 4 and the monograph for more information):
  - Central nervous system depressant
  - Naltrexone
  - CYP3A4 inhibitors (clinically insignificant impact of this type of interaction with BUP-XR due to avoided hepatic first pass – see Appendix 4 for more information)
  - CYP3A4 inducers (clinically insignificant impact of this type of interaction with BUP-XR due to avoided first hepatic pass – see Appendix 4 for more information)
  - Some antivirals
  - Monoamine oxidase inhibitors
  - Serotonergic drugs
  - Diuretics
  - Anticholinergic agents
  - Medications that may prolong QTc



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## Injection-related risks

- Non-subcutaneous injection of BUP-XR poses significant risks of serious effects or death due to the depot it forms upon contact with body fluids.[1]
- Intravenous administration may cause occlusion, localized tissue damage, and thromboembolic events such as life-threatening pulmonary embolism.[1]

## Pain management

- BUP-XR has not been the subject of a comparative study of pain management.
- Regardless of its formulation, buprenorphine is a partial agonist at the mu (μ) opioid receptor, with a high affinity for these receptors. These pharmacologic properties must be duly considered when the addition of another opioid agent is clinically indicated. In this case, it is recommended to use a pure mu (μ)-opioid receptor agonist that also has high affinity for these receptors, such as hydromorphone, in order to achieve the desired effect.22
- The following strategies should be implemented, in sequence, to manage pain in persons taking OAT:
  - Encourage the use of non-pharmacologic measures (ice, acupuncture, physical therapy, etc.).
  - Encourage coanalgesia with non-opioid agents (acetaminophen, nonsteroidal anti-inflammatory drugs, infiltration, gabapentinoids).[23]
  - When adding an opioid is indicated, higher doses may sometimes be required to provide adequate relief. This treatment strategy is only for short-term use.
  - If the person is still uncomfortable, consult an OAT or pain expert.

## Pregnancy and Breastfeeding

### Pregnancy

#### Induction

- Due to the lack of human data, and because of the teratogenic effects observed in animals of one component of Atrigel® – N-methyl-2-pyrrolidone (NMP) –, it is not recommended to induce BUP-XR during pregnancy. Instead, induction with conventional oral therapies, such as buprenorphine-naloxone, methadone, or once-daily extended-release morphine is indicated.

#### Continued treatment

- Once a pregnancy is discovered, BUP-XR therapy must only be continued after considering the associated benefits and risks (see Appendix 7 for more information). This decision should be made only after obtaining the free and informed consent of the pregnant person, and should include consultation with an expert in perinatal care and OAT, since the current lack of data makes it difficult to accurately predict the effects of treatment on the person and their fetus.

  **Potential benefits of maintaining BUP-XR:**

  - When the person already has experience with and tolerates the treatment, it is generally recommended to avoid making changes to OAT during pregnancy in order to preserve the clinical stability of the pregnant person (due to the risk of episodes of withdrawal associated with any changes in OAT).[23]
  - BUP-XR's sustained release profile could be an additional theoretical benefit to the person's clinical stability, given the stability of buprenorphine plasma concentrations, avoiding peak and trough episodes.
  - Consideration should also be given to the benefits associated with monthly administration of BUP-XR (fewer pharmacy visits, easier adherence, overdose prevention due to the blocking of mu receptors).

  **Risks associated with maintaining BUP-XR:**

  - The rigidity of BUP-XR dosing and the difficulties around rapidly adjusting treatment, as well as the unpredictable but potentially significant pharmacokinetic changes expected during pregnancy and postpartum, all pose significant constraints. It may be preferable to use a preparation whose dosage can be rapidly adjusted;
  - The lack of data on use in humans, and the risk of NMP's teratogenicity; and
  - The impact of exposure to high doses of buprenorphine (especially with 300 mg injections) is difficult to predict in terms of the risk of the person developing neonatal withdrawal syndrome, as well as in terms of its severity.
- In the event that a decision is made to discontinue BUP-XR treatment, it is recommended to transfer the person to an oral formulation of buprenorphine-naloxone. (See the transfer of treatment section for more information.)
- Obstetrical, fetal, and neonatal monitoring, and the intra and postpartum pain management approaches used should be the same as for persons treated with buprenorphine-naloxone.



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## Breastfeeding

- BUP-XR should only be used during breastfeeding after giving due consideration to the associated benefits and risks (see Appendix 7 for more information), and after obtaining the person's free and informed consent. In all cases, the decision to breastfeed or to transfer the person on BUP-XR to another OAT should only be made after consulting with professionals experienced in postpartum and pediatric follow-up in the context of OAT during pregnancy.
  - The following should be considered in any such deliberations:
    - The lack of data on the use of BUP-XR during breastfeeding and the likely passage of NMP into breast milk (although with limited risk of accumulation).
    - The high plasma concentrations of buprenorphine, particularly when using a dosage of 300 mg/month, lead to higher exposures for infants than what has been documented to date. This expected high exposure poses a risk of adverse effects in the nursing infant (sedation, lethargy, respiratory depression, constipation, nausea). The person receiving treatment should be advised of these effects and counseled on how to address them.
    - Due to the fact that buprenorphine exposure peaks in the first few days after administration of BUP-XR and then slowly declines, the child should be more closely monitored in the 48 to 72 hours following injection. Mixed breastfeeding may be used, on a temporary basis, during this period, although this approach also carries risks of provoking withdrawal symptoms in the child.
    - Some factors increase the risk of adverse effects in infants:
      - Combination therapy with sedative medications or with substances whose sedative effects may add to those of buprenorphine (e.g., cannabis, alcohol);
      - When high doses are required (e.g., BUP-XR at 300 mg per month, or BUP-XR at 100 mg per month with top-up doses often required);
      - Exclusive breastfeeding of a very young child (e.g., younger than 2 months), who is more susceptible to sedative effects and whose immature metabolic pathways predispose them to drug accumulation;
      - A newborn with one or more medical conditions.
  - In breastfeeding, the risks need to be weighed against the benefits (e.g., optimal nutrition, strengthening the immune system, development of an attachment to the parent, decreased neonatal withdrawal symptoms in the initial days of life, etc.). Certain protective factors may also influence the potential risks (e.g., access to family or nursing support, a newborn who is hospitalized for treatment of neonatal withdrawal, and the resultant close monitoring).
  - When a combination of factors makes breastfeeding risky, it should be discouraged. If protective factors are present, mixed breastfeeding could be suggested to reduce the child's exposure.
- Considering the potential risk that breastfed children will be exposed to BUP-XR, regular pediatric follow-up and support is essential during weaning from breastfeeding, for all the molecules used in OAT.
  - Breastfeeding should be discontinued gradually to avoid the development of signs of opioid withdrawal in the child.
- In the event that it is decided to discontinue treatment with BUP-XR, it is recommended to transfer the person to an oral formulation of buprenorphine-naloxone. (See the transfer of treatment section for more information.)

## Available resources

- Canadian Pediatric Society
- Journal of Obstetrics and Gynaecology Canada



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### Québec resources for support

- Centre IMAGe (Info-Médicaments en Allaitement et Grossesse), CHU Sainte-Justine
  Telephone information centre for health professionals.
  Telephone: 514-345-2333 (Monday to Friday)
  www.chusj.org/image
- Rond-Point, an expertise centre on perinatal and family addiction
  2135 Alexandre-DeSève Street, Room KR-1203
  Montréal (Québec) H2L 2W5
  Telephone: 438 386-4050
  Fax: 514 528-2433
  rondpoint@pediatriesociale-cs.org
- CHUM, Neonatology Unit, Obstetrics and Gynecology Department
  1051 Sanguinet Street, Montréal (Québec) H2X 0C1
  Telephone: 514 890-8000, ext. 27244
  Fax: 514 412-7604

**L'Équipe de soutien clinique et organisationnel** en dépendance et itinérance

## Contact us

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**Phone line and text messages**, available from 9 a.m. to 5 p.m., Monday to Friday: 514-863-7234
**Email**: escodi.ccsmtl@ssss.gouv.qc.ca
**Website**: dependanceitinerance.ca

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# APPENDICES

**Appendix 1:** Contraindications

**Appendix 2:** Starter Kit (treatment tracking tool and prescription template)

**Appendix 3:** Dosage Adjustments

**Appendix 4:** Common Extended-Release Buprenorphine (Sublocade®) Drug Interactions

**Appendix 5:** Extended-release buprenorphine (Sublocade®): Frequently asked questions

**Appendix 6:** Summary of steps in the induction of Extended-Release Buprenorphine (Sublocade®)

**Appendix 7:** Summary of the report entitled *Innocuité de la buprénorphine à libération prolongée pour injection sous-cutanée durant la grossesse et l'allaitement en opioid agonist therapy dans le cadre du traitement des troubles liés à l'utilisation des opioïdes* (in French only), by the Centre IMAGe (Info-Médicaments en Allaitement et Grossesse), 2022



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# APPENDIX 1
# Contre-indications

## Absolute contraindications to the use of BUP-XR

- Hypersensitivity to the drug or to any of its non-medicinal ingredients, such as components of the Atrigel® delivery system (N-methyl-2-pyrrolidone, Poly(DL-lactide-co-glycolide))
  - There have been reports of severe hypersensitivity in the form of bronchospasm, Quincke's edema, or even anaphylactic shock.
  - More commonly, there have been reports of hypersensitivity in the form of a skin rash, urticaria or pruritus.
- Severe respiratory failure (asthma with severe bronchospasm, severe chronic obstructive pulmonary disease [COPD])
- Acute respiratory depression
- Acute hepatic failure
- Chronic hepatic failure, moderate to severe (Child class B and C cirrhosis). For more information, see Appendix 3: Dosage Adjustments
- Severe central nervous system depression, such as significant acute intoxication with a central nervous system depressant (opioid, alcohol, benzodiazepine, etc.)
- Gastrointestinal obstruction (including paralytic ileus)
- Concomitant use, or use within the last 14 days, of a monoamine oxidase inhibitor (MAOI)
  - Like any opioid, BUP-XR can cause a significant interaction with MAOIs.

## Relative contraindications to the use of BUP-XR

- Hypersensitivity to other opioid analgesics
- Mild to moderate respiratory failure (asthma or mild to moderate chronic obstructive pulmonary disease (COPD))
- Acute abdomen (e.g. appendicitis or acute pancreatitis)
- Delirium tremens
- Seizure disorders:
  - Before starting BUP-XR, it is recommended to assess the person's seizure risk (presence of a long-term seizure disorder, use of psychoactive substances and/or use of medication that lowers the seizure threshold). As with any opioid, BUP-XR may lower the seizure threshold, which may lead to de novo seizures or exacerbate an already known epilepsy. Conducting a benefit-risk assessment with the person is therefore recommended prior to initiating treatment.
- Concomitant use of a central nervous system depressant:
  - Before starting BUP-XR treatment, it is essential that the person be advised of the risks associated with the concomitant use of BUP-XR and central nervous system depressants (alcohol, benzodiazepines, other opioids, certain psychiatric medications, etc.). Such combinations increase the risk of adverse effects and serious complications, including overdose and death from respiratory failure.
- Mild hepatic impairment. For more information, see Appendix 3: Dosage Adjustments
- Craniocerebral injury, mainly if associated with intracranial hypertension
- Increased risk of arrhythmia:
  - Heart rhythm disorder
  - Congenital long QT syndrome or prolonged QT interval
  - Uncorrected hypokalemia, hypomagnesemia, or hypocalcemia
- Impending surgery that is associated with a significant risk of acute pain

In this document, contraindications have been broken down into two categories – absolute and relative – based on clinical judgment and pharmacological references. It should be noted that the Sublocade® monograph makes no distinction between absolute and relative contraindications.



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APPENDIX 2

# Starter Kit (treatment tracking tool and prescription template)

## Tool for tracking treatment of a person treated with extended-release buprenorphine (Sublocade®)

Name:

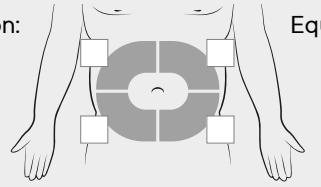
Date of birth (yyyy-mm-dd): File number:

**Injection #** **Vial batch #**

Date (yyyy-mm-dd): Vital signs:

Dosage : 300 mg ☐
100 mg ☐
Other ☐

Location:



Equipment used: 19G ☐
20G ☐
Other ☐

Observation(s):

Date of the post-injection follow-up (yyyy-mm-dd):

**Post-injection follow-up #**

Date (yyyy-mm-dd):

Vital signs: COWS :

Observation(s):

Adjustment(s) to the treatment plan:

Date of the next injection (yyyy-mm-dd):



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## Prescription template

[Patient contact information]

**PHARMACEUTICAL PRESCRIPTION**
**EXTENDED-RELEASE BUPRENORPHINE (SUBLOCADE®)**

**Hospital** ☐ **Recovery housing** ☐ **Rehabilitation** ☐ **Frontline** ☐

Allergie(s): _____ None known: ☐ Adverse reactions to medications: _____

**EXTENDED-RELEASE BUPRENORPHINE (SUBLOCADE®)**

**INDICATION**
QHR notice: **Substitution treatment for opioid use disorder (opioid agonist therapy )**
Prescription approved by RAMQ for the period FROM _____ /_____ /_____ TO _____ /_____ /_____

**Step 1 (loading doses): Extended-release buprenorphine (Sublocade®)** _____ mg S/C au niveau de l'abdomen q28 jours x 2:

- Total quantity prescribed: _____ injection(s)
- Serve 1 dose every _____ days

**Step 2 (maintenance dose): Extended-release buprenorphine (Sublocade®)** _____ mg S/C in the abdomen q28 days thereafter:

- Total quantity prescribed: _____ injection(s)
- Serve 1 dose every _____ days

- Expected date of injection (it is recommended to record this date in the QHR for each injection): _____
- If necessary, check the appropriate box:
  - ☐ Deliver to: _____
  - ☐ Administered by a nurse in a pharmacy (if available)
  - ☐ Provide the naloxone kit and please provide instructions on how to use it.
- **The drug must be administered within 26 to 42 days of the last injection. If it cannot be administered within this therapeutic window, the pharmacist should consult the prescriber about readjusting.**
- **Discontinue the previous buprenorphine-naloxone (Suboxone®) prescriptions on the day of the first injection of extended-release buprenorphine (Sublocade®). The first injection is usually administered 24 hours after the last dose of buprenorphine-naloxone (Suboxone®). However, there is no need to delay the injection if the last dose was given on the same day.**

**OTHER MEDICATIONS**

**CONFIDENTIAL TRANSMISSION BY FAX**

Pharmacy: _____
Fax number: _____ Date/Time: _____

[Identification of the prescriber's location of practice]

**Prescriber's name** (block letters): _____ **Permit no.**: _____

**Prescriber's signature**: _____ **Date and time**: _____

**As the prescribing physician of extended-release buprenorphine (Sublocade®), I hereby confirm that:**

- ☐ **I have completed the training required by Health Canada and received the certification developed by Indivior.**
- ☐ **I have sent a copy of my certification to the pharmacy.**

**PHARMACEUTICAL PRESCRIPTION**
**EXTENDED-RELEASE BUPRENORPHINE (SUBLOCADE®)**



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# APPENDIX 3
# Dosage Adjustments

## Acute or chronic hepatic failure

The relationship between BUP-XR use and hepatic failure, whether acute or chronic, has not been formally studied. However, studies on the effects of sublingual buprenorphine have demonstrated the importance of exercising caution about hepatic failure. Since the main metabolic pathway for sublingual buprenorphine is hepatic (via cytochrome 3A4), the risk of accumulation is significant in hepatic impairment. Even though subcutaneous administration of BUP-XR sidesteps the first hepatic passage, caution should be exercised. The extended-release formulation is still associated with a significant risk of accumulation, among other things, because any dosage adjustments will not be rapidly seen in buprenorphine plasma levels.[1] In addition, the current data on BUP-XR dosages do not provide a reliable basis for comparison with the data on buprenorphine-naloxone dosages.

For all of these reasons, BUP-XR is not recommended for use in moderate to severe chronic hepatic failure (Child class B and C cirrhosis), even though the monograph only targets severe chronic hepatic failure (Child class C cirrhosis) in the contraindications and stresses the importance of exercising caution in moderate chronic hepatic failure (Child class B cirrhosis). Thus, BUP-XR is only indicated in the case of mild chronic hepatic failure (Child class A cirrhosis).[2] In addition, although no dose adjustments are recommended in mild chronic hepatic failure, some experts suggest that buprenorphine-naloxone should be maintained at stabilization doses for more than 7 days in order to observe the buprenorphine's effect on liver function before the first injection is administered. It should be noted that the clinical guidelines make various recommendations on the use of BUP-XR in cases of moderate chronic hepatic failure (Child class B cirrhosis).[1,3] Following a thorough analysis of treatment options, if the benefits of treatment outweigh the risks, these guidelines recommend exercising caution in use of BUP-XR in persons with moderate chronic hepatic failure, and they propose an induction dose of 100 mg instead of 300 mg.

In addition to the precautions concerning chronic hepatic failure, the literature reports cases of treatment-related secondary acute hepatic failure. If the person develops moderate to severe hepatic failure following initiation of BUP-XR therapy, they should be closely monitored for several months.[1] This follow-up should include monitoring hepatic function, but also looking for signs and symptoms of buprenorphine toxicity or overdose, which is a potential result as plasma levels of the molecule increase.[1] It may even be necessary to remove the BUP-XR depot within 14 days of injection.[2] In such cases, removal of the depot may result in an improvement in the liver function test.[1]

## Renal impairment

No dosage adjustments are recommended in the monograph. In studies of the pharmacokinetics of buprenorphine, renal impairment is not associated with increased buprenorphine plasma levels.[4] Caution is suggested in cases of severe renal impairment.

## Geriatric population

The monograph does not recommend any dosage adjustments for the geriatric population. However, as with any opioid, caution needs to be exercised, given the higher risk of hepatic, renal, cardiac, and/or respiratory failure, in addition to the higher rate of polypharmacy and/or multiple physical co-morbidities in this population, and the fact that the dosage cannot be adjusted once the injection has been administered.[4,5]



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## REFERENCES FOR APPENDIX 3


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# APPENDIX 4
# Common Extended-Release Buprenorphine (Sublocade®) Drug Interactions

### Central nervous system depressant (benzodiazepines, barbituates, H1 antihistamines, sedatives, pregabalin, gababentin, etc.), including alcohol and other opioids

Increased cardiorespiratory risk, ranging from hypotension to life-threatening respiratory distress.

### Naltrexone

Naltrexone is an opioid antagonist and can therefore precipitate opioid withdrawal syndrome or reverse virtually all the therapeutic effects of opioids.

### Inhibitors of CYP3A4 (erythromycin, ketoconazole, ritonavir)

There is a theoretical risk of increased buprenorphine plasma concentrations (CYP3A4 substrate) due to the way certain medications can inhibit CYP3A4. However, since hepatic first-pass metabolism is avoided with subcutaneous administration of buprenorphine, the impact of interactions via CYP3A4 becomes negligible, and few effects are expected.

### Inducers of CYP3A4 (rifampin, carbamazepine, phenytoin, phenobarbital)

There is a theoretical risk of decreased buprenorphine plasma concentrations (CYP3A4 substrate) due to the way certain drugs can induce CYP3A4. However, since hepatic first-pass metabolism is avoided with subcutaneous administration of buprenorphine, the impact of interactions via CYP3A4 becomes negligible, and few effects are expected.

### Some antivirals

#### Etravirine

increase in buprenorphine Cmax, the area under the curve (AUC), and Cmin by 11%, 25%, and 40%, respectively. An 8% increase in norbuprenorphine Cmax, with 12% and 25% decreases in norbuprenorphine AUC and Cmin, respectively. The inductive effect requires monitoring for signs and symptoms of opioid withdrawal. It should be noted that these observations have been documented with buprenorphine-naloxone and, therefore, with a higher proportion of norbuprenorphine.

#### Darunavir/cobicistat

There is no specific study that has evaluated this co-administration. However, due to the impact on UGT2B7 and UGT1A1 glucuronidation, there is a theoretical risk of increased plasma concentrations of buprenorphine and norbuprenorphine. Signs and symptoms of overdose will therefore need to be monitored.

#### Efavirenz

Decreased the buprenorphine AUC by 50% and decreased the norbuprenorphine AUC by 71%. The inductive effect requires monitoring for signs and symptoms of opioid withdrawal.

#### Protease inhibitors coadministered with ritonavir

Results in no significant change in buprenorphine plasma concentrations, but increases norbuprenorphine plasma concentrations. However, no meaningful clinical effect is expected.



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### Monoamine oxidase inhibitors (MAOIs) (moclobemide, selegiline, phenelzine, tranylcypromine)

Increased risk of serious drug interactions affecting the central nervous system and cardiorespiratory function (e.g. serotonin syndrome). The risk is present with concomitant use of MAOIs and for 14 days after discontinuation.

### Serotonergic drugs (antidepressants including SSRIs, SNRIs, tricyclics and mirtazapine; some psychiatric drugs including buspirone, lithium and trazodone; antimigraine drugs including triptans; antiemetics including ondansetron; other serotonergic drugs including linezolid, dextromethorphan, cyclobenzaprine, St. John's wort and tryptophan; etc.)

Theoretical risk of serotonin syndrome (clinical triad of altered mental status, autonomic hyperactivity and neuromuscular abnormalities such as myoclonus and hyperreflexia).

### Diuretics

Like other opioids, BUP-XR reduces the effectiveness of diuretics by inducing the release of antidiuretic hormone (ADH). In addition, BUP-XR can provoke acute urinary retention by causing spasms of the bladder sphincter. So the risk of urinary retention increases in people treated with BUP-XR.

### Anticholinergic agents

Increased risk of constipation and urinary retention. In combination, opioids and anticholinergic agents may contribute to decreased gastric motility and, consequently, paralytic ileus.

### Medications at risk of QTc prolongation (antiarrhythmics, antipsychotics, SSRI or SNRI antidepressants, tricyclic antidepressants, macrolide antibiotics, quinolone antibiotics, azole antifungals [ketoconazole, fluconazole, voriconazole], domperidone, etc.)

Like any other opioid, BUP-XR can affect QTc, so it may be associated with an increased risk of cardiac arrhythmia. The risk is more significant in persons with multiple conditions or taking multiple medications associated with QTc prolongation.



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APPENDIX 5

# EXTENDED-RELEASE BUPRENORPHINE (SUBLOCADE®)
# Frequently asked questions

## What is this medication?

Extended-release buprenorphine is a drug of the opioid class, like morphine, hydromorphone (Dilaudid®), heroin, fentanyl, etc.

This medication comes in the form of a liquid that is injected under the skin (in the abdomen). It is administered once a month by a health professional. Buprenorphine is then continuously released into the body until the next injection.

In the syringe, the medication is in liquid form. When injected under the skin, it solidifies to form a solid mass.

## When is this medication prescribed?

For someone with an opioid addiction (now called opioid use disorder—OUD), the scientific evidence shows that the most effective and safest treatment is long-term opioid agonist therapy (OAT).

The best-known opioid agonists are methadone, buprenorphine-naloxone (Suboxone®), and once-daily slow-release morphine (Kadian®).

OAT is a long-term treatment, also recognized as a "maintenance" treatment. It consists of taking medication that reduces withdrawal symptoms, decreases cravings, and causes minimal drowsiness or euphoria.

## Are there any requirements for this treatment?

Before a first injection can be administered, the person needs to have taken buprenorphine-naloxone (Suboxone® tablet or film) for at least 7 days and be comfortable at a dose of 8 mg or more.

## How is this medication taken?

This medication must be injected, under the skin (subcutaneously) in the abdomen, by a health professional.

Injections other than subcutaneous, such as intravenous injections, can cause serious complications and even lead to death.

Ideally, this treatment is started after a phase of stabilization with buprenorphine-naloxone lasting at least 7 days. This transition period is needed to avoid precipitating withdrawal, and ensures that buprenorphine is the right choice of medication for OAT.

Usually, the starting dose is 300 mg and is given for the first 2 injections (the first 2 months). This is followed by the maintenance dose, which is usually 100 mg every month.

At the beginning of the treatment, and when the person has not yet reached a state of comfort, it is possible to add a prescription of buprenorphine-naloxone in tablet or film form. This is taken in addition to the injection.

## What is good to know after the injection?

The mass that forms under the skin following the injection will remain visible for several weeks. However, it will become less and less visible as time passes.

After the injection, you should not rub, massage, or scratch the mass. It is recommended to wear clothing that is loose enough that it will not press tightly on the skin or irritate the skin in this area.

## How long does the treatment last?

Stopping treatment for opioid dependence is generally not recommended because of the risks associated with opioid withdrawal, including the risk of relapse and overdose when an opioid is restarted. If the decision is nevertheless made to stop treatment, it is important to have the support of the partner care team. Treatment can be resumed at any time.



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## What if I miss a dose?

It is important not to miss scheduled injections, as this can cause you to experience withdrawal symptoms. If this occurs, it is important to contact the partner care team right away. Injections should be given once a month, but it is possible to go 26 to 42 days between injections without causing withdrawal symptoms.

## What are the side effects?

The injection may be somewhat painful, especially at the beginning of treatment. To alleviate the pain, it is usually suggested to apply ice 15 minutes before the injection.

The side effects are similar to those of other opioids, i.e. constipation, nausea and vomiting, drowsiness, and headache. In the case of extended-release buprenorphine, it is also important to watch for side effects at the injection site (redness, swelling, infection, etc.). If these side effects inconvenience you, contact the partner care team to reduce their impact.

## Can alcohol or other psychoactive substances be consumed during treatment?

The use of opioids, even an OAT, in combination with alcohol or other depressants such as benzodiazepines (Ativan®, Xanax®, Rivotril®, etc.) or GHB causes drowsiness. This use can carry a particularly dangerous risk of overdose and, in some cases, can lead to death.

If you want to continue opioid use during treatment, it is important to discuss this with the partner care team. The prescriber may prescribe medications as alternatives to what you usually use. This is called safer supply.

## Can I drive and do manual labour?

Like any opioid, this medication can cause drowsiness, dizziness, and make you feel weak. These effects occur more often in the first few days after receiving an injection and at the start of treatment. For these reasons, it is not recommended to drive or operate machinery at the beginning of your treatment, as long as the treatment has not stabilized and you're still experiencing drowsiness. In the eyes of the law, everyone is responsible for their actions.

## Can I take this medication during pregnancy or while breastfeeding?

If you are planning to become pregnant in the near future, taking this medication is not recommended. If you become pregnant during treatment, discuss it immediately with the partner care team so that they can determine whether you can continue treatment or whether another treatment would be more appropriate.

If you want to breastfeed, you are strongly recommended to discuss this with the partner care team so that, together, you can evaluate the benefits and risks associated with breastfeeding while taking this medication.

## What if I'm taking other medications or natural health products?

If you are taking other drugs or natural health products, it is important to inform the prescriber and other health professionals involved in the health assessment, as well as the pharmacist. They will assess the risk of interactions between the medications and with the natural health products. Some drug combinations can cause serious side effects.

## Who should I speak to if I need help or have questions?

If you have questions about the treatment, if you are experiencing side effects and it is difficult to know if they are normal, or if you continue to have withdrawal symptoms or cravings, it is important to contact a member of the partner care team. The community pharmacist on the care team is also able to quickly provide advice.

## Naloxone and safer injecting, safer smoking, and safer sex supplies: everywhere, all the time, for everyone!

Give out naloxone and instructions on how to use it, as well as safe drug use equipment and personal



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protection equipment. Do this at every meeting with the team.

Naloxone, which is sometimes referred to as the “opioid overdose antidote”, saves lives by reversing the effects of an opioid overdose. This is why it is important to include the person’s family and friends when distributing naloxone and giving instructions on its use. In addition, the distribution of safe drug use equipment and personal protective equipment helps reduce the risk of infection.

Health and social service facilities may distribute naloxone and provide safer injecting, safer smoking, and safer sex supplies as part of their services. People undergoing treatment and their family and friends can also obtain it from pharmacies and certain community organizations.

## Safer injecting, safer smoking and safer sex supplies


- [ ] **Naloxone kits:**
  Find a resource providing naloxone

- [ ] **Safer injecting, safer smoking and safer sex supplies:**
  - ✓ Syringes and injection equipment
  - ✓ Pyrex tubes
  - ✓ Recovery bin
  - ✓ Condoms

***Document inspired by the CHUM Addiction Medicine Department***
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APPENDIX 6

# Summary of steps in the induction of extended-release buprenorphine (Sublocade®)

## BEFORE START OF TREATMENT

- [ ] Check for contraindications and drug interactions.
- [ ] Confirm the treatment plan.
- [ ] Ensure that the medication is available at the person's pharmacy.
- [ ] Take the training on how to administer Sublocade®.
- [ ] Send a copy of your certification along with the prescription to the person's community pharmacy.
- [ ] Complete the RAMQ request.
- [ ] Obtain the person's free and informed consent (present the tool "Making an Informed Choice of OAT Medication").

## THE DAY OF THE INJECTION

### Before administering the medication

- [ ] Take the medication out and apply ice to the injection site for 15 minutes before the injection.
- [ ] Open the package in front of the person. If the person has brought their own medication, ensure that the storage instructions have been followed.
- [ ] Change the 19G needle for a 20G needle if that seems clinically preferable.
- [ ] Ask the person which position they would like to take.
- [ ] Inform the person that the injection must be administered slowly and is a bit painful.

### Après l'administration du médicament

- [ ] Explain to the person that the depot should not be played with, and that it will disappear about 2 months after the injection.
- [ ] Remind the person of the side effects to watch for, including injection site complications and withdrawal symptoms.
- [ ] Agree on follow-up arrangements with the person, including a call within the first few days of the injection.
- [ ] Plan the date of the next injection and inform the pharmacy.



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# APPENDIX 7

## Summary of the report entitled *Innocuité de la buprénorphine à libération prolongée pour injection sous-cutanée durant la grossesse et l'allaitement en opioid agonist therapy dans le cadre du traitement des troubles liés à l'utilisation des opioïdes* (in French only), by the Centre IMAGe (Info-Médicaments en Allaitement et Grossesse), 2022.

*Full report available upon request.*

## DATA SUMMARY AND EVALUATION

There are virtually no published sources on clinical experience with the use of the extended-release subcutaneous injectable formulation (Sublocade®) during pregnancy and breastfeeding. Most learned societies and expert groups have not yet taken positions on the use of this product in pregnant or breastfeeding people.

The Canadian product monograph does not provide explicit contraindications on the use of Sublocade® in this group. It asks clinicians and their patients to balance the risks (excipients and adjustment problems due to relatively inflexible dosing) against the expected benefits (stability of the OAT).

Here follows a summary of these issues, as well as our analysis of the expected implications for pregnancy and breastfeeding.

## PREGNANCY

### Excipients

- The Sublocade® subcutaneous sustained-release formulation contains a novel medication release system (Atrigel) that includes the solvent n-methyl-2-pyrrolidone (NMP). This solvent is quickly released after subcutaneous administration and is completely eliminated within a few days.
- The developmental toxicity of this solvent (e.g., embryo or fetal loss, skeletal abnormalities) has received considerable attention in the scientific literature. The margins of safety in published animal studies are sometimes relatively narrow (1 to 3 times the human dose, based on body surface area) compared to the amounts contained in Sublocade®. In these studies, NMP was administered repeatedly by a dermal, inhalation, oral, or intraperitoneal route, and often resulted in maternal toxicity.
- In animal studies carried out by the manufacturer in which the complete Sublocade® product was administered subcutaneously (buprenorphine + Atrigel), the no observed adverse effect levels (NOAELs) were in the range of 2 to 15 times the maximum human buprenorphine doses (based on AUC), depending on the animal species. For NMP on its own, the NOAELs were 15 times the exposure to the maximum monthly dose of NMP provided by Sublocade® (based on AUC).
- The differences between the calculated safety factors may be due to the different routes of administration used, the type of exposure (chronic or acute), the species tested, and the dose equivalencies chosen, among other things.

### Release profile of buprenorphine: pharmacokinetics and adjustment difficulties

- In the first few days following administration of Sublocade®, buprenorphine plasma concentrations peak and then slowly decline until the next dose. A steady state is reached after several months.
- At steady-state, the buprenorphine exposure achieved with Sublocade® is at least equivalent to or higher than exposures achieved with the maximum doses of the sublingual formulations:
  - The mean plasma buprenorphine concentrations achieved at steady-state with 100 mg of Sublocade® are similar to those for a daily 24 mg dose of sublingual Subutex®.
  - The mean plasma buprenorphine concentrations achieved at steady-state with 300 mg of Sublocade® are two to three times higher than those for a daily 24 mg dose of sublingual Subutex®.



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- There is no information on pregnancy's effect on the pharmacokinetics of buprenorphine released from the extended-release subcutaneous formulation. It is possible that the absorption kinetics are altered, and it is likely that buprenorphine clearance is increased. The resulting physiological changes are difficult to predict and could vary between trimesters and between people. The pharmacokinetic changes associated with pregnancy are expected to be reversed within the first few weeks postpartum.
- In theory, the sustained release profile of this formulation could promote efficacy during pregnancy, and possibly improve safety for the fetus, given the stability of the buprenorphine plasma concentrations, with peak and trough episodes avoided. However, to date, there is no evidence that the release profile of these formulations would result in significant differences in fetal or obstetrical complications compared to sublingual or buccal formulations of buprenorphine.
- This formulation, which releases a partial mu-receptor agonist over a prolonged period of time, may represent an additional challenge for intra- and postpartum pain management.
- As with any opioid, exposure to buprenorphine in the third trimester and until delivery is associated with a risk of neonatal opioid withdrawal syndrome. To date, there are no data comparing the time of onset, frequency, and severity of the withdrawal syndrome between different formulations of buprenorphine (short-acting or extended release). The impact of the very high exposure to buprenorphine associated with 300 mg of Sublocade® is difficult to predict, as the severity of neonatal opioid withdrawal syndrome does not correlate solely with the maternal dose.

## Implications for pregnancy

- Given the margin of safety in animal studies with the NMP excipient, **it is reasonable to reassure a person treated in the first trimester before they know they are pregnant**. The usual obstetrical follow-up is recommended.
- Nevertheless, given this relatively small margin, **it is preferable to avoid initiating treatment during pregnancy**, and particularly during the first trimester, until more information is available on the safety of this formulation during pregnancy.
- However, **if the formulation has concrete benefits for the stability of the patient's condition, it is still reasonable to consider initiating or continuing treatment**, given the significant benefits of a stable condition for the person themselves, for their pregnancy and for their fetus. In this case, the issues raised by the animal studies of the NMP solvent should be explained to the patient and family, as well as the limitations of these data and the difficulties inherent in extrapolating them to humans. The usual obstetrical follow-up is recommended. A fetal growth assessment in the 3rd trimester is suggested.
- There are significant constraints to using Sublocade® with pregnant people: the inflexible doses of this formulation and the inability to easily adjust doses, coupled with the unpredictable but potentially significant pharmacokinetic changes expected during pregnancy and postpartum. **Sublingual or buccal formulations, which are more easily adjustable, should be preferred during pregnancy**.
- However, if Sublocade® is thought to present practical advantages for stabilizing the person's condition and treatment is started or continued during pregnancy, **patients should be closely monitored: a steady state may be difficult to achieve** due to the expected physiological changes. Supplemental doses of sublingual or oral buprenorphine may be required.
- **Regular reassessments throughout the pregnancy and during the first few weeks after delivery** are necessary to detect any changes in the stability of the parent's condition and to avoid the risk of opioid abuse, cravings, withdrawal signs and symptoms, or signs of toxicity.
- In the absence of specific data for this formulation, the obstetrical and fetal monitoring and intra- and postpartum pain management approaches used should be the same as those used with people treated with sublingual or oral buprenorphine. A fetal growth assessment in the 3rd trimester is suggested.
- In the absence of specific data for this formulation, neonatal monitoring of infants exposed *in utero* to Sublocade® is essential and should be the same as that recommended for buprenorphine by the sublingual or buccal route. It is nevertheless important to consider the fact that an infant whose parent receives Sublocade® (particularly if received at the dosage level of 300 mg/month) has been exposed to high doses of buprenorphine *in utero*.



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## BREASTFEEDING

### Excipients

- The transfer of the solvent NMP present in Sublocade® into breast milk has not been assessed, but it is likely to occur, given NMP's physical and chemical characteristics.
- The safety of NMP has not been assessed in very young children, and we cannot be sure of the impact that this exposure will have on an infant. Nevertheless, one of the considerations in the decision to use this formulation in a breastfeeding person is the safety margin of toxicity in animal studies and the fact that this exposure is intermittent, not continuous, which limits the risk of accumulation.

### Release profile of buprenorphine: pharmacokinetics and adjustment difficulties

- With sublingual administration of Subutex® at doses usually not exceeding 6 mg per day, buprenorphine and its metabolite are found in small concentrations in breast milk, and their low oral bioavailability limits exposure for the infant. Plasma concentrations have been measured in infants, especially those infants whose parents were receiving high doses (16 mg and more per day), and they were often low, but sometimes within the therapeutic range. Signs of impregnation and toxicity were recently reported in a two-week-old breast-fed infant whose parent was receiving 16 mg daily. However, most of the breastfed infants described in the literature did not develop complications.
- Limited data indicate that lactated concentrations of buprenorphine correlate with parental plasma concentrations.
- For Sublocade®, plasma concentrations of buprenorphine are elevated at steady state, in particular when a dosage of 300 mg per month is used (see the Pregnancy section). Exposure peaks in the first few days following administration and then declines slowly over a month. The infant whose parent receives Sublocade® is therefore exposed to higher concentrations than those documented to date in the scientific literature. With 300 mg of Sublocade®, the expected exposure could be three times higher than the highest doses evaluated to date in breastfeeding. Exposure is highest in the first few days following administration.
- The sustained release profile avoiding peaks and valleys does not present an advantage in breastfeeding.

### Implications for breastfeeding

- The high plasma concentrations observed with Sublocade® formulations (particularly when the 300 mg per month dosage is used) will lead to higher exposures for infants than previously documented.
- The decision on whether or not to initiate breastfeeding, or to continue treatment when breastfeeding has begun, should be evaluated in light of this **significant exposure. This exposure constitutes a risk of adverse effects and warrants close and regular monitoring of potential impacts on the breastfed child (sedation, lethargy, respiratory depression, constipation, nausea).** The risks are even greater in the presence of other risk factors, such as if the parent is being treated with other sedative drugs or exposed to other psychoactive substances, if the breastfed child is young (less than two months old) or if they are exclusively breastfed. This monitoring is particularly important if the transition to Sublocade® is carried out while the parent is breastfeeding.
- Nothing is known for certain about the impact of exposure to NMP through breast milk following administration. The parents need to be informed about the lack of data concerning the effects of this product on a young child. Exposure is intermittent only, and it is likely that the amounts found in the parent's milk are below the toxic thresholds set out in the scientific literature.
- Plasma concentrations are highest in the first few days after subcutaneous administration of extended-release formulations. **Increased monitoring is indicated for potential adverse effects in both the parent and child, particularly during the first one or two weeks following subcutaneous injection, to take into account possible accumulation.**
- Regular monitoring of the infant's health should be organized, going **beyond the immediate neonatal monitoring period** (monitoring of alertness, hydration status, growth, development).
- Discontinuation of breastfeeding should be undertaken gradually to avoid signs of opioid withdrawal in the child.
- Lastly, if the buprenorphine doses were increased at the end of pregnancy (by additional sublingual or buccal doses or by increasing the dosage of Sublocade®), they should be re-evaluated regularly during the postpartum period to avoid toxicity for both the parent and the breastfed child.



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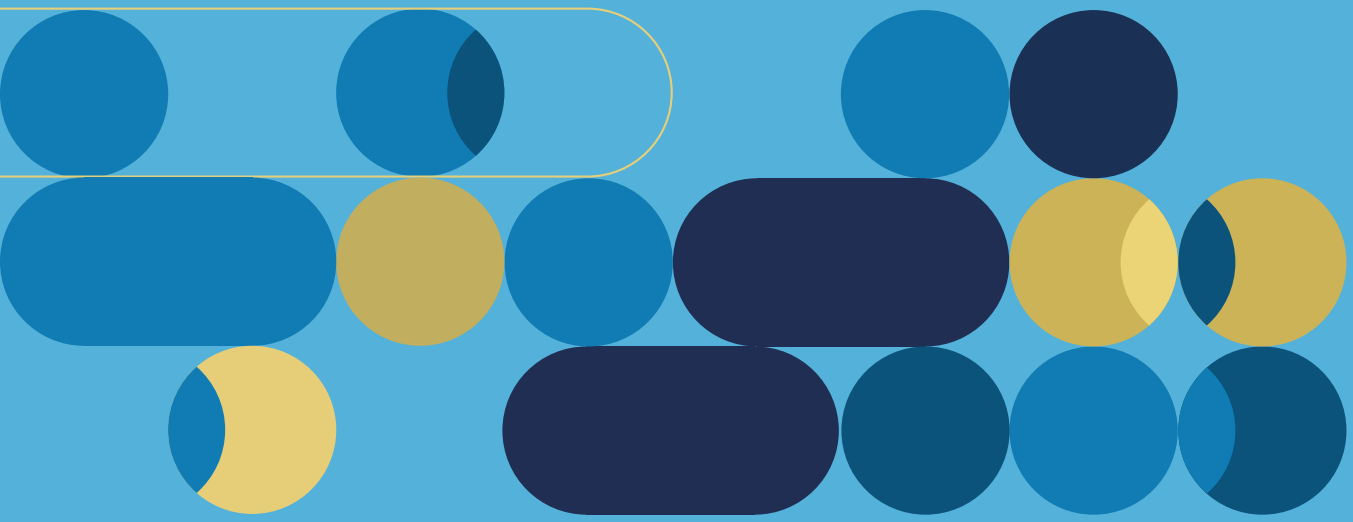

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