A guide to the use of depot buprenorphine

INTRODUCTION

Subcutaneous 28-day depot buprenorphine injection (hereafter BUP-XR, trade name Sublocade) is an alternative mode of delivering buprenorphine that can be a good choice for people who have difficulty attending a pharmacy regularly, use high-potency opioids such as fentanyl, or experience withdrawal symptoms or side effects with sublingual buprenorphine/naloxone (BUP-SL). BUP-XR is on the Ontario Drug Benefit (ODB) formulary as a Limited Use drug (LU 577), as well as most other provincial formularies, the NIHB program, and most private plans. In this document, we summarize the evidence for BUP-XR's effectiveness and adverse effects and present a practical guide for its use based on our collective initial experience with this product and current research. Given the relative novelty of depot products, much of the current research is industry sponsored, and information here is subject to change as new research becomes available. For a full discussion of depot buprenorphine's pharmacology and side effects, please refer to the product monograph (1).

EVIDENCE OF EFFECTIVENESS

BUP-XR vs. placebo

An industry-sponsored phase three randomized trial showed that BUP-XR was **significantly more effective than placebo at reducing opioid use** (2). At week 24, 41% of the 100mg group and 43% of the 300mg group had urine samples negative for illicit opioids, compared to 5% for the placebo group ($p < 0.0001$). High-dose BUP-XR may be particularly effective for people who inject opioids. A post-hoc analysis (3) of an industry-sponsored controlled trial (4) showed that people injecting opioids receiving 300mg monthly had more days of continuous abstinence than those receiving 100 mg monthly. This difference was not found for subjects who were using oral opioids. The industry-sponsored study (4) found that participants on 300mg and 100mg had improved satisfaction scores, higher percentage of employment, and fewer hospital days per person-year compared to placebo. Additionally, in a rollover open-label phase three multicentered study (5) of flexible 300mg and 100mg BUP-XR dosing, 61.5% of the 257 previously placebo-controlled and 75.8% of 412 de novo participants were abstinent, with retention rates of 50.6% and 50.5% for the rollover and de novo participants respectively.

BUP-XR vs. BUP-SL vs. methadone

A 24-week placebo-controlled trial compared BUP-SL to a different depot buprenorphine injection product not currently available in Canada (6). The proportion of opioid-negative urine samples was higher in the depot buprenorphine group (35.1%) than in the BUP-SL group (28.4%, $p < 0.001$), and treatment completion rates in the two groups were similar. The results of this trial do not necessarily apply to the depot product approved in Canada.

A six-month observational study conducted in Canada compared patient characteristics and overdose (OD) events on depot buprenorphine, BUP-SL, and methadone (7). Those on depot buprenorphine had the highest adherence and lowest nonfatal OD events, but authors recognize a patient selection bias. Those on methadone (at doses of 15–210mg) had the highest rate of OD events, but also the highest rates of injection drug use, HIV, hepatitis C, and mental health disorders. Furthermore, while BUP-XR had the greatest adherence, methadone demonstrated the highest retention at six months.

ABOUT BUP-XR

Patient-centred outcomes

In a twelve-month follow-up on the phase three industry-sponsored randomized controlled trial (8), participants reported high rates of satisfaction with BUP-XR treatment and improvements in most life domains. Qualitative studies (9, 10) have found that people with opioid use disorder think that depot medications would decrease stigma, discrimination, and embarrassment, as they would not have to take medication in front of other customers at the pharmacy. They also thought it would improve their quality of life, allowing them to live their daily lives more freely, and they would no longer have to have contact with other people who use drugs. On the other hand, some stated that they would miss the daily routine of pharmacy attendance, and others felt they would be less likely to receive counselling and psychosocial support. In an open-label randomized clinical trial in Australia of 119 participants receiving either buprenorphine film daily or an injectable weekly or monthly (11), patient satisfaction was significantly higher with the buprenorphine injectable formulation.

Pharmacokinetics and protective factors

BUP-XR produces a steady serum level with no daily variation and bioavailability six to eight times higher compared with BUP-SL. The product monograph (1) states that the average plasma concentrations of BUP-XR at steady state are 3.21ng/mL for the 100mg dose and 6.54ng/mL for the 300mg dose. In an extensive review of brain imaging studies on buprenorphine receptor occupancy in volunteers who use heroin, the authors conclude that a buprenorphine serum level of around 1ng/mL (achieved with a dose of less than 16mg BUP-SL per day) is associated with 50% mu receptor occupancy, and will relieve withdrawal symptoms in most patients (12). A concentration of 2–3ng/mL or above (closer to 24mg) is associated with 70–80% receptor occupancy and will attenuate the reinforcing and euphoric effect of typical doses of commonly used opioids (13, 14). These studies suggest that BUP-XR will block the euphoric effects of opioids more effectively than BUP-SL.

There is experimental evidence that higher buprenorphine levels may protect against fentanyl-induced respiratory depression. In an industry-sponsored study of eight subjects with high opioid tolerance (15), all subjects were given placebo, followed by intravenous buprenorphine infusions titrated to achieve serum levels of 1, 2, or 5ng/mL. They were then given escalating doses of intravenous fentanyl up to 0.7mg/kg. Seven of the eight subjects on placebo had apnea, and three had both apnea and low oxygen saturation. The 1ng/mL group had declines in respiratory volume after the fentanyl challenge, but the 2ng/mL and 5ng/mL groups did not. The depot formulation may provide better protection against fentanyl-induced respiratory depression than the sublingual form; at steady state, the minimum serum level conferred by 100mg BUP-XR is greater than 2ng/mL, while even at 24mg the sublingual formulation provides a plasma concentration of less than 2ng/mL (16).

ADVERSE EFFECTS, PRECAUTIONS, AND CONTRAINDICATIONS

Adverse effects

In the phase three trial (2), between 5% and 10% of the subjects in the BUP-XR groups experienced headache, nausea, constipation, and/or pruritis at the injection site. Overall, these side effects were mild and comparable to those documented for BUP-SL. These were also the most commonly noted adverse events in a randomized controlled trial (6) in which adverse events occurred in 22.3% of the BUP-SL group and 18.8% of the BUP-XR group. In an open-label study in which participants received up to twelve monthly injections (5), treatment emergent adverse events were again similar, mostly mild to moderate

in severity, with a lower incidence in the second six months of treatment compared to the first six months. Injection site reactions were reported in 16.3% of de novo and 8.2% of rollover participants; the most commonly reported injection site reactions were pain (6.9%), erythema (4.0%), and pruritis (3.9%). Mean injection site pain scores decreased with each injection.

The product monograph lists other common reactions, including fatigue, insomnia, and elevated hepatic enzymes, and less common reactions, including blurred vision, dizziness, postural syncope, and euphoric mood (1).

Precautions and contraindications[1]

CNS and respiratory: BUP-XR can be presumed to be safe in patients who show no sedation or respiratory impairment with BUP-SL at a dose of 8mg or above. However, serum levels of buprenorphine slowly rise with BUP-XR and at steady state are significantly higher than with BUP-SL; it is possible, therefore, that **patients who are on benzodiazepines or other sedating drugs or who have respiratory impairment could experience sedation and respiratory depression when starting depot buprenorphine**. These patients should be advised to self-monitor for sedation for the first few days after a BUP-XR injection, particularly when driving.

QT prolongation: Clinical studies of BUP-SL have not found cases of QT interval increase above 500msec (17, 18) or increased reporting of torsades de pointes in an adverse drug reaction database (19). However, the product monograph notes cases of increased QT interval, and one case of QT interval beyond 500msec (1). Because serum levels of buprenorphine are higher with BUP-XR than with BUP-SL, the clinician might consider ordering an ECG before and after initiation if the patient has other risk factors for QT prolongation.

Hepatic: There have been case reports of severe liver disease and death in patients taking buprenorphine; however, most cases had other factors that could have contributed or caused the liver disease, such as hepatitis C. Although BUP-SL was not associated with elevations in hepatic transaminases in randomized trials and cohort studies (20, 21), 7% of subjects in phase three trials receiving BUP-XR 300mg maintenance dose had elevated transaminases, compared to 4.5% in the 100mg group and 3% in the placebo group (2). BUP-XR was discontinued due to possible hepatic injury in 1.5% of subjects in the 300mg group, whereas it was not discontinued in either of the other groups. The product monograph states that hepatic impairment slows the metabolism of buprenorphine, causing significant elevations in serum buprenorphine levels (1). For this reason, the monograph recommends that caution be used when administering BUP-XR to patients with moderate hepatic impairment, and its use is contraindicated in patients with severe hepatic impairment. Moderate hepatic impairment should be assumed in patients with cirrhosis who have laboratory signs of impaired liver function: low albumin, high INR, low platelets, or high bilirubin. Severe hepatic impairment should be assumed in patients with overt signs of cirrhosis (firm liver edge, spider nevi, jaundice) or in patients who have been in liver failure (i.e., encephalopathy, ascites, jaundice). BUP-XR should not be delayed merely because of elevated transaminases in the absence of clinical or laboratory evidence of hepatic dysfunction.

Pregnancy: While BUP-SL is safe in pregnancy, BUP-XR contains an excipient that has been shown to be fetotoxic in animal studies, although as yet there have been no reports of fetotoxicity among humans. Patients who could become pregnant should be told about this risk and advised to use effective contraception if sexually active. Patients who indicate that they might be pregnant should be given a urine b-hCG test before receiving their injection.

[1] See product monograph for full list.

One case study (22) reports two persons being exposed to BUP-XR in pregnancy; one received eight injections total with the last injection received at seventeen weeks gestation, and the other received six injections total with the last injection received at the time of the last menstrual period. No form of buprenorphine was continued for the duration of the pregnancies; no birth anomalies were identified. In both cases, urine drug screens were negative throughout the pregnancy, with the exception of buprenorphine and norbuprenorphine.

At this time and until more patient data is available, if a patient learns they are pregnant while taking BUP-XR, the potential risks should be reviewed and they should be encouraged to return to BUP-SL for the duration of their pregnancy.

All other contraindications to the use of buprenorphine products apply to this formulation; see the product monograph for a full list (1).

GUIDE FOR PRESCRIBING AND ADMINISTERING DEPOT BUPRENORPHINE

Certification

Prescribers must be certified to prescribe depot buprenorphine. Some pharmacies may request documentation of certification. Injectors (e.g., RN, RPN, RPh) can also complete the certification course and can consider receiving practical training prior to injecting (though this is not required).

Indications

The product monograph recommends that BUP-XR be started after the patient has been on a stable dose of BUP-SL of 8–24mg for at least seven days. However, earlier administration appears to be safe (see below).

BUP-XR may be of particular benefit for patients with the following characteristics:

- Find frequent attendance at a pharmacy difficult, because of distance, cost, work, housing, family obligations, etc.
- Frequently miss their BUP-SL dose, leading to other opioid use.
- Have persistent cravings and withdrawal symptoms while on a maximum dose of BUP-SL.
- Have persistent difficulty reducing use of illicit opioids while on BUP-SL.
- Are at high risk for treatment discontinuation or relapse (e.g., about to be released from prison).
- Have difficulty tolerating sublingual formulations (e.g., bad taste, long time to dissolve).
- Are unable to safely store medication at home.
- Would derive psychological benefit from discontinuing a daily drug regimen.
- Want to taper and discontinue BUP-SL (theoretically easier with BUP-XR because of its slower and smoother decline in serum levels).

Patients who use opioids such as fentanyl or heroin from the unregulated supply are often good candidates for BUP-XR, because they tend to have more difficulty with daily attendance at a pharmacy. Also, the depot product generates a much higher and more constant serum buprenorphine level than the sublingual product, and thus may be more effective at relieving withdrawal symptoms and retaining patients in treatment. Further research is required on the comparative effectiveness of these two buprenorphine products.

Patients should be switched from BUP-XR to another form of OAT if they have intolerable side effects, if they have persistent severe cravings and withdrawal symptoms, or if their opioid use does not decline according to their goals.

Rapid initiation

There is a growing body of evidence indicating that BUP-XR is safe even if it is administered before seven days of stabilization on BUP-SL. In a case series (23), five participants received BUP-XR on days two and three of BUP-SL with no precipitated withdrawal (PW) or adverse events after injection. In another case series (24), ten individuals received BUP-XR day seven of BUP-SL with no reported PW, though nine required supplemental BUP-SL for withdrawal and cravings. In an open-label trial (25), five participants were provided BUP-XR within 185min of BUP-SL initiation, with none experiencing protracted PW or elevation in sedation score. Finally, in an open-label phase four rapid initiation study (26), BUP-XR was provided one hour after a single 4mg dose of BUP-SL to 24 participants; two participants experienced PW, but all withdrawal symptoms and opioid craving scores decreased within twelve hours.

Dosing

The BUP-XR product currently available in Canada is a subcutaneous injection (100mg or 300mg) that is administered by a health care professional every 28 days. Dose may be administered up to two days early; that is, a minimum of 26 days is required between consecutive doses. Doses may be administered up to fourteen days late without reinitiating BUP-SL. Doses should be administered as follows:

- Two loading doses of 300mg 28 days apart.
- A maintenance dose of 100mg every 28 days.

For patients previously on 8–18mg BUP-SL, consider 100mg BUP-XL as the second loading dose, unless instability was noted following the first 300mg injection. In general, 100mg doses are associated with fewer side effects and greater treatment retention (1).

For patients who experience a return of withdrawal symptoms before their next injection is due, the following strategies can be considered:

- Provide supplemental doses of BUP-SL (2–8mg/day).
- Early (off-label) provision of the next injection (e.g., 21-day interval).

For patients who continue to use opioids due to withdrawal, pain, or cravings, the following strategies can be considered:

- Provide supplemental doses of BUP-SL (e.g., 2–4mg/day).
- Conversion to 300mg BUP-XR q 28 days as a maintenance dose.
- Addition of daily dispensed slow-release oral morphine or hydromorphone.
- Conversion to another form of opioid agonist therapy (e.g., methadone +/- slow-release oral morphine).

Injection technique

BUP-XR comes as a pre-filled syringe with a #19-gauge needle supplied (do not change the needle). **The injection must be given subcutaneously**. When the contents of the pre-filled syringe are injected, BUP-XR forms a solid mass that can occlude blood vessels, causing clots or emboli. Intravenous and intramuscular injection must be avoided.

Use the following injection technique:

- See the product monograph for appropriate injection sites below the rib cage and above the pelvic brim.
- Avoid injecting into scars, including stretch marks.
- The patient should be in a supine position if possible.
- Tell the patient to expect a burning sensation at the injection site with injection.
- Consider icing the area before and after the injection to reduce pain.
- Use a pinch-and-lift technique to avoid injecting intramuscularly.
- Inject on a 45° angle into the abdomen for subcutaneous depot formation.
- The medication is very viscous and requires steady pressure. Speed of injection is per patient preference.
- Advise the patient that they may have a palpable lump for several weeks to months, and not to rub/manipulate the area of the depot.
- Rotate injection sites (previous injection sites may still be palpable for months after the injection).

Storage

BUP-XR must be maintained in a cold chain, between 2–8°C, for storage and transportation, and must be delivered directly from the pharmacy to the clinic with no patient handling. It should be not be removed from the refrigerator until it has been confirmed that the patient will be receiving the injection, and it should be allowed to come to room temperature for at least fifteen minutes prior to injection. Once it is out of the refrigerator, it can be stored in the original packing at room temperature for seven days maximum (discard if left at room temperature any longer). If a dose has been removed from the refrigerator, not used, and then returned to the refrigerator, it can be out of the refrigerator for seven days minus the time it was originally out of the cold chain (be sure to indicate time the time out of the cold chain on the box).

Cost

BUP-XR costs $550 per dose (for 300mg or 100mg dose) plus dispensing fees. It is covered by most private insurance plans, NIHB, and ODB with LU code 577. As many pharmacies do not regularly stock depot buprenorphine, notify the pharmacy/send a prescription prior to the planned injection date to ensure that the medication is available when needed.

CLINICAL Q&A

When should my patient take the last dose of BUP-SL before their first injection?

As buprenorphine concentrations will begin to rise immediately after the injection, patients should ideally take their last dose of BUP-SL the day before their first injection. For patients on split dosing, the morning dose can be taken on the day of the injection, to prevent withdrawal symptoms or pain exacerbation. If a full once-daily dose of BUP-SL was taken the day of the injection, it is likely still safe to proceed, as peak buprenorphine concentration will not be reached until 24 hours after the injection. Be mindful of the patient's high total daily dose and advise the patient to monitor for euphoric effects or sedation, which will likely begin few hours after the injection and may last for several days.

What about precipitated withdrawal (PW)?

If following the product monograph, clients will have been on a dose of BUP-SL for at least seven days before they are transitioned to BUP-XL. As buprenorphine is already occupying the opioid receptors with BUP-SL, there is no risk of PW when transitioning to BUP-XL, another buprenorphine product.

With a more rapid initiation of BUP-XR, risk of PW with BUP-XR can be avoided by providing BUP-SL doses and monitoring for at least one hour after administration. If PW then occurs, do not initiate BUP-XR, and manage the PW by either stopping BUP-SL initiation and providing symptomatic support, stopping BUP-SL initiation and providing opioids, or continuing to provide BUP-SL in high or "macro" doses until withdrawal symptoms resolve. In studies of rapid BUP-XR initiation, PW was not common, only occurred when BUP-XR was provided on the same day (within four hours) of BUP-SL initiation, occurred within two hours of the injection, was managed symptomatically, and dissipated or resolved within twelve hours of the initiation (25, 26).

After the first dose of 300mg, my patient experienced moderate to severe withdrawal symptoms around day 21. How should this be managed?

The minimum buprenorphine concentration at day 28 after the initial 300mg injection can fall below 2ng/mL, putting the patient at risk of withdrawal and cravings. Consider providing BUP-SL (e.g., 2–4mg) once daily to control symptoms until the next injection can be provided, which can be as early as 26 days after the previous injection. You may also choose to provide the second 300mg loading dose to the patient earlier than the 26 days, explaining that this is off-label. Tell your patient that early withdrawal or cravings are likely to occur only after the first injection, as levels do not fall this low again after the second loading dose of 300mg is provided.

My patient continues to experience withdrawal symptoms with the 100mg maintenance doses. How do I decide between offering BUP-SL and increasing the maintenance dose to 300mg?

If a patient is experiencing any withdrawal, cravings, or pain while on the 100mg maintenance dose, it is worth considering an increase to the 300mg maintenance dose. If the patient's symptoms are suspected to be short-term due to situational circumstances (e.g., dental work) and likely to resolve, BUP-SL can be provided for symptom management until the next injection can be provided. If the symptoms recur, the patient likely needs a maintenance dose of 300mg.

My patient will be travelling and unavailable between days 26 and 42 after their last injection. What do I do?

It is best to plan dose adjustments well ahead of the travel days. For example, if a stable patient will be away during the 26- to 42-day window of their fourth injection, consider providing the third injection later than 42 days, to avoid travel days with their fourth injection. If a patient is not stable, or reports withdrawal or cravings return any time between 26 and 42 days in the past, do not delay injections. Instead, provide injections earlier than 26 days if required to avoid scheduled doses during travel, and consider providing BUP-SL carry doses to take with them.

My patient wants to transition back to BUP-SL. How do I go about this?

To avoid withdrawal symptoms, consider starting the patient on 4mg BUP-SL when their next injection would have been due and titrate weekly based on an assessment of their withdrawal symptoms. The maintenance BUP-SL dose will not necessarily be the same as the dose they were on prior to BUP-XR.

What if my patient wants to get high sometimes?

It is best to discuss your patient's goals when considering BUP-XR. For some people, BUP-XR helps to reduce opioid use because the high is effectively blocked by stable serum buprenorphine levels, making use redundant. However, BUP-XR can still be beneficial for people who do not wish to be abstinent. People on BUP-XR usually use opioids less often and in lower amounts because they no longer need to use to relieve withdrawal symptoms and cravings; their use becomes a choice rather than a biological imperative. In addition, if they do use opioids, the buprenorphine on board will provide substantial protection against respiratory depression and overdose. With these protective factors in mind, if a patient still feels their BUP-XR is blocked too much of their desired opioid effect, their maintenance dose can be lowered from 300mg to 100mg, or the patient can be converted back to BUP-SL. Work with your patient to find the option that works best for their individual goals.

How do I manage missed or late doses of depot buprenorphine?

The more injections a patient has had, the closer they will be to steady state, with less fluctuation of serum levels and emergence of withdrawal symptoms in the case of a delay. Steady state for BUP-XR occurs around the fourth injection. If fewer than four injections have been given, and the patient presents more than 42 days after their last injection, a restart should be considered. A rapid BUP-XR initiation may be considered by providing 8mg or greater of BUP-SL (in 2mg increments if tolerance is uncertain) and waiting one hour. The BUP-XR dose may then be administered if the BUP-SL dose was tolerated, and precipitated withdrawal did not occur.

If the patient has already received four or more doses, their next injection can be safely given up to 56 days later (16). Beyond this, a restart should be considered, including a rapid restart as described above if appropriate.

How do I talk to my patient about discontinuation of depot buprenorphine?

Opioid agonist therapy (OAT) should be considered a long-term treatment. The rate of relapse is significant if OAT is discontinued less than a year after it is started. Many factors, including social supports and mental and physical well-being should be reviewed in discussing OAT discontinuation. Clients that are considering discontinuation of BUP-XR should be encouraged to receive at least four injections prior. This will ensure that their buprenorphine level is at a steady state, and it will delay the emergence of withdrawal symptoms upon discontinuation. With a half-life of 43 to 60 days, clients that have received at least four injections of 300mg could experience withdrawal symptoms three to nine months after their last 300mg injection, or two to six months after their last 100mg injection (16). In a study tracking buprenorphine levels 22 to 37 months after last injection, 55–63% of people had detectable urine buprenorphine during this time. However, plasma buprenorphine concentrations may be low during this time, as detection in urine is affected by hydration status and can vary over time (1). Clinical effectiveness cannot be guaranteed with treatment discontinuation. If BUP-XR is discontinued, regular ongoing patient check-ins can prevent, monitor for, and treat withdrawal and return to use. The prescriber might consider prescribing 2mg doses of BUP-SL for the patient to have on hand should withdrawal or cravings return after BUP-XR discontinuation.

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