HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SUBLOCADE® safely and effectively. See full prescribing information for SUBLOCADE.

SUBLOCADE (buprenorphine extended-release) injection, for subcutaneous use, CIII

Initial U.S. Approval: 2002

WARNING: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION; SUBLOCADE RISK EVALUATION AND MITIGATION STRATEGY

See full prescribing information for complete boxed warning.

- **Serious harm or death could result if administered intravenously. (5.1)**
- **SUBLOCADE is only available through a restricted program called the SUBLOCADE REMS Program. Healthcare settings and pharmacies that order and dispense SUBLOCADE must be certified in this program and comply with the REMS requirements. (5.2)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.2, 2.3, 2.6)	03/2021
Warnings and Precautions (5.1, 5.4, 5.5, 5.6)	03/2021
Dosage and Administration (2.4)	05/2021
Dosage and Administration (2.5)	06/2021

----------INDICATIONS AND USAGE----------

SUBLOCADE contains buprenorphine, a partial opioid agonist, and is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days. (1)

SUBLOCADE should be used as part of a complete treatment program that includes counseling and psychosocial support. (1)

----------DOSAGE AND ADMINISTRATION----------

Prescription use of this product is limited under the Drug Addiction Treatment Act. (2.1)

SUBLOCADE should only be prepared and administered by a healthcare provider. (2.2)

SUBLOCADE is administered monthly only by subcutaneous injection in the abdominal region. (2.2)

Strongly consider prescribing naloxone at the time SUBLOCADE is initiated or renewed because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose. (2.3*)*

The recommended dose of SUBLOCADE is two monthly initial doses of 300 mg followed by 100 mg monthly maintenance doses. (2.4)

Increasing the maintenance dose to 300 mg monthly may be considered for patients in which the benefits outweigh the risks. (2.4)

Examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot. (2.5)

See Full Prescribing Information for administration instructions. (2.6)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 mg/0.5 mL and 300 mg/1.5 mL provided in a prefilled syringe with a 19 Gauge 5/8-inch needle. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to buprenorphine or any other ingredients in SUBLOCADE. (4)

----------WARNINGS AND PRECAUTIONS----------

Addiction, Abuse, and Misuse: Buprenorphine can be abused in a manner similar to other opioids. Monitor patients for conditions indicative of diversion or progression of opioid dependence and addictive behaviors. (5.3)

Respiratory Depression: Life-threatening respiratory depression and death have occurred in association with buprenorphine. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with SUBLOCADE. (5.4, 5.5)

Risk of Serious Injection Site Reactions: Likelihood may be increased with inadvertent intramuscular or intradermal administration. Evaluate and treat as appropriate. (5.6).

Neonatal Opioid Withdrawal Syndrome: Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy. (5.7)

Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)

Risk of Opioid Withdrawal With Abrupt Discontinuation: If treatment with SUBLOCADE is discontinued, monitor patients for several months for withdrawal and treat appropriately. (5.9)

Risk of Hepatitis, Hepatic Events: Monitor liver function tests prior to and during treatment. (5.10)

Risk of Withdrawal in Patients Dependent on Full Agonist Opioids: Verify that patient is clinically stable on transmucosal buprenorphine before injecting SUBLOCADE. (5.12)

Treatment of Emergent Acute Pain: Treat pain with a non-opioid analgesic whenever possible. If opioid therapy is required, monitor patients closely because higher doses may be required for analgesic effect. (5.13)

----------ADVERSE REACTIONS----------

Adverse reactions commonly associated with SUBLOCADE (in ≥5% of subjects) were constipation, headache, nausea, injection site pruritus, vomiting, increased hepatic enzymes, fatigue, and injection site pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Indivior Inc. at 1-877-782-6966 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

CYP3A4 Inhibitors and Inducers: Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over- or under-dosing. (7)

Serotonergic Drugs: If concomitant use is warranted, monitor for serotonin syndrome, particularly during treatment initiation, and during dose adjustment of the serotonergic drug. (7)

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Buprenorphine passes into the mother's milk. (8.2)

Geriatric Patients: Monitor for sedation or respiratory depression. (8.5)

Moderate to Severe Hepatic Impairment: Not recommended. (5.15, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION; SUBLOCADE RISK EVALUATION AND MITIGATION STRATEGY

- **Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, if administered intravenously. (5.1)**
- **Because of the risk of serious harm or death that could result from intravenous self-administration, SUBLOCADE is only available through a restricted program called the SUBLOCADE REMS Program. Healthcare settings and pharmacies that order and dispense SUBLOCADE must be certified in this program and comply with the REMS requirements. (5.2)**

1 INDICATIONS AND USAGE

SUBLOCADE is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.

SUBLOCADE should be used as part of a complete treatment plan that includes counseling and psychosocial support.

2 DOSAGE AND ADMINISTRATION

2.1 Drug Addiction Treatment Act

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to healthcare providers who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

2.2 Important Dosing and Administration Information

FOR ABDOMINAL SUBCUTANEOUS INJECTION ONLY. DO NOT ADMINISTER SUBLOCADE INTRAVENOUSLY, INTRAMUSCULARLY OR INTRADERMALLY *[see Dosage and Administration (2.6), Warnings and Precautions (5.1,5.6)]*.

- Only healthcare providers should prepare and administer SUBLOCADE.
- Administer SUBLOCADE monthly with a minimum of 26 days between doses.
- Initiating treatment with SUBLOCADE as the first buprenorphine product has not been studied. Initiate SUBLOCADE treatment only following induction and dose-adjustment with a transmucosal buprenorphine-containing product *[see Dosage and Administration (2.4)]*.
- Administer each injection only using the syringe and safety needle included with the product *[see Dosage and Administration (2.6)]*.

2.3 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver. Because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose, strongly consider prescribing naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with SUBLOCADE. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose *[see Warnings and Precautions (5.4)]*.

Advise patients and caregivers that naloxone may also be administered for a known or suspected overdose with buprenorphine itself. Higher than normal doses and repeated administration of naloxone may be necessary due to the long duration of action of buprenorphine and its affinity for the mu-opioid receptor *[see Overdosage (10)]*.

Inform patients and caregivers of their options for obtaining naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Patient Counseling Information (17)]*.

2.4 Recommended Dosing

Initiation of Treatment following Induction

Patients should first undergo induction and stabilization by initiating a buprenorphine-containing product, delivering the equivalent of 8-24 mg/day of transmucosal buprenorphine for a minimum of 7 days. Dosing and induction with buprenorphine-containing products should be based on instructions in their appropriate product label. One SUBOXONE® (buprenorphine and naloxone) 8 mg/2 mg sublingual tablet provides equivalent buprenorphine exposure to one SUBUTEX® (buprenorphine HCl) 8 mg sublingual tablet or one Bunavail® (buprenorphine and naloxone) 4.2 mg/0.7 mg buccal film or one Zubsolv® (buprenorphine and naloxone) 5.7 mg/1.4 mg sublingual tablet.

The recommended dose of SUBLOCADE following induction is 300 mg monthly for the first two months followed by a maintenance dose of 100 mg monthly.

The maintenance dose may be increased to 300 mg monthly for patients who tolerate the 100 mg dose, but do not demonstrate a satisfactory clinical response, as evidenced by self-reported illicit opioid use or urine drug screens positive for illicit opioid use.

A patient who misses a dose should receive the next dose as soon as possible, with the following dose given no less than 26 days later. Occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.

For patients in established treatment of 100 mg monthly, there may be instances when allowance for a two-month dosing interval may be appropriate (e.g., extended travel); in those instances, a single 300 mg dose may be given to cover a two-month period. Thereafter, the 100 mg monthly regimen would resume. Patients should be cautioned that the peak plasma level after injection of a 300 mg dose will be higher than their usual monthly dose and that they may experience sedation or other buprenorphine-related effects.

Transition of Patients Established on Long-term Treatment with Transmucosal Buprenorphine

Patients established on long-term treatment with transmucosal buprenorphine (8-24 mg/day) and

whose disease symptoms are controlled may be directly transitioned to SUBLOCADE [*see* Table 1]. At steady-state, buprenorphine plasma concentrations achieved with 100-mg monthly dosing are contained within the range obtained with transmucosal treatment; peak concentrations with SUBLOCADE may be lower, while average and trough concentrations may be higher. Potential differences in steady state levels need to be taken into consideration when transitioning a patient established on long term treatment with transmucosal buprenorphine to SUBLOCADE [see *Clinical Pharmacology (12.3),* Table 7].

Table 1 Transition of Patients Established on Long-term Treatment with Transmucosal Buprenorphine Whose Disease Symptoms are Controlled

Transmucosal Buprenorphine Doses	SUBLOCADE		
	Injection #1	Injection #2	Maintenance Dose
8 – 18 mg/day	300 mg	100 mg*	100 mg
20 – 24 mg/day	300 mg	300 mg	100 mg

*For patients still experiencing craving or withdrawal symptoms after the initial 300-mg dose, consider giving 300 mg as the second dose

2.5 Clinical Supervision

Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot.

Due to the chronic nature of opioid use disorder, the need for continuing medication-assisted treatment should be re-evaluated periodically. There is no maximum recommended duration of maintenance treatment. For some patients, treatment may continue indefinitely. If considering stopping treatment, the clinical status of the patient should be considered.

If SUBLOCADE is discontinued, its extended-release characteristics should be considered and the patient should be monitored for several months for signs and symptoms of withdrawal and treated appropriately. After steady-state has been achieved (4-6 months), patients discontinuing SUBLOCADE may have detectable plasma and urine levels of buprenorphine for twelve months or longer *[see Clinical Pharmacology (12.3)]*.

2.6 Instructions for Use

IMPORTANT INFORMATION:

- For abdominal subcutaneous injection only. Do not inject intravenously, intramuscularly, or intradermally *[see Warnings and Precautions (5.1, 5.6)]*.
- To be prepared and administered by a healthcare provider only.
- Please read the instructions carefully before handling the product.
- As a universal precaution, always wear gloves.
- Remove SUBLOCADE from the refrigerator prior to administration. The product requires at least 15 minutes to reach room temperature. Do not open the foil pouch until the patient has arrived for his or her injection.
- Discard SUBLOCADE if left at room temperature for longer than 7 days.

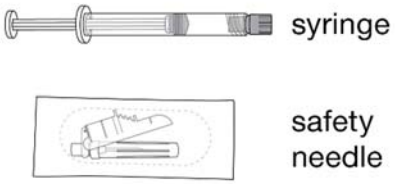
- Do not attach the needle until time of administration.

STEP 1: GETTING READY

Remove the foil pouch and safety needle from the carton. Open the pouch and remove the syringe.

Discard the oxygen absorber pack. It is not needed.

Figure 1

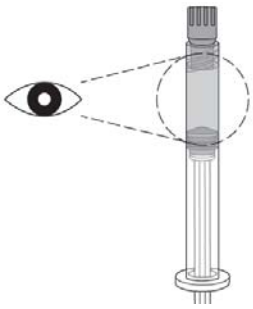


STEP 2: CHECK THE LIQUID CLARITY

Check that the medication does not contain contaminants or particles. SUBLOCADE ranges from colorless to yellow to amber. Variations of color within this range do not affect the potency of the product.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Figure 2



STEP 3: ATTACH THE SAFETY NEEDLE

Remove the cap from the syringe and the safety needle supplied in the carton from its sterile package.

Gently twist the needle clockwise until it is tight and firmly attached.

Do not remove the plastic cover from the needle.

Figure 3

STEP 4: PREPARE THE ABDOMINAL INJECTION SITE

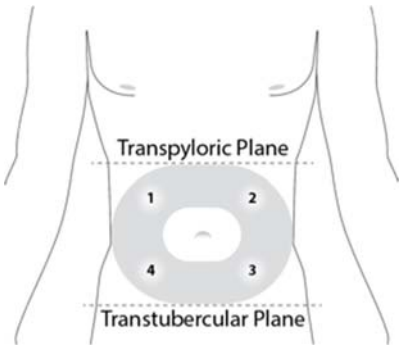
Choose an injection site on the abdomen between the transpyloric and transtubercular planes with adequate subcutaneous tissue that is free of skin conditions (e.g., nodules, lesions, excessive pigment). It is recommended that the patient is in the supine position.

Do not inject into an area where the skin is irritated, reddened, bruised, infected or scarred in any way.

Clean the injection site well with an alcohol swab.

To avoid irritation, rotate injection sites following a pattern similar to the illustration in Figure 4. Record the location of the injection to ensure that a different site is used at the time of the next injection.

Figure 4



STEP 5: REMOVE EXCESS AIR FROM SYRINGE

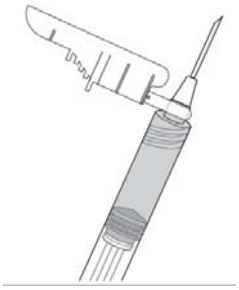
Hold the syringe upright for several seconds to allow air bubbles to rise. Due to the viscous nature of the medication, bubbles will not rise as quickly as those in an aqueous solution.

Remove needle cover and slowly depress the plunger to push out the excess air from the syringe.

- Small bubbles may remain in the medication. Large air gaps, however, can be minimized by pulling back on the plunger rod to pop air bubbles prior to expelling the air very slowly. Air should be expelled very carefully to avoid loss of medication.

If medication is seen at the needle tip, pull back slightly on the plunger to prevent medication spillage.

Figure 5



STEP 6: PINCH THE INJECTION SITE

Pinch the skin around the injection area. Be sure to pinch enough skin to accommodate the size of the needle. Lift the adipose tissue from the underlying muscle to prevent accidental intramuscular injection.

Figure 6

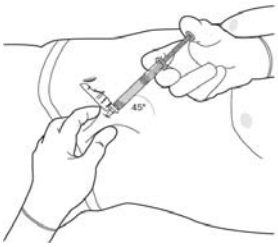
STEP 7: INJECT THE MEDICATION

SUBLOCADE is for subcutaneous injection only. Do not inject intravenously, intramuscularly, or intradermally *[see Warnings and Precautions (5.1, 5.6)]*.

Insert needle fully into the abdominal subcutaneous tissue. Actual angle of injection will depend on the amount of subcutaneous tissue.

Use a slow, steady push to inject the medication. Continue pushing until all of the medication is given.

Figure 7

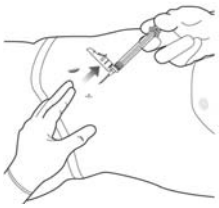


STEP 8: WITHDRAW THE NEEDLE

Withdraw the needle at the same angle used for insertion and release the pinched skin.

Do not rub the injection area after the injection. There may be a small amount of blood or fluid at the injection site; wipe with a cotton ball or gauze before applying a gauze pad or bandage using minimal pressure.

Figure 8

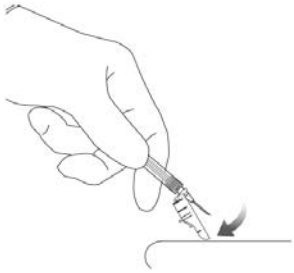


STEP 9: LOCK THE NEEDLE GUARD AND DISCARD THE SYRINGE

Lock the needle guard into place by pushing it against a hard surface such as a table (Figure 9).

Dispose of all syringe components in a secure sharps disposal container.

Figure 9



STEP 10: INSTRUCT THE PATIENT

Advise the patient that they may have a lump for several weeks that will decrease in size over time. Instruct the patient not to rub or massage the injection site and to be aware of the placement of any belts or clothing waistbands.

2.7 Limits on Distribution

SUBLOCADE is subject to a risk evaluation and mitigation strategy (REMS) program that includes, among other elements, a restricted distribution system. The purpose of the restricted distribution system is to ensure that SUBLOCADE is only administered by a health care provider *[see Warnings and Precautions (5.2)]*.

2.8 Removal of the Depot

In the event the depot must be removed, it can be surgically excised under local anesthesia within 14 days of injection. Only the most recently-injected depot can be removed.

The removed depot should be handled with adequate security, accountability, and proper disposal, per facility procedure for a Schedule III drug product and pharmaceutical biohazardous waste, and per applicable federal, state, and local regulations.

The residual plasma concentrations from previous injections will decrease gradually over subsequent

months *[see Clinical Pharmacology (12.3)]*.

Patients who have the depot removed should be monitored for signs and symptoms of withdrawal and treated appropriately *[see Warnings and Precautions (5.9)]*.

3 DOSAGE FORMS AND STRENGTHS

SUBLOCADE is available in dosage strengths of 100 mg/0.5 mL and 300 mg/1.5 mL buprenorphine. Each dose is a clear, colorless to yellow to amber solution provided in a prefilled syringe with a 19 gauge 5/8-inch needle.

4 CONTRAINDICATIONS

SUBLOCADE should not be administered to patients who have been shown to be hypersensitive to buprenorphine or any component of the ATRIGEL® delivery system *[see Warnings and Precautions (5.11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Harm or Death With Intravenous Administration

Intravenous injection presents significant risk of serious harm or death as SUBLOCADE forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, could result if administered intravenously *[see Warnings and Precautions (5.2), Drug Abuse and Dependence (9.2)]*. Do not administer intravenously, intramuscularly, or intradermally *[see Warnings and Precautions (5.6)]*.

5.2 SUBLOCADE Risk Evaluation and Mitigation Strategy (REMS) Program

SUBLOCADE is available only through a restricted program called the SUBLOCADE REMS Program because of the risk of serious harm or death that could result from intravenous self-administration. The goal of the REMS is to mitigate serious harm or death that could result from intravenous self-administration by ensuring that healthcare settings and pharmacies are certified and only dispense SUBLOCADE directly to a healthcare provider for administration by a healthcare provider.

Notable requirements of the SUBLOCADE REMS Program include the following:

- Healthcare Settings and Pharmacies that order and dispense SUBLOCADE must be certified in the SUBLOCADE REMS Program.
- Certified Healthcare Settings and Pharmacies must establish processes and procedures to verify SUBLOCADE is provided directly to a healthcare provider for administration by a healthcare provider, and the drug is not dispensed to the patient.
- Certified Healthcare Settings and Pharmacies must not distribute, transfer, loan, or sell SUBLOCADE.

Further information is available at www.SublocadeREMS.com or call 1-866-258-3905.

5.3 Addiction, Abuse, and Misuse

SUBLOCADE contains buprenorphine, a Schedule III controlled substance that can be abused in a manner similar to other opioids. Buprenorphine is sought by people with opioid use disorder and is

subject to criminal diversion. Monitor all patients for progression of opioid use disorder and addictive behaviors *[see Drug Abuse and Dependence (9.2)]*.

5.4 Risk of Life-Threatening Respiratory and Central Nervous System (CNS) Depression

Buprenorphine has been associated with life-threatening respiratory depression and death. Many, but not all, postmarketing reports regarding coma and death involved misuse by self-injection or were associated with the concomitant use of buprenorphine and benzodiazepines or other CNS depressants, including alcohol. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with SUBLOCADE *[see Warnings and Precautions (5.5), Drug Interactions (7), Patient Counseling Information (17)].*

Use SUBLOCADE with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

Due to its extended-release characteristics, if SUBLOCADE is discontinued as a result of compromised respiratory function, monitor patients for ongoing buprenorphine effects for several months.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Patient Counseling Information (17)]*.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.8)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver.

Because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose, strongly consider prescribing naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with SUBLOCADE. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose *[see Dosage and Administration (2.3)].*

Advise patients and caregivers that naloxone may also be administered for a known or suspected overdose with buprenorphine itself. Higher than normal doses and repeated administration of naloxone may be necessary due to the long duration of action of buprenorphine and its affinity for the mu-opioid receptor *[see Overdosage (10)]*.

Inform patients and caregivers of their options for obtaining naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Educate patients and caregivers on how to recognize respiratory depression and, if naloxone is prescribed, how to treat with naloxone. Emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered *[see Patient Counseling Information (17)].*

5.5 Managing Risks From Concomitant Use of Benzodiazepines Or Other CNS Depressants With Buprenorphine

Concomitant use of buprenorphine and benzodiazepines or other CNS depressants increases the risk of adverse reactions including overdose, respiratory depression, and death. Medication-assisted treatment of opioid use disorder, however, should not be categorically denied to patients taking these drugs. Prohibiting or creating barriers to treatment can pose an even greater risk of morbidity and mortality due to the opioid use disorder alone.

As a routine part of orientation to buprenorphine treatment, educate patients about the risks of concomitant use of benzodiazepines, sedatives, opioid analgesics, and alcohol.

Develop strategies to manage use of prescribed or illicit benzodiazepines or other CNS depressants at initiation of buprenorphine treatment, or if it emerges as a concern during treatment. Adjustments to induction procedures and additional monitoring may be required. There is no evidence to support dose limitations or arbitrary caps of buprenorphine as a strategy to address benzodiazepine use in buprenorphine-treated patients. However, if a patient is sedated at the time of buprenorphine dosing, delay or omit the buprenorphine dose if appropriate.

Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use with buprenorphine. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off of a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate.

For patients in buprenorphine treatment, benzodiazepines are not the treatment of choice for anxiety or insomnia. Before co-prescribing benzodiazepines, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments to address anxiety or insomnia. Ensure that other healthcare providers prescribing benzodiazepines or other CNS depressants are aware of the patient's buprenorphine treatment and coordinate care to minimize the risks associated with concomitant use.

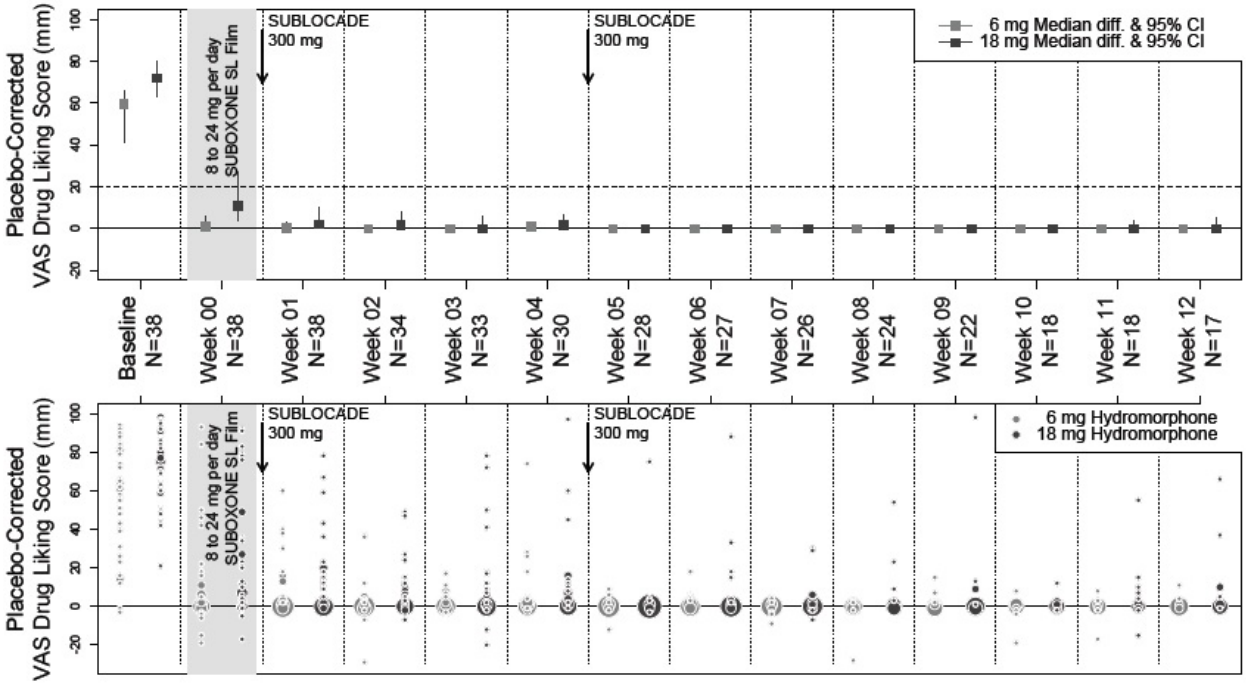
If concomitant use is warranted, strongly consider prescribing naloxone for the emergency treatment of opioid overdose, as is recommended for all patients in buprenorphine treatment for opioid use disorder *[see Warnings and Precautions (5.4)].*

In addition, take measures to confirm that patients are taking their medications as prescribed and are not diverting or supplementing with illicit drugs. Toxicology screening should test for prescribed and illicit benzodiazepines *[see Drug Interactions (7)]*.

5.6 Risk of Serious Injection Site Reactions

Injection site reactions are most commonly manifested by pain, erythema and pruritis. In some post-marketing case reports injection site reactions have involved abscess, ulceration, and necrosis. Some cases resulted in surgical depot removal, debridement, antibiotic administration, and SUBLOCADE

Figure 12 Median (95% Confidence Interval) of Placebo-Corrected Drug-Liking Scores by Hydromorphone Dose and by Week



- Key to Figure: The grey shaded area indicates the period where subjects were stabilized with 8 to 24 mg/day sublingual (SL) buprenorphine; the two vertical arrows represent treatment injections of SUBLOCADE, with 300 mg of buprenorphine.
- The light grey and dark grey squares represent the median E_{max} drug-liking scores, placebo-corrected (VAS drug liking for that week's 0 mg dose subtracted) during the hydromorphone challenge of 6 and 18 mg, respectively. This median Placebo-Corrected E_{max} is shown by treatment week, together with its 95% confidence interval (CI; vertical line). In some cases, 95% CI are not visible as the median was equal to the confidence limit. The horizontal line at 20 mm delineates the non-inferiority margin for opioid blockade. Next to median estimates, individual data are summarized by circles, the area of which is proportional to the number of subjects at that location.
- The X axis shows how many weeks following injection #1 that each weeks' Placebo-Corrected Drug-Liking Score was measured. Beneath that treatment week indicator, is the number of subjects (N) who provided those VAS measurements for all three challenges with placebo, 6 and 18 mg hydromorphone.

14.2 Study 13-0001, NCT02357901

The efficacy of SUBLOCADE for the treatment of opioid use disorder was evaluated in a Phase 3, 24-week, randomized, double-blind, placebo-controlled, multicenter trial in treatment-seeking patients who met the DSM-5 criteria for moderate or severe opioid use disorder. Patients were randomized to one of following dosing regimens: 6 once-monthly 300 mg doses, 2 once-monthly 300 mg doses followed by 4 once-monthly 100 mg doses, or 6 once-monthly SC injections of placebo. All doses were administered by a physician or suitably qualified designee and were separated by 28 ± 2 days. In addition to study medication, all subjects received manual-guided psychosocial support at least once a week (Individual Drug Counseling = IDC).

Prior to the first dose, treatment was initiated with SUBOXONE® (buprenorphine/naloxone) sublingual film (SUBOXONE SL Film); doses were adjusted from 8/2mg to 24/6 mg per day over a period of 7-14 days. Patients were randomized to SUBLOCADE injection or placebo after cravings and withdrawal symptoms were clinically controlled. After randomization, supplemental dosing with SUBOXONE SL Film was not permitted during the study.

Efficacy was evaluated over Weeks 5 through 24 based on weekly urine drug screens combined with self-reported use of illicit opioid use. A "grace period" was applied for Weeks 1 through 4 to allow patients to stabilize in treatment. During this period, opioid use, if it occurred, was not considered in the analysis. Missing urine drug screen samples and/or self-reports during Weeks 5-24 were counted as positive for illicit opioids.

A total of 504 patients were randomized 4:4:1:1 [203 subjects in the 300 mg/100 mg group, 201 patients in the 300 mg/300 mg group and 100 patients in the placebo group (2 groups of volume-matched placebo)]. Patients demographics and baseline characteristics are provided in Table 8.

Table 8 Patient Demographics and Baseline Characteristics

	SUBLOCADE 300/100 mg %	**SUBLOCADE 300/300 mg %**	**Placebo %**
Mean Age (years)	40.4	39.3	39.2
Sex			
Male	66.0	67.3	64.6
Female	34.0	32.7	35.4
Race or Ethnicity			
White	68.0	71.4	77.8
Black or African American	28.9	27.6	20.2
Hispanic or Latino	6.2	9.2	10.1
Substance Use At Screening			
Opioid Use - Injectable Route	43.3	40.8	50.5
Tobacco	91.8	92.3	92.9
Alcohol	78.4	79.1	80.8
Drug Use History			
Cannabinoids	54.6	47.4	52.5
Cocaine	47.4	39.8	42.4
Amphetamine/Methamphetamine	25.3	14.8	19.2
Medical History			
Depression	14.4	11.2	13.1
Anxiety	9.3	9.7	10.1
Back Pain	14.9	16.3	13.1

Based on the cumulative distribution function (CDF) of the percentage of urine samples negative for illicit opioids combined with self-reports negative for illicit opioid use collected from Week 5 through Week 24 (Table 9), regardless of dose, SUBLOCADE was superior to the placebo group with statistical significance. The proportion of patients achieving treatment success (defined as patients with ≥80% opioid-free weeks) was statistically significantly higher in both groups receiving SUBLOCADE compared to the placebo group (28.4% [300 mg/100 mg], 29.1% [300 mg/300mg], 2% [placebo]).

For various percentages of opioid-free weeks, Table 9 shows the fraction of patients achieving that

criterion. The table is cumulative, so that a patient whose percent of opioid-free weeks is, for example, 50%, is also included at every level of opioid-free week percentage below 50%. Missing values and values after premature discontinuation were considered positive.

Figure 13 Subjects Achieving Varying Percentages of Opioid-Free Weeks

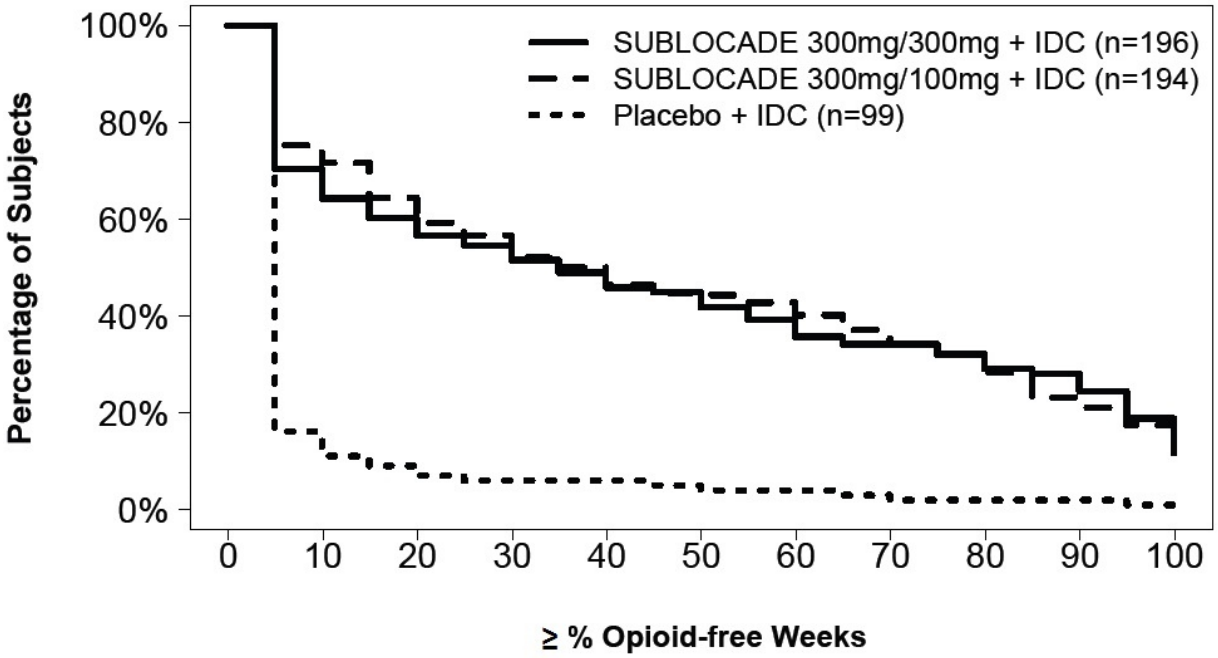


Table 9 Cumulative Distribution Function of Percentage of Opioid-Free Weeks

Percentage Opioid-Free Weeks	Number (%) of Subjects		
	SUBLOCADE 300mg/100mg + IDC (N = 194)	SUBLOCADE 300mg/300mg + IDC (N = 196)	Placebo + IDC (N = 99)
≥ 0%	194 (100.0)	196 (100.0)	99 (100.0)
≥ 10%	139 (71.6)	126 (64.3)	11 (11.1)
≥ 20%	115 (59.3)	111 (56.6)	7 (7.1)
≥ 30%	101 (52.1)	101 (51.5)	6 (6.1)
≥ 40%	90 (46.4)	90 (45.9)	6 (6.1)
≥ 50%	86 (44.3)	82 (41.8)	4 (4.0)
≥ 60%	78 (40.2)	70 (35.7)	4 (4.0)
≥ 70%	66 (34.0)	67 (34.2)	2 (2.0)
≥ 80%	55 (28.4)	57 (29.1)	2 (2.0)
≥ 90%	41 (21.1)	48 (24.5)	2 (2.0)
= 100%	25 (13)	23 (12)	1 (1.0)

16 HOW SUPPLIED/STORAGE AND HANDLING

SUBLOCADE is available as a sterile, clear, viscous, colorless to yellow to amber solution in a single dose, prefilled syringe with safety needle.

SUBLOCADE, 100 mg/0.5 mL – NDC 12496-0100-1

SUBLOCADE, 300 mg/1.5 mL – NDC 12496-0300-1

Storage and Handling

Store refrigerated at 2 - 8°C (35.6 - 46.4°F).

Once outside the refrigerator this product may be stored in its original packaging at room temperature, 15 – 30°C (59 – 86°F), for up to 7 days prior to administration. Discard SUBLOCADE if left at room temperature for longer than 7 days.

SUBLOCADE is a Schedule III drug product. Handle with adequate security and accountability. After administration, syringes should be properly disposed, per facility procedure for a Schedule III drug product, and per applicable federal, state, and local regulations.

Rx Only.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

SUBLOCADE Risk Evaluation and Mitigation Strategy (REMS)

Advise patients that because of the risk of serious harm or death due to intravenous self-administration, SUBLOCADE is available only through a restricted program called the SUBLOCADE REMS Program. Healthcare settings and pharmacies are certified and only dispense SUBLOCADE directly to a healthcare provider for administration by healthcare providers *[see Warnings and Precautions (5.2)]*.

Life Threatening Respiratory Depression

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions 5.4)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Because patients being treated for opioid use disorder are at risk for relapse, discuss the importance of having access to naloxone with the patient and caregiver. Also discuss the importance of having access to naloxone if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose.

Inform patients and caregivers of the options for obtaining naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Educate patients and caregivers on how to recognize the signs and symptoms of an opioid overdose.

Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered. Repeat administration may be necessary, particularly for overdose involving buprenorphine, because naloxone is often not effective at the doses available for patient access *[see Dosage and Administration (2.3), Warnings and Precautions (5.4), Overdosage (10)]*.

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can easily access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do

Interaction With Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if SUBLOCADE is used with benzodiazepines or other CNS depressants, including alcohol. Counsel patients that such medications should not be used concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.4, 5.5), Drug Interactions (7)].*

Serotonin Syndrome

Inform patients that SUBLOCADE could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications *[see Drug Interactions (7)].*

Adrenal Insufficiency

Inform patients that SUBLOCADE could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.8)].*

Anaphylaxis

Inform patients that anaphylaxis has been reported with buprenorphine. Advise patients how to recognize such a reaction and when to seek medical attention *[see Warnings and Precautions (5.11)].*

Driving or Operating Heavy Machinery

Caution patients that SUBLOCADE may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving or operating hazardous machinery. Instruct patients not to drive or operate hazardous machinery until they are reasonably certain that SUBLOCADE does not adversely affect their ability to engage in such activities *[see Warnings and Precautions (5.17)]*.

Dependence and Withdrawal

Inform patients that SUBLOCADE can cause drug dependence and that withdrawal signs and symptoms may occur when the medication is discontinued *[see Warnings and Precautions (5.9, 5.12)].*

Orthostatic Hypotension

Inform patients that, like other opioids, SUBLOCADE may produce orthostatic hypotension in ambulatory individuals *[see Warnings and Precautions (5.18)].*

Long Duration of Action

Inform patients that they may have detectable levels of buprenorphine for a prolonged period of time after treatment with SUBLOCADE. Considerations of drug-drug interactions, buprenorphine effects, and analgesia may continue to be relevant for several months after the last injection *[see Clinical Pharmacology (12.3)]*.

Drug Interactions

Instruct patients to inform their healthcare providers of any other prescription medications, over the-counter medications, or herbal preparations that are prescribed or currently being used *[see Drug Interactions (7)].*

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Advise women that if they are pregnant while being treated with SUBLOCADE, the baby may have signs of withdrawal at birth and that withdrawal is treatable *[see Warnings and Precautions (5.6), Use in Specific Populations (8.1)].*

Embryofetal Toxicity

Advise women of childbearing potential who become pregnant or are planning to become pregnant to consult their healthcare provider regarding the possible effects of using SUBLOCADE during pregnancy *[see Use in Specific Populations (8.1)].*

Lactation

Warn patients that buprenorphine passes into breast milk. Advise the nursing mother taking buprenorphine to monitor the infant for increased drowsiness and breathing difficulties *[see Use in Specific Populations (8.2)].*

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3), Clinical Pharmacology (12.2)].*

Emergency Analgesia

Patients should be advised to instruct their family members to, in the event of emergency, inform the treating healthcare provider or emergency room staff that the patient is physically dependent on an opioid and that the patient is being treated with SUBLOCADE *[see Warnings and Precautions (5.13)]*.

Clinical Monitoring

Tell your patients to seek emergency attention if they have signs or symptoms of respiratory or CNS depression or overdose *[see Warnings and Precautions (5.4, 5.5)]*.

Tell your patients not to tamper with or try to remove their depot *[see Dosage and Administration (2.8)].*

Manufactured for Indivior Inc.

North Chesterfield, VA 23235

By AMRI

Burlington, MA 01803

MEDICATION GUIDE

SUBLOCADE (SUB-lo-kade) (buprenorphine extended-release) injection, for subcutaneous use, (CIII)

What is the most important information I should know about SUBLOCADE?

- Because of the serious risk of potential harm or death from self-injecting SUBLOCADE into a vein (intravenously), it is only available through a restricted program called the SUBLOCADE REMS Program.
  - SUBLOCADE is not available in retail pharmacies.
  - Your SUBLOCADE injection will only be given to you by a certified healthcare provider.
- SUBLOCADE contains a medicine called buprenorphine. Buprenorphine is an opioid that can cause serious and life-threatening breathing problems, especially if you take or use certain other medicines or drugs.
- Talk to your healthcare provider about naloxone. Naloxone is a medicine that is available to patients for the emergency treatment of an opioid overdose. If naloxone is given, you must call 911 or get emergency medical help right away to treat overdose or accidental use of an opioid.
- SUBLOCADE may cause serious and life-threatening breathing problems. Get emergency help right away if you:
  - feel faint
  - feel dizzy
  - are confused
  - Feel sleepy or uncoordinated
  - have blurred vision
  - have slurred speech
  - are breathing slower than normal
  - cannot think well or clearly

Do not take certain medicines during treatment with SUBLOCADE. Taking other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) while on SUBLOCADE can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

- In an emergency, have family members tell emergency department staff that you are physically dependent on an opioid and are being treated with SUBLOCADE.
- You may have detectable levels of SUBLOCADE in your body for a long period after stopping treatment with SUBLOCADE.

What is SUBLOCADE?

SUBLOCADE is a prescription medicine used to treat adults with moderate to severe addiction (dependence) to opioid drugs (prescription or illegal) who:

- have received treatment with an oral transmucosal (used under the tongue or inside the cheek) buprenorphine-containing medicine for 7 days **and**
- are taking a dose that controls withdrawal symptoms for at least seven days.
- SUBLOCADE is part of a complete treatment plan that should include counseling.

Who should not take SUBLOCADE?

Do not use SUBLOCADE if you are allergic to buprenorphine or any ingredient in the prefilled syringe (ATRIGEL® delivery system). See the end of this Medication Guide for a list of ingredients in SUBLOCADE.

Before starting SUBLOCADE, tell your healthcare provider about all your medical conditions, including if you have:

- trouble breathing or lung problems
- a curve in your spine that affects your breathing
- Addison's disease
- an enlarged prostate (men)
- problems urinating
- liver, kidney, or gallbladder problems
- alcoholism
- a head injury or brain problem
- mental health problems
- adrenal gland or thyroid gland problems

Tell your healthcare provider if you are:

- **pregnant or plan to become pregnant.** If you receive SUBLOCADE while pregnant, your baby may have symptoms of opioid withdrawal at birth that could be life-threatening if not recognized and treated. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- **breastfeeding or plan to breastfeed.** SUBLOCADE can pass into your breast milk and harm your baby. Talk to your

healthcare provider about the best way to feed your baby during treatment with SUBLOCADE. Monitor your baby for increased drowsiness and breathing problems if you breastfeed during treatment with SUBLOCADE.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

How will I receive SUBLOCADE?

- You will receive SUBLOCADE by your healthcare provider as an injection just under the skin (subcutaneous) of your stomach (abdomen). You will receive SUBLOCADE monthly (with at least 26 days between doses).
- SUBLOCADE is injected as a liquid. After the injection, SUBLOCADE changes to a solid form called a depot. The depot may be seen or felt as a small bump under your skin at the injection site on your abdomen for several weeks. The depot will get smaller over time.
- Do not try to remove the depot.
- Do not rub or massage the injection site.
- Try not to let belts or clothing waistbands rub against the injection site.
- If you miss a dose of SUBLOCADE, see your healthcare provider to get your SUBLOCADE injection as soon as possible.

What should I avoid while being treated with SUBLOCADE?

- **Do not drive, operate heavy machinery, or perform any other dangerous activities until you know how SUBLOCADE affects you.** Buprenorphine can cause drowsiness and slow reaction times. SUBLOCADE can make you sleepy, dizzy, or lightheaded. This may happen more often in the first few days after your injection and when your dose is changed.
- **You should not drink alcohol** or take prescription or over-the-counter medicines that contain alcohol during treatment with SUBLOCADE, because this can lead to loss of consciousness or even death.

What are the possible side effects of SUBLOCADE?

SUBLOCADE can cause serious side effects, including:

- **Trouble breathing.** Taking other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants during treatment with SUBLOCADE can cause breathing problems that can lead to coma and death.
- **Sleepiness, dizziness, and problems with coordination.**
- **Physical dependence.**
- **Liver problems**. Call your healthcare provider right away if you notice any of these symptoms:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or “tea-colored” urine
  - light colored stools (bowel movements)
  - loss of appetite
  - pain, aching, or tenderness on the right side of your stomach area
  - nausea
- Your healthcare provider should do blood tests to check your liver before you start and during treatment with SUBLOCADE.
- **Allergic reaction.** You may have a rash, hives, swelling of your face, wheezing, low blood pressure, or loss of consciousness. Call your healthcare provider or get emergency help right away.
- **Opioid withdrawal.** Call your healthcare provider right away if you get any of these symptoms:
  - shaking
  - sweating more than normal
  - feeling hot or cold more than normal
  - runny nose
  - watery eyes
  - goose bumps
  - diarrhea
  - vomiting
  - muscle aches
- **Decrease in blood pressure.** You may feel dizzy when you get up from sitting or lying down.
- **The most common side effects of SUBLOCADE include:**

- constipation
- headache
- nausea
- injection site itching
- vomiting
- increase in liver enzymes
- tiredness
- injection site pain

- SUBLOCADE may affect fertility in males and females. Talk to your healthcare provider if this is a concern for you.

These are not all the possible side effects of SUBLOCADE.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

General information about SUBLOCADE

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your doctor or pharmacist for information that is written for healthcare professionals.

What are the ingredients in SUBLOCADE?

Active ingredient: buprenorphine

ATRIGEL® delivery system: biodegradable 50:50 poly(DL-lactide-co-glycolide) polymer and a biocompatible solvent, *N*-methyl-2-pyrrolidone (NMP).

Manufactured for Indivior Inc., North Chesterfield, VA 23235 by AMRI, Burlington, MA 01803

SUBLOCADE® is a registered trademark of Indivior UK Limited.

For more information, go to www.SUBLOCADE.com or call 1-877-782-6966.

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