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)**

----------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 transmucosal 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)

The recommended dose of SUBLOCADE is two monthly initial doses of 300 mg followed by 100 mg monthly maintenance doses. (2.3)

Increasing the maintenance dose to 300 mg monthly may be considered for patients in which the benefits outweigh the risks. (2.3)

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)

Neonatal Opioid Withdrawal Syndrome: Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy. (5.6)

Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)

Risk of Opioid Withdrawal With Abrupt Discontinuation: If treatment with SUBLOCADE is discontinued, monitor patients for several months for withdrawal and treat appropriately. (5.8)

Risk of Hepatitis, Hepatic Events: Monitor liver function tests prior to and during treatment. (5.9)

Risk of Withdrawal in Patients Dependent on Full Agonist Opioids: Verify that patient is clinically stable on transmucosal buprenorphine before injecting SUBLOCADE. (5.11)

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. (5.12)

----------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. (5.14, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2018

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 transmucosal 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 OR INTRAMUSCULARLY *[see Warnings and Precautions (5.1), Dosage and Administration (2.6)]*.

- 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 Recommended Dosing

The recommended dose of SUBLOCADE following induction and dose adjustment with transmucosal buprenorphine 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.

2.4 Patient Selection

Patients appropriate for SUBLOCADE are adults who have initiated treatment on a transmucosal buprenorphine-containing product delivering the equivalent of 8 to 24 mg of buprenorphine daily. The patient may only be transitioned to SUBLOCADE after a minimum of 7 days.

Initiation of treatment with transmucosal 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) 4.2mg/0.7 mg buccal film or one Zubsolv® (buprenorphine and naloxone) 5.7 mg/1.4 mg sublingual tablet.

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 levels of buprenorphine for twelve months or longer. The correlation between plasma concentrations of buprenorphine and those detectable in urine is not known.

2.6 Instructions for Use

IMPORTANT INFORMATION:

- For abdominal subcutaneous injection only *[see Warnings and Precautions (5.1)]*.
- 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.

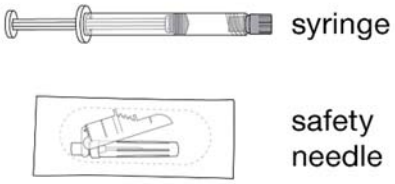
- Remove SUBLOCADE from the refrigerator prior to administration. The product requires at least 15 minutes to reach room temperature. Do not open the foil pouch until the patient has arrived for his or her injection.
- Discard SUBLOCADE if left at room temperature for longer than 7 days.
- Do not attach 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

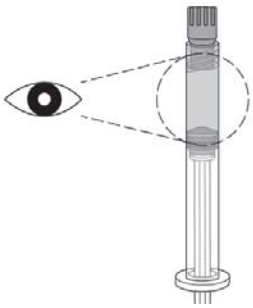


STEP 2: CHECK THE LIQUID CLARITY

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

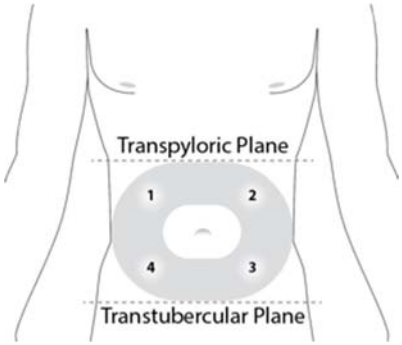
Choose an injection site on the abdomen between the transpyloric and transtubercular planes with adequate subcutaneous tissue that is free of skin conditions (e.g., nodules, lesions, excessive pigment). It is recommended that the patient is in the supine position.

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

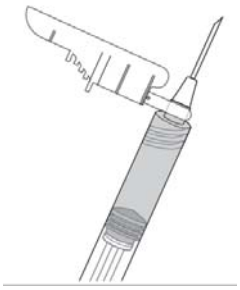
Hold the syringe upright for several seconds to allow air bubbles to rise. Due to the viscous nature of the medication, bubbles will not rise as quickly as those in an aqueous solution.

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

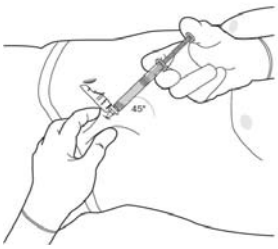
STEP 7: INJECT THE MEDICATION

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

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

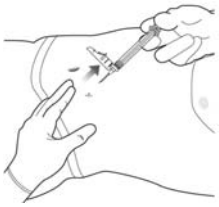


STEP 8: WITHDRAW THE NEEDLE

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

Do not rub the injection area after the injection. If there is bleeding, apply a gauze pad or bandage but use minimal pressure.

Figure 8

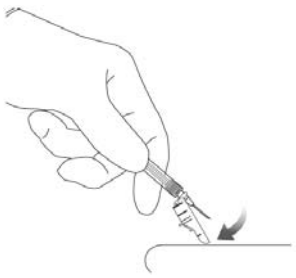


STEP 9: LOCK THE NEEDLE GUARD AND DISCARD THE SYRINGE

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

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.

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 Neonatal Opioid Withdrawal Syndrome

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically-authorized or illicit. Unlike opioid withdrawal syndrome in adults, NOWS may be life-threatening if not recognized and treated in the neonate. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly *[see Use in Specific Populations (8.1)]*.

Advise pregnant women receiving opioid addiction treatment with SUBLOCADE of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1)]*. This risk should be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. Therefore, prescribers should discuss the importance of management of opioid addiction throughout pregnancy.

5.7 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.8 Risk of Opioid Withdrawal With Abrupt Discontinuation of SUBLOCADE Treatment

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by withdrawal signs and symptoms upon abrupt discontinuation. The withdrawal syndrome is milder than that seen with full agonists and may be delayed in onset *[see Drug Abuse and Dependence (9.3)]*.

Withdrawal signs and symptoms were not observed in the month following discontinuation of SUBLOCADE. Considering the long half-life, any withdrawal signs and symptoms that may occur would be expected to be delayed *[see Clinical Pharmacology (12.2)]*. Model simulations indicate that steady-state buprenorphine plasma concentrations decreased slowly over time following the last injection and remained at therapeutic levels for 2 to 5 months on average, depending on the dosage administered (100 or 300 mg, respectively).

Patients who elect to discontinue treatment with SUBLOCADE should be monitored for withdrawal signs

and symptoms. Consider transmucosal buprenorphine if needed to treat withdrawal after discontinuing SUBLOCADE.

5.9 Risk of Hepatitis, Hepatic Events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through postmarketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. Withdrawal of buprenorphine has resulted in amelioration of acute hepatitis in some cases, however, in other cases no dose reduction was necessary. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. In one subject in the SUBLOCADE clinical program, surgical removal was followed by improvement in liver enzymes.

Liver function tests, prior to initiation of treatment, are recommended to establish a baseline. Monthly monitoring of liver function during treatment, particularly with 300 mg maintenance dose, is also recommended. An etiological evaluation is recommended when a hepatic adverse event is suspected.

5.10 Hypersensitivity Reactions

Cases of hypersensitivity to buprenorphine-containing products have been reported both in clinical trials and in the postmarketing experience. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, hives, and pruritus. A history of hypersensitivity to buprenorphine is a contraindication to the use of SUBLOCADE *[see Contraindications (4)]*.

5.11 Precipitation of Opioid Withdrawal in Patients Dependent on Full Agonist Opioids

Because of the partial opioid agonist properties of buprenorphine, buprenorphine may precipitate opioid withdrawal signs and symptoms in persons who are currently physically dependent on full opioid agonists such as heroin, morphine, or methadone before the effects of the full opioid agonist have subsided. Verify that patients have tolerated and are dose adjusted on transmucosal buprenorphine before subcutaneously injecting SUBLOCADE.

5.12 Risks Associated With Treatment of Emergent Acute Pain

While on SUBLOCADE, situations may arise where patients need acute pain management, or may require anesthesia. Treat patients receiving SUBLOCADE with a non-opioid analgesic whenever possible. Patients requiring opioid therapy for analgesia may be treated with a high-affinity full opioid analgesic under the supervision of a physician, with particular attention to respiratory function. Higher doses may be required for analgesic effect. Therefore, a higher potential for toxicity exists with opioid administration. If opioid therapy is required as part of anesthesia, patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy should be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the

establishment and maintenance of a patent airway and assisted ventilation.

Advise patients of the importance of instructing their family members, in the event of emergency, to 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 Patient Counseling Information (17)]*.

The above guidance should also be considered for any patient who has been treated with SUBLOCADE within the last 6 months.

5.13 Use in Opioid Naïve Patients

There have been reported deaths of opioid naïve individuals who received a 2 mg dose of buprenorphine as a sublingual tablet. SUBLOCADE is not appropriate for use in opioid naïve patients.

5.14 Use in Patients With Impaired Hepatic Function

In a pharmacokinetic study with transmucosal buprenorphine, buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment. The effect of hepatic impairment on the pharmacokinetics of SUBLOCADE has not been studied.

Because of the long-acting nature of the product, adjustments to dosages of SUBLOCADE are not rapidly reflected in plasma buprenorphine levels. Because buprenorphine levels cannot be rapidly decreased, patients with pre-existing moderate to severe hepatic impairment are not candidates for treatment with SUBLOCADE.

Patients who develop moderate to severe hepatic impairment while being treated with SUBLOCADE should be monitored for several months for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

5.15 Use in Patients at Risk for Arrhythmia

Buprenorphine has been observed to prolong the QTc interval in some patients participating in clinical trials. Consider these observations in clinical decisions when prescribing buprenorphine to patients with hypokalemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Periodic electrocardiographic (ECG) monitoring is recommended in these patients. Avoid the use of buprenorphine in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval *[see Clinical Pharmacology (12.2)]*.

5.16 Impairment of Ability to Drive or Operate Machinery

SUBLOCADE may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery especially during the first few days following treatment and dose adjustment. Buprenorphine plasma levels accumulate during the first two months and are maintained with the 100 mg maintenance dose; further accumulation occurs with the 300 mg maintenance dose, which achieves steady-state after the fourth monthly injection. Caution patients about driving or operating hazardous machinery until they are reasonably certain that

SUBLOCADE does not adversely affect their ability to engage in such activities.

5.17 Orthostatic Hypotension

Buprenorphine may produce orthostatic hypotension in ambulatory patients.

5.18 Elevation of Cerebrospinal Fluid Pressure

Buprenorphine may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

5.19 Elevation of Intracholedochal Pressure

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

5.20 Effects in Acute Abdominal Conditions

Buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

5.21 Unintentional Pediatric Exposure

Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Addiction, Abuse, and Misuse [*see Warnings and Precautions (5.3)*]
- Respiratory and CNS Depression *[see Warnings and Precautions (5.4)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.6)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.7)]*
- Opioid Withdrawal *[see Warnings and Precautions (5.8, 5.11)]*
- Hepatitis, Hepatic Events *[see Warnings and Precautions (5.9)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.10)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.17)]*
- Elevation of Cerebrospinal Fluid Pressure *[see Warnings and Precautions (5.18)]*
- Elevation of Intracholedochal Pressure *[see Warnings and Precautions (5.19)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of SUBLOCADE was evaluated in 848 opioid-dependent subjects (see Table 1). In these

studies, there was a total of 557 subjects who received at least 6 monthly SC injections of SUBLOCADE and 138 subjects who received 12 monthly SC injections. Adverse events led to premature discontinuation in 4% of the group receiving SUBLOCADE compared with 2% in the placebo group (13-0001, NCT02357901).

In the Phase 3 open-label study (13-0003, NCT02510014), adverse events leading to drug dose reductions were reported in 7.3% of subjects receiving SUBLOCADE.

Table 1. Total Subjects Exposed to SUBLOCADE

Study 13-0001 (NCT02357901) Up to 6 Injections			Study 13-0003 (NCT02510014)				Total Subjects Exposed To SUBLOCADE
			Roll-Over Up to 6 Injections			De-Novo Up to 12 Injections	
SUBLOCADE 300/100 mg	SUBLOCADE 300/300 mg	Placebo	From SUBLOCADE 300/100 mg To SUBLOCADE 300/Flex†	From SUBLOCADE 300/300 mg To SUBLOCADE 300/Flex†	From Placebo To SUBLOCADE 300/Flex†	SUBLOCADE 300/Flex	
N = 203	N = 201	N = 100*	N = 112‡	N = 113‡	N= 32	N = 412	N = 848

*Not included in total subjects exposed to SUBLOCADE

† FLEX = 300 mg initial dose with an option to receive either 100 mg or 300 mg for subsequent dosing per clinician's discretion

‡ = Not included in total unique subjects exposed to SUBLOCADE, already accounted for in Study 13-0001 section of table

Table 2 shows the non-injection site-related adverse reactions (ADRs) for the groups receiving SUBLOCADE 300/300 mg (6 doses of 300 mg SC injections) 300/100 mg (300 mg SC injections for the first two doses followed by 4 doses of 100 mg SC injections) and placebo (volume-matched ATRIGEL® delivery system subcutaneous injections) reported following administration in the 6 month, double-blind, placebo-controlled study. The systemic safety profile for SUBLOCADE, given by a healthcare provider in clinical trials, was consistent with the known safety profile of transmucosal buprenorphine. Common adverse reactions associated with buprenorphine included constipation, nausea, vomiting, abnormal liver enzymes, headache, sedation and somnolence. Dose dependent hepatic effects observed in the Phase 3, double-blind study (13-0001, NCT02357901) included the incidence of ALT more than 3 times the upper limit of normal (> 3 × ULN) in 12.4%, 5.4%, and 4.0% of the SUBLOCADE 300/300-mg, SUBLOCADE 300/100-mg, and placebo groups, respectively. The incidence of AST > 3 × ULN was 11.4%, 7.9%, and 1.0%, respectively. Adverse drug reactions [by MedDRA Preferred Terms (PT)] reported in at least 2% of subjects receiving SUBLOCADE are grouped by System Organ Class (SOC).

Table 2. Adverse Reactions for Phase 3 Double-Blind Study: ≥2% of Subjects Receiving SUBLOCADE

System Organ Class Preferred Term	PLACEBO Count (%)	SUBLOCADE 300/100 mg Count (%)	SUBLOCADE 300/300 mg Count (%)
Total	**N = 100**	**N = 203**	**N = 201**
Gastrointestinal disorders	12 (12%)	51 (25.1%)	45 (22.4%)
Constipation	0	19 (9.4)	16 (8)
Nausea	5 (5)	18 (8.9)	16 (8)
Vomiting	4 (4)	19 (9.4)	11 (5.5)

System Organ Class Preferred Term	PLACEBO Count (%)	SUBLOCADE 300/100 mg Count (%)	SUBLOCADE 300/300 mg Count (%)
General disorders and administration site conditions	17 (17%)	40 (19.7%)	49 (24.4%)
Fatigue	3 (3)	8 (3.9)	12 (6)
Investigations*	2 (2%)	21 (10.3%)	19 (9.5%)
Alanine aminotransferase increased (ALT)	0	2 (1)	10 (5)
Aspartate aminotransferase increased (AST)	0	7 (3.4)	9 (4.5)
Blood creatine phosphokinase increased (CPK)	1 (1)	11 (5.4)	5 (2.5)
Gamma-glutamyl transferase increased (GGT)	1 (1)	6 (3)	8 (4)
Nervous system disorders	7 (7%)	35 (17.2%)	25 (12.4%)
Headache	6 (6)	19 (9.4)	17 (8.5)
Sedation	0	7 (3.4)	3 (1.5)
Dizziness	2 (2)	5 (2.5)	3 (1.5)
Somnolence	0	10 (4.9)	4 (2)

*There were no cases of serious liver injury attributed to study drug.

Table 3 shows the injection site-related adverse events reported by ≥2 subjects in the Phase 3 studies. Most injection site adverse drug reactions (ADRs) were of mild to moderate severity, with one report of severe injection site pruritus. None of the injection site reactions were serious. One reaction, an injection site ulcer, led to study treatment discontinuation.

Table 3. Injection Site Adverse Drug Reactions Reported by ≥2 Subjects in the Phase 3 Studies

	13-0001 (Ph3DB)			13-0003 (Ph3OL)				All Phase 3*
				Roll–over			De-novo	
Preferred term, n (%)	SUBLOCADE 300/300 (N = 201)	SUBLOCADE 300/100 (N = 203)	Placebo (N = 100)	SUBLOCADE 300 → SUBLOCADE 300/Flex (N = 113)	SUBLOCADE 100 → SUBLOCADE 300/Flex (N = 112)	Placebo → SUBLOCADE 300/Flex (N = 32)	SUBLOCADE 300/Flex (N = 412)	Total SUBLOCADE (N = 848)
Subjects with any injection site reactions	38 (18.9%)	28 (13.8%)	9 (9.0%)	6 (5.3%)	13 (11.6%)	2 (6.3%)	61 (14.8%)	140 (16.5%)
Injection site pain	12 (6.0%)	10 (4.9%)	3 (3.0%)	4 (3.5%)	2 (1.8%)	2 (6.3%)	33 (8.0%)	61 (7.2%)
Injection site pruritus	19 (9.5%)	13 (6.4%)	4 (4.0%)	2 (1.8%)	6 (5.4%)	1 (3.1%)	17 (4.1%)	56 (6.6%)
Injection site erythema	6 (3.0%)	9 (4.4%)	0	1 (0.9%)	4 (3.6%)	0	21 (5.1%)	40 (4.7%)
Injection site induration	2 (1.0%)	2 (1.0%)	0	0	1 (0.9%)	0	7 (1.7%)	12 (1.4%)
Injection site bruising	2 (1.0%)	2 (1.0%)	0	0	0	0	2 (0.5%)	6 (0.7%)

Injection site swelling	1 (0.5%)	2 (1.0%)	0	1 (0.9%)	1 (0.9%)	0	1 (0.2%)	6 (0.7%)
Injection site discomfort	1 (0.5%)	1 (0.5%)	0	0	0	0	3 (0.7%)	5 (0.6%)
Injection site reaction	1 (0.5%)	0	0	0	3 (2.7%)	0	1 (0.2%)	5 (0.6%)
Injection site cellulitis	0	1 (0.5%)	0	0	0	0	2 (0.5%)	3 (0.4%)
Injection site infection	1 (0.5%)	0	1 (1.0%)	0	0	0	2 (0.5%)	3 (0.4%)

*Patients received SUBOXONE film for a run-in period before they switched to SUBLOCADE injection.

Longer-term experience

In an interim analysis of the ongoing open-label long-term safety study (13-0003), safety was evaluated for up to 12 injections over the course of a year (see Table 1). Adverse events were reported for 432 of 669 subjects during the treatment period. The overall adverse event profile was similar to the double-blind trial described above.

6.2 Postmarketing Experience

The most frequently reported systemic postmarketing adverse event observed with buprenorphine sublingual tablets was drug misuse or abuse. The most frequently reported systemic postmarketing adverse event with buprenorphine/naloxone sublingual tablets and film was peripheral edema.

The following adverse reactions have been identified during post-approval use of buprenorphine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in SUBLOCADE.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with SUBLOCADE.

Table 4. Clinically Significant Drug Interactions

Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effects, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention:	Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. 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. Similarly, cessation of other CNS depressants is preferred when possible. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments *[see Warnings and Precautions (5.4, 5.5)]*.
Examples:	Alcohol, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids.
Inhibitors of CYP3A4	
Clinical Impact:	The effects of co-administered CYP3A4 inhibitors on buprenorphine exposure in subjects treated with SUBLOCADE have not been studied and the effects may be dependent on the route of administration; however, such interactions have been established in studies using transmucosal buprenorphine. Buprenorphine is metabolized to norbuprenorphine primarily by CYP3A4; therefore, potential interactions may occur when SUBLOCADE is given concurrently with agents that affect CYP3A4 activity. The concomitant use of sublingual buprenorphine and CYP3A4 inhibitors (e.g., ketoconazole) can increase the plasma concentration of buprenorphine, resulting in increased or prolonged opioid effects.
Intervention:	Patients who transfer to SUBLOCADE treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inhibitors [e.g., azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir)] should be monitored to ensure that the plasma buprenorphine level provided by SUBLOCADE is adequate. If patients already on SUBLOCADE require newly-initiated treatment with CYP3A4 inhibitors, the patients should be monitored for signs and symptoms of over-medication. Within 2 weeks of SUBLOCADE administration, if signs and symptoms of buprenorphine toxicity or overdose occur but the concomitant medication cannot be reduced or discontinued, it may be necessary to remove the depot and treat the patient with a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilized on SUBLOCADE in the setting of concomitant medication that is a CYP3A4 inhibitor, and the concomitant medication is discontinued, the patient should be monitored for withdrawal. If the dose of SUBLOCADE is not adequate in the absence of the concomitant medication, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The effects of co-administered CYP3A4 inducers on buprenorphine exposure in subjects treated with SUBLOCADE have not been studied.

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 (5.12)]*.

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)].*

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Manufactured for Indivior Inc.

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By AMRI

Burlington, MA 01803

Medication Guide

SUBLOCADE (SUB-lo-kade)

(buprenorphine extended-release)

injection, for subcutaneous use (CIII)

Read this Medication Guide before starting SUBLOCADE and each time you receive SUBLOCADE. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider. Talk to your healthcare provider if you have questions about SUBLOCADE.

Share this important information in this Medication Guide with members of your household.

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.
- In an emergency, you or your family should tell the emergency medical staff that you are physically dependent on an opioid and are being treated with SUBLOCADE.
- Buprenorphine, the medicine in SUBLOCADE, can cause serious and life-threatening problems, especially if you take or use certain other medicines or drugs. Call your healthcare provider right away or get emergency help if you:
  - feel faint or dizzy
  - have mental changes such as confusion
  - have slower breathing than you normally have
  - have severe sleepiness
  - have blurred vision
  - have problems with coordination
  - have slurred speech
  - cannot think well or clearly
  - have a high body temperature
  - have slowed reflexes
  - feel agitated
  - have stiff muscles
  - have trouble walking

These can be signs of an overdose or other serious problems.

- Death or serious harm can happen if you take anxiety medicines or benzodiazepines, sleeping pills, tranquilizers, muscle relaxants, or sedatives, antidepressants, or antihistamines, or drink alcohol during treatment with SUBLOCADE. Tell your healthcare provider if you are taking any of these medicines and if you drink alcohol.

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.

It is not known if SUBLOCADE is safe or effective in children.

SUBLOCADE is a controlled substance (CIII) because it contains buprenorphine that can be a target for people who abuse prescription medicines or street drugs.

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.

SUBLOCADE may not be right for you. Before starting SUBLOCADE, tell your healthcare provider about all of your medical conditions, including:

- Trouble breathing or lung problems
- An enlarged prostate gland (men)
- A head injury or brain problem
- Problems urinating
- A curve in your spine that affects your breathing (scoliosis)
- Liver problems
- Gallbladder problems
- Adrenal gland problems
- Addison's disease
- Low thyroid hormone levels (hypothyroidism)
- A history of alcoholism
- Mental problems such as hallucinations (seeing or hearing things that are not there).
- Are pregnant or plan to become pregnant. If you receive SUBLOCADE while pregnant, your baby may have symptoms of opioid withdrawal at birth.
- Are breastfeeding or plan to breastfeed. SUBLOCADE can pass into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby during treatment with SUBLOCADE. Watch your baby for increased drowsiness and breathing problems.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. SUBLOCADE may affect the way other medicines work and other medicines may affect how SUBLOCADE works. Some medicines may cause serious or life-threatening medical problems when taken with SUBLOCADE.

- The doses of certain medicines may need to be changed if used during treatment with SUBLOCADE. Do not take any medicine during treatment with SUBLOCADE until you have talked with your healthcare provider. Your healthcare provider will tell you if it is safe to take other medicines during treatment with SUBLOCADE.
- You should not take anxiety medicines or benzodiazepines (such as Valium® or Xanax®), sleeping pills, tranquilizers, muscle relaxants, or sedatives (such as Ambien®), antidepressants, or antihistamines that are not prescribed to you during treatment with SUBLOCADE, as this can lead to slowed breathing, drowsiness, delayed reaction time, loss of consciousness or even death. If a healthcare provider is considering prescribing such a medicine for you, remind the healthcare provider that you are being treated with SUBLOCADE.
- You may have detectable levels of SUBLOCADE in your body for a long period after stopping treatment with SUBLOCADE.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine.

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 this medicine affects you.** Buprenorphine can cause drowsiness and slow reaction times. This may happen more often in the first few days after your injection and when your dose is changed.
- **Do not drink alcohol** during treatment with SUBLOCADE, as this can lead to slowed breathing, drowsiness, slow reaction time, loss of consciousness or even death.

What are the possible side effects of SUBLOCADE?

SUBLOCADE can cause serious side effects, including:

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

- **Physical dependence and withdrawal.** Your body can develop a physical need for SUBLOCADE (dependence). If you stop receiving SUBLOCADE, you could have opioid withdrawal symptoms such as:
  - shaking, goose bumps, muscle aches
  - sweating more than normal
  - feeling hot or cold more than normal
  - runny nose and watery eyes
  - diarrhea or vomiting

  These symptoms may start weeks to months after your last dose of SUBLOCADE
- **Liver problems**. Call your healthcare provider right away if you notice any of these signs of liver problems:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - urine turns dark
  - bowel movements (stools) turn light in color
  - decreased appetite
  - stomach (abdomen) pain or nausea

Your healthcare provider may do tests before and during treatment with SUBLOCADE to check your liver.

- **Allergic reaction.** Call your healthcare provider or get emergency help right away if you get:
  - rash, hives, itching
  - swelling of your face
  - wheezing
  - dizziness, or a decrease in consciousness
- **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
- Long-term (chronic) use of opioids, including SUBLOCADE, may cause fertility problems 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. This Medication Guide summarizes important information about SUBLOCADE. If you would like more information talk with your healthcare provider. You can ask your healthcare provider 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

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.
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