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.

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)]*.

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.

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)]*.

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)
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

Preferred term, n (%)	13-0001 (Ph3DB)			13-0003 (Ph3OL)				All Phase 3*
				Roll–over			De-novo	
	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

Clinical Considerations

Advise breastfeeding women taking buprenorphine products to monitor the infant for increased drowsiness and breathing difficulties.

Data

Data were consistent from two studies (N=13) of breastfeeding infants whose mothers were maintained on sublingual doses of buprenorphine ranging from 2.4 to 24 mg/day, showing that the infants were exposed to less than 1% of the maternal daily dose.

In a study of six lactating women who were taking a median sublingual buprenorphine dose of 0.29 mg/kg/day 5 to 8 days after delivery, breast milk provided a median infant dose of 0.42 mcg/kg/day of buprenorphine and 0.33 mcg/kg/day of norbuprenorphine, equal to 0.2% and 0.12%, respectively, of the maternal weight-adjusted dose (relative dose/kg (%) of norbuprenorphine was calculated from the assumption that buprenorphine and norbuprenorphine are equipotent).

Data from a study of seven lactating women who were taking a median sublingual buprenorphine dose of 7 mg/day an average of 1.12 months after delivery indicated that the mean milk concentrations (C_{avg}) of buprenorphine and norbuprenorphine were 3.65 mcg/L and 1.94 mcg/L respectively. Based on the study data, and assuming milk consumption of 150 mL/kg/day, an exclusively breastfed infant would receive an estimated mean absolute infant dose (AID) of 0.55 mcg/kg/day of buprenorphine and 0.29 mcg/kg/day of norbuprenorphine, or a mean relative infant dose (RID) of 0.38% and 0.18%, respectively, of the maternal weight-adjusted dose.

8.3 Females and Males of Reproductive Potential

Human Data

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2)]*.

Animal Data

Infertility

Male

Male fertility may be reduced based on animal data demonstrating adverse effects of SUBLOCADE on sperm parameters *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

The safety and effectiveness of SUBLOCADE have not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of SUBLOCADE did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience with buprenorphine has not identified differences in responses between geriatric and younger patients.

Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in geriatric patients, the decision to prescribe SUBLOCADE should be made cautiously in

individuals 65 years of age or older and these patients should be monitored for signs and symptoms of toxicity or overdose.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of SUBLOCADE has not been studied.

The effect of hepatic impairment on the pharmacokinetics of sublingual buprenorphine has been evaluated in a pharmacokinetic study. While no clinically significant changes have been observed in subjects with mild hepatic impairment, the plasma levels have been shown to be higher and half-life values have been shown to be longer for buprenorphine in subjects with moderate and severe hepatic impairment.

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 adjusted, 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 signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. If signs and symptoms of toxicity or overdose occur within 2 weeks of SUBLOCADE administration, removal of the depot may be required *[see Dosage and Administration (2.8), Warnings and Precautions (5.9), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Clinical studies of SUBLOCADE did not include subjects with renal impairment. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

SUBLOCADE contains buprenorphine, a Schedule III substance under the Controlled Substances 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.

9.2 Abuse

SUBLOCADE contains buprenorphine, a Schedule III controlled substance that can be abused similar to other opioids. Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with or referred for more intensive and structured treatment. Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

SUBLOCADE is distributed through a restricted distribution system, which is intended to prevent the direct distribution to a patient. SUBLOCADE should only be dispensed directly to a healthcare provider

for administration by a healthcare provider. It is supplied in prefilled syringes and is intended for administration only by subcutaneous injection by a healthcare provider. The entire contents of the prefilled syringe should be administered. After administration, a small amount (approximately 0.1 mL) of SUBLOCADE will remain in the needle and syringe and should be properly disposed of *[see How Supplied/Storage and Handling (16)]*.

SUBLOCADE is injected as a liquid, and the subsequent precipitation of the poly (DL-lactide-co-glycolide) polymer creates a solid depot which contains buprenorphine. After initial formation of the depot, buprenorphine is released via diffusion from, and the biodegradation of, the depot. Clinical monitoring for evidence at the injection site of tampering or attempting to remove the depot should be ongoing throughout treatment. No accounts of subjects removing or attempting to remove the depot after administration of SUBLOCADE were reported in premarketing studies.

9.3 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset *[see Warnings and Precautions (5.11)]*.

Due to the long-acting nature of SUBLOCADE, withdrawal signs and symptoms may not be evident immediately following the discontinuation of treatment.

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy *[see Warnings and Precautions (5.6)]*.

10 OVERDOSAGE

Clinical Presentation

The manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.

Treatment of Overdose

In the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully. When respiratory or cardiac functions are depressed, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, IV fluids, vasopressors, and other supportive measures should be considered as indicated. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

Clinicians should consider the potential role and contribution of buprenorphine, other opioids, and other CNS depressant drugs in a patient's clinical presentation. Clinical data are limited with regards to the possible surgical removal of the depot. Two cases of surgical removal were reported in premarketing clinical studies.

11 DESCRIPTION

SUBLOCADE (buprenorphine extended-release) injection is a clear, viscous, colorless to yellow to amber, sterile solution for subcutaneous injection only. It is designed to deliver buprenorphine at a controlled rate over a one month period.

The active ingredient in SUBLOCADE is buprenorphine free base, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist.

Buprenorphine is dissolved in the ATRIGEL® delivery system at 18% by weight.

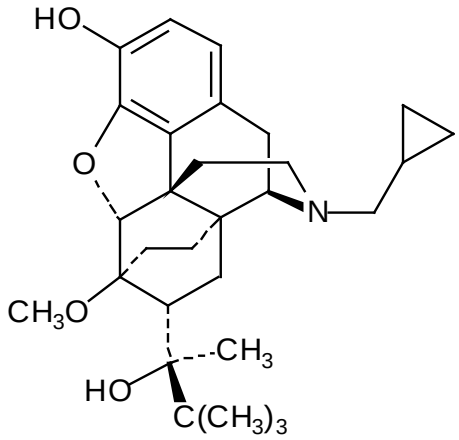
The ATRIGEL® delivery system is a biodegradable 50:50 poly(DL-lactide-co-glycolide) polymer and a biocompatible solvent, *N*-methyl-2-pyrrolidone (NMP).

SUBLOCADE is provided in dosage strengths of 100 mg and 300 mg. Table 5 presents the delivered amounts of the raw materials and the approximate delivered volume for the two dosage strengths.

Table 5. Amounts of Raw Materials and Delivered Volume for the Dosage Strengths

Raw Materials in SUBLOCADE	100 mg Dosage	300 mg Dosage
Buprenorphine	100 mg	300 mg
Poly(DL-lactide-co-glycolide)	178 mg	533 mg
N-methyl-2-pyrrolidone	278 mg	833 mg
Approximate Delivered Volume	0.5 mL	1.5 mL

The molecular weight of buprenorphine free base is 467.6, and its molecular formula is $C_{29}H_{41}NO_4$. Chemically, buprenorphine is (2S)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol. The structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SUBLOCADE Injection contains buprenorphine. Buprenorphine is a partial agonist at the mu- opioid receptor and an antagonist at the kappa-opioid receptor.

12.2 Pharmacodynamics

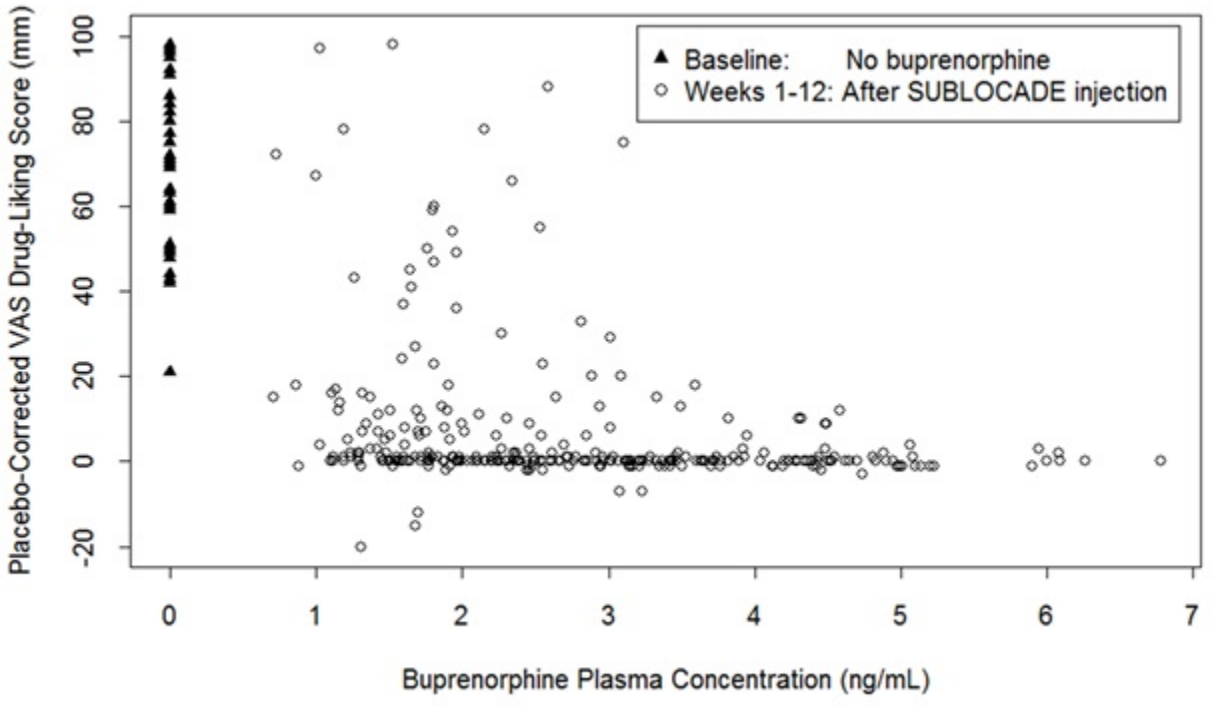
Mu-Opioid Receptor Occupancy and Association With Opioid Blockade

In a Positron Emission Tomography (PET) study with SUBLOCADE in 2 subjects (one subject receiving 200 mg SC injections and one subject receiving 300 mg SC injections) with opioid use disorder, 75 to 92% occupancy of the mu-opioid receptors in the brain was maintained for 28 days following the last dose under steady-state conditions.

The opioid blockade study evaluated the blockade of subjective opioid effects, pharmacokinetics (PK) and safety of SC injections of SUBLOCADE. Stabilization doses of SL buprenorphine prior to injection of SUBLOCADE failed to provide full blockade of subjective effects of hydromorphone 18 mg IM. After SUBLOCADE injections at Weeks 0 and 4, on average, subjective effects of both 6 mg and 18 mg doses of hydromorphone were blocked; however, wide variability was seen across subjects. Complete blockade continued throughout the 8 weeks of observation that followed the 2nd SUBLOCADE injection *[see Clinical Studies (14.1)]*.

Figure 10 illustrates the relationship between buprenorphine plasma level and drug liking after 18 mg hydromorphone IM.

Figure 10. Drug Liking VAS vs. Plasma Buprenorphine Concentration Following 18 mg Hydromorphone Challenges



Exposure-response relationships were assessed for illicit opioid use, based on urine samples negative for illicit opioids combined with self-reports negative for illicit opioid use, and withdrawal symptoms using data obtained from 489 opioid dependent patients in the double-blind Phase 3 Study (13-0001).

The observed plateau for maximal response was reached at buprenorphine plasma concentrations of approximately 2-3 ng/mL for illicit opioid use and 4 ng/mL for opioid withdrawal symptoms.

Population PK/PD modeling indicated that patients using opioids by the injectable route at baseline may require higher buprenorphine exposure compared to patients not using opioids by the injectable route at baseline.

Cardiac Electrophysiology

Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of SUBLOCADE on the QT interval in five clinical studies including the Phase 3 study. In a Phase 3 study, seven patients had an increase from baseline QTc greater than 60 msec at any time [2/203 patients (1.0%) in the 300 mg/100 mg group and 5/201 patients (2.0%) in the 300 mg/300 mg group] and one patient in the 300 mg/300 mg group was found to have a QTc greater than 500 msec. These QTc findings were all sporadic and transient and none led to aberrant ventricular rhythm. Review of ECG and adverse event data provided no evidence for syncope, seizure, or ventricular tachycardia or fibrillation.

Physiological Effects

Buprenorphine in IV (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses have been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory, and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3 hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed. The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree.

In clinical studies conducted with SUBLOCADE at doses ranging from 50 to 300 mg, no incidences of temperature elevations, or clinically significant lowering of oxygen saturation were observed.

Androgen Deficiency

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics (PK) of buprenorphine following subcutaneous injection of SUBLOCADE was evaluated in subjects with opioid use disorder after single doses (50 mg to 200 mg) and repeated doses (50 to 300 mg) separated by 28 days for up to 12 injections.

After SUBLOCADE injection, an initial buprenorphine peak was observed and the median T_{max} occurred at 24 hours after injection. After the initial buprenorphine peak, the plasma buprenorphine concentrations decreased slowly to a plateau. Steady-state was achieved at 4-6 months. Observed mean buprenorphine concentrations levels for C_{avg}, C_{max} and C_{min} are presented in Table 6.

Table 6. Comparison of Buprenorphine Mean Pharmacokinetic Parameters Between SUBUTEX and SUBLOCADE

Pharmacokinetic parameters	SUBUTEX daily stabilization		SUBLOCADE		
Mean	12 mg (steady-state)	24 mg (steady-state)	300 mg# (1st injection)	100 mg* (steady-state)	300 mg* (steady-state)
$C_{avg,ss}$ (ng/mL)	1.71	2.91	2.19	3.21	6.54
$C_{max,ss}$ (ng/mL)	5.35	8.27	5.37	4.88	10.12
$C_{min,ss}$ (ng/mL)	0.81	1.54	1.42†	2.48	5.01

#Exposure after 1 injection of 300 mg SUBLOCADE following 24 mg SUBUTEX stabilization

†Mean plasma concentration of 1.86 ng/mL was observed on last day of the dosing interval (Day 29)

*Steady-state exposure after 4 injections of 100 mg or 300 mg SUBLOCADE, following 2 injections of 300 mg SUBLOCADE

Distribution

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Elimination

Buprenorphine is metabolized and eliminated in urine and feces. The apparent terminal plasma half-life of buprenorphine following subcutaneous injection of SUBLOCADE ranged between 43 to 60 days as a result of the slow release of buprenorphine from the subcutaneous depot.

Metabolism

Buprenorphine is metabolized to its major metabolite, norbuprenorphine, primarily by CYP3A4. Norbuprenorphine can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors *in vitro*; however, it has not been studied clinically for opioid-like activity. Norbuprenorphine steady-state plasma concentrations in humans after subcutaneous injection of SUBLOCADE are low compared to buprenorphine (AUC norbuprenorphine/buprenorphine ratio of 0.20 to 0.40).

Excretion

A mass balance study of buprenorphine administered by IV infusion in humans showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine were conjugated (buprenorphine: 1% free and 9.4% conjugated; norbuprenorphine: 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine: 33% free and 5% conjugated; norbuprenorphine: 21% free and 2% conjugated).

Drug Interaction Studies

CYP3A4 Inhibitors and Inducers

The effects of co-administered CYP3A4 inhibitors and inducers on buprenorphine exposure in subjects treated with SUBLOCADE have not been studied; however, such interactions have been established in studies using transmucosal buprenorphine. The effects of buprenorphine may be dependent on the route of administration.

Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when SUBLOCADE is given concurrently with agents that affect CYP3A4 activity. The effects of co-administered CYP3A4 inducers or inhibitors have been established in studies using transmucosal buprenorphine. Patients who transfer to SUBLOCADE treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inhibitors (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), or HIV protease inhibitors, or CYP3A4 inducer (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) should be monitored to ensure that the plasma buprenorphine level provided by SUBLOCADE is adequate and not excessive *[see Drug Interactions (7)]*.

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in in vitro studies employing human liver microsomes. However, the plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic SUBLOCADE doses are not expected to significantly affect metabolism of other co-medications.

Specific Populations

Based on population pharmacokinetic analyses, age, sex and race do not have a clinically meaningful effect on PK of SUBLOCADE.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of SUBLOCADE has not been studied. However, the effect of hepatic impairment on the PK of buprenorphine has been evaluated in a study using 2 mg/0.5 mg buprenorphine/naloxone sublingual tablet in subjects with various degrees of hepatic impairment as indicated by Child-Pugh criteria. While no clinically relevant changes were observed in subjects with mild hepatic impairment, buprenorphine plasma exposure was increased by 64% and 181% in subjects with moderate and severe hepatic impairment, respectively, compared to healthy subjects *[see Use in Specific Populations (8.6)]*.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of SUBLOCADE has not been studied. Clinical studies of SUBLOCADE did not include subjects with severe renal impairment.

Less than 1% is excreted as unchanged buprenorphine in urine following IV buprenorphine administration. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine *[see Use in Specific Populations (8.7)]*.

Population PK analyses indicated no notable relationship between creatinine clearance and steady-state buprenorphine plasma concentrations.

HCV infection

In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine were not clinically significant in comparison to healthy subjects without HCV infection. No dose adjustment is needed in patients with HCV infection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Long-term studies in animals performed to evaluate carcinogenic potential of SUBLOCADE have not been conducted. However, the carcinogenic potential of the active drug substance in SUBLOCADE, buprenorphine, has been evaluated in Sprague-Dawley rats and CD-1 mice.

In the carcinogenicity study conducted in Sprague-Dawley rats, buprenorphine was administered in the diet at doses of 0.6, 5.5, and 56 mg/kg/day (approximately 0.5, 5, and 50 times the recommended human monthly SC dose of 300 mg of buprenorphine) for 27 months. A statistically significant dose-related increase in Leydig cell tumors occurred. In an 86 week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (approximately 45 times the recommended human monthly SC dose of 300 mg of buprenorphine).

NMP, an excipient in SUBLOCADE, produced an increase in hepatocellular adenomas and carcinomas in male and female mice at 6 and 8 times the maximum daily dose (MDD) of NMP via SUBLOCADE. The clinical significance of these findings is unclear. No tumors were noted at 1 and 1.3 times the MDD. In 2-year inhalation and dietary studies in rats, NMP did not result in evidence of carcinogenicity.

Mutagenicity

No evidence of mutagenic potential for subcutaneous SUBLOCADE was found in *in vivo* subcutaneous micronucleus test using rats' marrow.

Mutagenic potential for buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae*) for recombinant, gene convertant, or forward mutations; negative in Bacillus subtilis "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (*E.*

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.*5.4*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 (5.7)].*

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 (5.10)].*

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 (5.16)]*.

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 (5.8, 5.11)].*

Orthostatic Hypotension

Inform patients that, like other opioids, SUBLOCADE may produce orthostatic hypotension in ambulatory individuals *[see Warnings and Precautions (5.17)].*

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 (5.12)]*.

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
  - dizziness, or a decrease in consciousness
  - wheezing
- **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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