

Sublocade™ (buprenorphine extended-release) injection for subcutaneous use Ⓢ 100mg•300mg

FOR MODERATE TO SEVERE OPIOID USE DISORDER



SUBLOCADE: Product Details, Clinical Information and Price

This announcement contains inside information.

See Important Safety Information on page 6, including BOXED WARNING.

SUBLOCADE™ is the first once-monthly injectable buprenorphine formulation for the treatment of moderate to severe opioid use disorder (OUD) in patients who have initiated treatment with a transmucosal buprenorphine-containing product followed by dose adjustment for a minimum of seven days. SUBLOCADE should be used as part of a complete treatment program that includes counseling and psychosocial support. SUBLOCADE should only be prepared and administered by a healthcare provider¹.

SUBLOCADE represents an evidence-based, paradigm shift from how we approach treatment of moderate to severe opioid use disorder today.

SUBLOCADE was reviewed and approved by the U.S. Food and Drug Administration (FDA) with Fast Track and Priority Review designation.

SUBLOCADE is a buprenorphine medication-assisted treatment, or BMAT, and offers a new treatment choice at a time when doctors and patients need multiple medication-assisted treatment options.

How SUBLOCADE Works

SUBLOCADE is a scientific innovation that represents a new treatment option to help patients attain more illicit opioid-free weeks during their treatment program.

SUBLOCADE is an injectable, extended-release formulation that uses the ATRIGEL® technology to deliver buprenorphine at a controlled rate over a one month period. As a once-monthly injectable, SUBLOCADE removes the need for patients to remember to take their medication every day, while providing them with the opportunity to focus on psychosocial support, which is an important part of their treatment program¹.

Opioid dependence and other opioid-related physiological effects depend on the activation of mu-opioid receptors in a person's brain. Mu-opioid receptors in the brain are known to

mediate the subjective effects of opioids, including drug-liking, which is the pleasure associated with opioid use².

SUBLOCADE is the first and only therapy that, at steady state, delivers buprenorphine plasma concentrations at a sustained rate of at least 2 ng/mL, over a one month period.

- In the SUBLOCADE clinical trial program, average buprenorphine plasma concentrations of 2-3 ng/mL were associated with mu-opioid receptor occupancy $\geq 70\%$ and the reduction of illicit opioid use¹.
- The average concentration of SUBLOCADE at steady-state was 3.21 ng/mL and 6.54 ng/mL for the 100 mg and 300 mg doses, respectively¹.
- This is important because 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 symptoms¹.

Pharmacokinetic parameters ¹	SL buprenorphine daily stabilization ¹		SUBLOCADE ¹		
	12 mg (steady-state)	24 mg (steady-state)	300 mg (1 st injection)	100 mg (steady-state)	300 mg (steady-state)
Mean					
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	1.25	2.48	5.01

In the 12-week Opioid Blockade Study (RB-US-13-0002), SUBLOCADE 300 mg completely blocked the drug-liking effects of low (6 mg) and high (18 mg) doses of hydromorphone, a potent opioid pain medication that is commonly used in human studies to evaluate opioid drug-liking. Wide variation was seen for individual patients. For comparison, stabilization doses of sublingual buprenorphine (8-24 mg daily) failed to provide full blockade of high dose (18 mg) hydromorphone¹.

SUBLOCADE was evaluated in a 24-week, Phase 3 pivotal study (RB-US-13-0001) in which patients were randomized to one of the following three regimens: six once-monthly SUBLOCADE 300 mg doses; two once-monthly SUBLOCADE 300 mg doses followed by four once-monthly 100 mg doses; or 6 once-monthly injections of placebo. All regimens received weekly individualized drug counseling (IDC). Both dosage regimens of SUBLOCADE were shown to be superior to placebo in achieving more illicit opioid-free weeks ($p < 0.0001$)^{1,6}.

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

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 baseline¹.

The overall safety profile of SUBLOCADE, given by a healthcare provider in clinical trials, was consistent with the known safety profile of transmucosal buprenorphine, except for injection site reactions. In the clinical trials, 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 pain¹.

The Impact of the Opioid Addiction Epidemic

There is an urgent public health need for new treatment options for patients with OUD. An average of four people die of an opioid overdose every hour of every day³.

Data published in 2016 presented the total costs of prescription opioid use disorder and overdose in the U.S. at \$78 billion in 2013. Of that, only 3.6 percent, or about \$2.8 billion, was for treatment⁴. A separate, recent analysis by the White House Council of Economic Advisers estimated the total annual cost of prescription opioid overdose, abuse and dependence in the U.S. at \$504 billion in the year 2015⁵.

SUBLOCADE Price

The wholesale acquisition cost (WAC) of SUBLOCADE in the U.S. will be \$1,580 per monthly dose. The price for both the 100 mg and 300 mg doses of SUBLOCADE will be the same.

We want to help ensure our products are affordable to appropriate patients. We will be offering a SUBLOCADE co-pay assistance program, and also a SUBOXONE[®] (buprenorphine and naloxone) Sublingual Film co-pay assistance program, that may reduce initial out-of-pocket costs for eligible patients to as little as \$5 each month.

When determining the price of SUBLOCADE, a number of factors were considered, including the value this new innovation delivers to patients with OUD, the significant new scientific evidence generated in the robust clinical development program, and the potential benefits to the healthcare system.

Indivior has an ongoing, prospective, observational study (RECOVER[™]) to understand the health economic value of the clinical, environmental and socioeconomic characteristics of OUD patients.

Indivior is committed to investing in new science and new technologies to treat the chronic relapsing diseases and co-occurring disorders of addiction. Future revenues from SUBLOCADE will enable Indivior to continue to invest in studies, building on current technologies and developing new treatment innovations.

We have designed, invested in and will implement a restricted distribution system that is intended to ensure SUBLOCADE is only dispensed directly to a healthcare provider for administration so that our product does not end up in a patient's hand.

SUBLOCADE is priced similar to other long-acting injectable medicines in the OUD and central nervous system disease area where adherence to treatment is a key objective.

SUBLOCADE Dosing and Administration

SUBLOCADE is available in dosage strengths of 100 mg/0.5 mL and 300 mg/1.5 mL buprenorphine. Each dose is provided in a prefilled syringe with a 19 gauge 5/8-inch needle. The recommended dose of SUBLOCADE following induction and dose adjustment with transmuscular 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 use¹.

SUBLOCADE should only be prepared and administered by a healthcare provider. It should be administered monthly only by subcutaneous injection in the abdominal region. Each injection should be administered only using the syringe and safety needle included with the product¹.

Due to the chronic nature of OUD, the need for continuing medication-assisted treatment (MAT) should be re-evaluated periodically. There is no maximum recommended duration of maintenance treatment, and for some patients, treatment may continue indefinitely. If considering stopping treatment, healthcare providers should consider the clinical status of the patient.

Safety and Restricted Distribution

The overall safety profile of SUBLOCADE, given by a healthcare provider in clinical trials, was consistent with the known safety profile of transmucosal buprenorphine, except for injection site reactions. Common adverse reactions associated with buprenorphine included constipation, nausea, vomiting, abnormal liver enzymes, headache, sedation and somnolence. In the Phase 3 study, 16.5% of participants had at least one injection site reaction; none of these reactions were reported as serious and only one led to treatment discontinuation¹.

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 intravenously¹.

SUBLOCADE will be distributed through a restricted distribution system, which is intended to prevent the direct distribution of the medication to a patient. Because of the risk of serious harm or death that could result from intravenous self-administration, SUBLOCADE will only be available through restricted distribution under the SUBLOCADE Risk Evaluation and Mitigation Strategy (REMS) Program. Pursuant to the SUBLOCADE REMS, all healthcare settings and pharmacies that order and dispense SUBLOCADE must be certified, and establish processes and procedures to verify the medication is dispensed directly to a healthcare provider for administration by a healthcare provider. Moreover, certified healthcare settings and pharmacies must not distribute, transfer, loan, or sell SUBLOCADE¹.

About SUBLOCADE™

INDICATION 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 a dose adjustment period for a minimum of seven days.

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

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.
- 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.

IMPORTANT SAFETY INFORMATION

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

CONTRAINDICATIONS

SUBLOCADE should not be administered to patients who have been shown to be hypersensitive to buprenorphine or any component of the ATRIGEL[®] delivery system

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse: SUBLOCADE contains buprenorphine, a Schedule III controlled substance that 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.

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.

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

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

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

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

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

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.

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.

The full prescribing information, including BOXED WARNING, for SUBLOCADE can be found here: <http://indivior.com/wp-content/uploads/2017/11/SUBLOCADE-Prescribing-Information.pdf>.

About SUBOXONE® (BUPRENORPHINE AND NALOXONE) SUBLINGUAL FILM (CIII)

Indication

SUBOXONE® (buprenorphine and naloxone) Sublingual Film (CIII) is a prescription medicine indicated for treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

Treatment should be initiated under the direction of healthcare providers qualified under the Drug Addiction Treatment Act.

Important Safety Information

Do not take SUBOXONE Film if you are allergic to buprenorphine or naloxone as serious negative effects, including anaphylactic shock, have been reported.

SUBOXONE Film can be abused in a manner similar to other opioids, legal or illicit.

SUBOXONE Film contains buprenorphine, an opioid that can cause physical dependence with chronic use. Physical dependence is not the same as addiction. Your healthcare provider can tell you more about the difference between physical dependence and drug addiction. Do not stop taking SUBOXONE Film suddenly without talking to your healthcare provider. You could become sick with uncomfortable withdrawal symptoms because your body has become used to this medicine.

SUBOXONE Film can cause serious life-threatening breathing problems, overdose and death, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other medications that act on the nervous system (ie, sedatives, tranquilizers, or alcohol). It is extremely dangerous to take nonprescribed benzodiazepines or other medications that act on the nervous system while taking SUBOXONE Film.

You should not drink alcohol while taking SUBOXONE Film, as this can lead to loss of consciousness or even death.

Death has been reported in those who are not opioid dependent.

Your healthcare provider may monitor liver function before and during treatment.

SUBOXONE Film is not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. However, SUBOXONE Film may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone.

Keep SUBOXONE Film out of the sight and reach of children. Accidental or deliberate ingestion of SUBOXONE Film by a child can cause severe breathing problems and death.

Do not take SUBOXONE Film before the effects of other opioids (eg, heroin, hydrocodone, methadone, morphine, oxycodone) have subsided as you may experience withdrawal symptoms.

Injecting the SUBOXONE Film product may cause serious withdrawal symptoms such as pain, cramps, vomiting, diarrhea, anxiety, sleep problems, and cravings.

Before taking SUBOXONE Film, tell your healthcare provider if you are pregnant or plan to become pregnant. If you are pregnant, tell your healthcare provider as withdrawal signs and symptoms should be monitored closely and the dose adjusted as necessary. If you are pregnant or become pregnant while taking SUBOXONE Film, alert your healthcare provider immediately and you should report it using the contact information provided below. *

Opioid-dependent women on buprenorphine maintenance therapy may require additional analgesia during labor.

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.

Before taking SUBOXONE Film, talk to your healthcare provider if you are breastfeeding or plan to breastfeed your baby. The active ingredients of SUBOXONE Film can pass into your breast milk. You and your healthcare provider should consider the development and health benefits of breastfeeding along with your clinical need for SUBOXONE Film and should also consider any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Do not drive, operate heavy machinery, or perform any other dangerous activities until you know how SUBOXONE Film affects you. Buprenorphine in SUBOXONE Film can cause drowsiness and slow reaction times during dose-adjustment periods.

Common side effects of SUBOXONE Film include nausea, vomiting, drug withdrawal syndrome, headache, sweating, numb mouth, constipation, painful tongue, redness of the mouth, intoxication (feeling lightheaded or drunk), disturbance in attention, irregular heartbeat, decrease in sleep, blurred vision, back pain, fainting, dizziness, and sleepiness.

This is not a complete list of potential adverse events associated with SUBOXONE Film. Please see [full Prescribing Information](#) for a complete list.

*To report pregnancy or side effects associated with taking SUBOXONE Film, please call 1-877-782-6966. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

For more information about SUBOXONE Film, SUBOXONE[®] (buprenorphine and naloxone) Sublingual Tablets (CIII), or SUBUTEX[®] (buprenorphine) Sublingual Tablets (CIII), please see the respective [full Prescribing Information](#) and [Medication Guide](#) at www.suboxoneREMS.com.

References

1. SUBLOCADE[™] label on file.
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3. Centers for Disease Control and Prevention. Understanding the Epidemic. Retrieved from <https://www.cdc.gov/drugoverdose/epidemic/index.html>. Accessed October 28, 2017.
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5. White House Council of Economic Advisers. (2017). The Underestimated Cost of the Opioid Crisis. Retrieved from <https://www.whitehouse.gov/sites/whitehouse.gov/files/images/The%20Underestimated%20Cost%20of%20the%20Opioid%20Crisis.pdf>. Accessed November 20, 2017.
6. Indivior Data on File.

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