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

Dear Members of the Department of Health and Human Services for the State of Nevada,

SUBLOCADE® (buprenorphine extended-release) injection for subcutaneous (SC) use (CIII) is an extended-release formulation of buprenorphine, a mu-opioid partial agonist. SUBLOCADE is indicated 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 7 days. SUBLOCADE should be used as part of a complete treatment plan which includes counseling and psychosocial support.[1]

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.**

SUBLOCADE should only be administered subcutaneously once a month in the abdominal region by a healthcare professional (HCP). SUBLOCADE is available in dosage strengths of 100 mg/0.5 mL and 300 mg/1.5 mL and is provided in a prefilled syringe to a DATA 2000 waivered healthcare professional to be administered to a patient in a healthcare setting only.[1]

The recommended dosing regimen for SUBLOCADE is two monthly initial doses of 300 mg followed by 100 mg monthly maintenance doses; 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.[1]

SUBLOCADE was specifically designed to achieve and maintain a sustained buprenorphine plasma concentration at levels predicted to block the liking effects of opioids over the full monthly dosing interval.[2]

- In a Phase 2 study, the hypothesis that monthly administration of SUBLOCADE 300 mg would block the drug-liking effects of a mu-opioid full agonist (i.e., hydromorphone) was tested.
  - Subjects were challenged with placebo, 6-mg hydromorphone or 18-mg hydromorphone administered IM, at various times during the study. All 12 weeks of the treatment period demonstrated blockade for both 6 mg and 18 mg hydromorphone following SUBLOCADE injection.[1]
- A pivotal Phase 3 clinical study evaluated the safety and efficacy of two different dosing regimens of SUBLOCADE compared to placebo.
  - The primary efficacy endpoint was participants' percentage abstinence from opioid use, defined as the percentage of each participant's negative urine sample and self-reports of illicit opioid use from week 5 to week 24. [1]
  - The number of patients achieving treatment success (defined as patients with ≥80% opioid-free weeks) was statistically significantly higher in both groups receiving SUBLOCADE compared to placebo (28.4% [300 mg/ 100mg], 29.1% [300 mg/300 mg], 2% [placebo]).[1]
  - The percentage of subjects who were completers was statistically significantly higher in the 300 mg/100 mg and 300 mg/300 mg groups compared with the placebo group, respectively, as follows in the full analysis set (FAS): 61.3% (n = 119/194) and 64.3% (n = 126/196) versus 33.3% (n = 33/99) ($P < 0.0001$ for both active treatment groups compared to placebo).[1]
- RECOVER is a 24-month prospective observational study that assessed opioid abstinence and life changes in patients with OUD who had received once monthly SUBLOCADE injections for up to 12 months as part of either a separate randomized clinical efficacy trial and/or a separate open-label safety study prior to entering RECOVER. We can now report 12-month preliminary outcomes of sustained opioid abstinence, which is defined as no days of opioid use, self-reported for the past 6 months, collected at the 6- and 12-month visits. Among the 425 of 533 enrolled participants who completed the 12-month visit, 51% self-reported sustained abstinence over 12 months. Study limitations to consider include self-reported assessments which are subject to recall bias, and study enrollment being limited to clinical trial participants may reduce generalizability. In addition, approximately 27% of study participants continued to receive SUBLOCADE after the study began.[3,4]

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

CONTRAINDICATIONS: SUBLOCADE should not be administered to patients who are 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. Buprenorphine is sought by people with opioid use disorder and is subject to criminal diversion. Monitor patients for conditions indicative of diversion or progression of opioid dependence and addictive behaviors.
- **Risk of Life-Threatening Respiratory Depression and Concomitant Use of Benzodiazepines or Other CNS Depressants with Buprenorphine**: Buprenorphine has been associated with life-threatening respiratory depression, overdose, and death, particularly when misused by self-injection or with concomitant use of benzodiazepines or other CNS depressants, including alcohol. Warn patients of the potential danger of self-administration of benzodiazepines, other CNS depressants, opioid analgesics, and alcohol while under treatment with SUBLOCADE. Counsel patients that such medications should not be used concomitantly unless supervised by a healthcare provider. Use 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). Opioids can cause sleep-related breathing disorders; e.g., central sleep apnea (CSA), sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. Consider decreasing the opioid using best practices for opioid taper if CSA occurs.
- **Neonatal Opioid Withdrawal Syndrome**: Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy. NOWS may be life-threatening if not recognized and treated in the neonate. Newborns should be observed for signs of NOWS and managed accordingly. Advise pregnant women receiving opioid addiction treatment with SUBLOCADE of the risk of neonatal opioid withdrawal syndrome.
- **Adrenal Insufficiency**: Adrenal insufficiency has been reported with opioid use. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off the opioid.
- **Discontinuation of SUBLOCADE Treatment**: Due to the long-acting nature of SUBLOCADE, if treatment is discontinued, monitor patients for several months for withdrawal and treat appropriately. 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.
- **Risk of Hepatitis, Hepatic Events**: Because cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine, monitor liver function tests prior to treatment and monthly during treatment.
- **Hypersensitivity Reactions**: Hypersensitivity to buprenorphine-containing products have been reported most commonly as rashes, hives, and pruritus. Some cases of bronchospasm, angioneurotic edema, and anaphylactic shock have also been reported.
- **Precipitation of Opioid Withdrawal in Patients Dependent on Full Agonist Opioids:** 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.
- **Risks Associated With Treatment of Emergent Acute Pain:** When patients need acute pain management, or may require anesthesia, treat patients receiving SUBLOCADE currently or within the last 6 months with a non-opioid analgesic whenever possible. If opioid therapy is required, patients may be treated with a high-affinity full opioid analgesic under the supervision of a physician, with particular attention to respiratory function, as higher doses may be required for analgesic effect and therefore, a higher potential for toxicity exists with opioid administration. 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.
- **Use in Opioid Naïve Patients**: Because death has been reported for opioid naïve individuals who received buprenorphine sublingual tablet, SUBLOCADE is not appropriate for use in opioid naïve patients.
- **Use in Patients With Impaired Hepatic Function**: Because buprenorphine levels cannot be rapidly decreased, SUBLOCADE is not recommended for patients with pre-existing moderate to severe hepatic impairment. 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.
- **Use in Patients at Risk for Arrhythmia**: Buprenorphine has been observed to prolong the QTc interval in some patients participating in clinical trials. Avoid 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.

- **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. 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.
- **Orthostatic Hypotension**: Buprenorphine may produce orthostatic hypotension.
- **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.
- **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.
- **Effects in Acute Abdominal Conditions**: Buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.
- **Unintentional Pediatric Exposure**: Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it.

ADVERSE REACTIONS: Adverse reactions commonly associated with SUBLOCADE (≥5% of subjects) during clinical trials were constipation, headache, nausea, vomiting, increased hepatic enzymes, fatigue, and injection site pain and pruritus. This is not a complete list of potential adverse events. Please see the full Prescribing Information for a complete list.

DRUG INTERACTIONS

- **CYP3A4 Inhibitors and Inducers**: Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over- or under-dosing.
- **Serotonergic Drugs**: If concomitant use with serotonergic drugs is warranted, monitor for serotonin syndrome, particularly during treatment initiation, and during dose adjustment of the serotonergic drug.

Consult the full Prescribing Information for SUBLOCADE for more information on potentially significant drug interactions.

USE IN SPECIFIC POPULATIONS

Pregnancy: Opioid-dependent women on buprenorphine maintenance therapy may require additional analgesia during labor.
Lactation: Buprenorphine passes into the mother's milk. Advise breastfeeding women to monitor the infant for increased drowsiness and breathing difficulties.
Fertility: Chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible.
Geriatric Patients: Monitor geriatric patients receiving SUBLOCADE for sedation or respiratory depression.

To report pregnancy or side effects associated with taking SUBLOCADE, please call 1-877-782-6966.

We thank you for allowing us to review today some key information about SUBLOCADE, including safety and dosing information, rationale for development of SUBLOCADE, notable clinical trials, as well as additional evidence – first for real world efficacy and outcomes and secondly for safety related to SUBLOCADE and patient and healthcare impact. Please consult the accompanying full Prescribing Information for SUBLOCADE, including BOXED WARNING, and Medication Guide, for additional safety information. For REMS information visit www.sublocadeREMS.com.

Publication references:

1. SUBLOCADE® (buprenorphine extended-release) Injection for Subcutaneous Use (CIII) [prescribing information]. North Chesterfield, VA: INDIVIOR Inc.; February 2020.
2. Haight BR, et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2019 Feb 23; 393(10173):778-790.
3. Ling W, et al. Remission from chronic opioid use-Studying environmental and socio-economic factors on recovery (RECOVER): Study design and participant characteristics. Contemp Clin Trials. 2019 Jan; 76:93-103.
4. Ling W, et al. Recovery from OUD Post-Monthly Buprenorphine-XR Treatment: 12-Month Longitudinal Outcomes, Poster session presented at: The American Society of Addiction Medicine 50th Annual Conference; 2019 April 4-7; Orlando, FL.

Signature Page for MED-BAG-US-00092 v2.0

Regulatory Approval	Jan English Regulatory 31-Mar-2020 02:20:01 GMT+0000

Legal Approval	Bryant Godfrey Legal 31-Mar-2020 02:30:26 GMT+0000

Medical Approval	Cheri Lindberg Medical 31-Mar-2020 12:32:17 GMT+0000

Owner Sign-Off	Valerie Ng Job Owner 31-Mar-2020 20:18:54 GMT+0000

Coordinator Signoff	Cheyenne Rudd Coordinator 31-Mar-2020 20:37:55 GMT+0000

Signature Page for MED-BAG-US-00092 v2.0