PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N]SUBLOCADE™

Buprenorphine extended-release injection

Solution; 100 mg / 0.5 mL, 300 mg / 1.5 mL; Subcutaneous Injection

Partial Opioid Agonist

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SUBLOCADE is indicated for the management of moderate to severe opioid use disorder in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product.

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

SUBLOCADE must only be administered subcutaneously in the abdominal region by a healthcare provider (see **DOSAGE AND ADMINISTRATION (4)**).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available in pediatrics. SUBLOCADE is not indicated in pediatrics.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): There were no patients ≥ 65 years of age in the controlled clinical trial of SUBLOCADE. In general, drug use for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, respiratory and/or cardiac function, concomitant disease or other drug therapies. If the decision is made to prescribe SUBLOCADE to individuals 65 years of age or older, patients should be monitored for signs and symptoms of toxicity or overdose.

2 CONTRAINDICATIONS

SUBLOCADE is contraindicated in:

- patients who are hypersensitive to this drug or any ingredient in the formulation, including any non-medicinal ingredient, or any component of the ATRIGEL® Delivery System. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING (6)**).
- patients with severe respiratory insufficiency: e.g., acute or severe bronchial asthma, chronic obstructive airway, status asthmaticus, acute respiratory depression and/or cor pulmonale.
- patients with severe hepatic impairment.
- patients with acute alcoholism or delirium tremens.
- patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis). Patients with severe central nervous system (CNS) depression, increased cerebrospinal or intracranial pressure, and head injury.
- patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- patients with convulsive or seizure disorders.
- congenital Long QT Syndrome or QT prolongation at baseline.
- uncorrected hypokalemia, hypomagnesemia, or hypocalcemia.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Incorrect Administration
Do not administer intravenously OR intramuscularly. SUBLOCADE forms a solid mass following subcutaneous administration. Serious harm or death could result if administered intravenously (see WARNINGS AND PRECAUTIONS (7)).

Limitations of Use
SUBLOCADE should only be administered by a healthcare provider.

Addiction, Abuse, and Misuse
Abuse and diversion of buprenorphine component of SUBLOCADE is possible. All patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS (7)).

Use During Pregnancy
SUBLOCADE should not be used in women of childbearing potential who are not using an effective and reliable method of contraception. SUBLOCADE should not be administered to pregnant women unless in the judgment of the physician, the potential benefit to the mother outweighs the risk to the fetus (see WARNINGS AND PRECAUTIONS, Special Populations (7.1), NON-CLINICAL TOXICOLOGY (16)).

Interaction with Alcohol
The co-ingestion of alcohol with SUBLOCADE should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS (7) and DRUG INTERACTIONS (9)).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of SUBLOCADE during pregnancy can result in a neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS (7)). Prolonged maternal use of opioids during pregnancy can also result in neonatal respiratory depression (see WARNINGS AND PRECAUTIONS (7), Pregnant Women, Labor or Delivery, Breastfeeding).

Interaction with other Central Nervous System Depressants
Risks from concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS (7), Neurologic and DRUG INTERACTIONS (9)).

- **Reserve concomitant prescribing of SUBLOCADE and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Consider dose reduction of CNS depressants in situations of concomitant prescribing.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

Cardiac
QTc prolongation (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, ACTION AND CLINICAL PHARMACOLOGY).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **FOR ABDOMINAL SUBCUTANEOUS INJECTION ONLY. SUBLOCADE must NOT be administered intravenously OR intramuscularly.**

- SUBLOCADE should only be administered by a healthcare provider.

- The use of SUBLOCADE in pregnant women or in women of childbearing potential requires that the benefits of its use be weighed against the risk to the fetus. The risks associated with using SUBLOCADE should be discussed with the patient. The use of a formulation allowing for dosage adjustment may be considered during pregnancy (see **WARNINGS AND PRECAUTIONS (7), Pregnant Women**).

- SUBLOCADE should be administered monthly only by subcutaneous injection in the abdominal region (see **DOSAGE AND ADMINISTRATION (4)**). Each injection should be administered only using the syringe and safety needle included with the product.

- Induction of patients with SUBLOCADE has not been studied.

Patient Selection

Patients appropriate for SUBLOCADE are adults who have agreed to be treated for opioid use disorder and who have undergone induction on a buprenorphine-containing product to suppress opioid withdrawal signs and symptoms (see below).

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 (see **WARNINGS AND PRECAUTIONS (7), Addiction, Abuse and Misuse**).

Due to the chronic nature of opioid use disorder, the need for continuing medication-assisted treatment plan should be re-evaluated periodically. If considering stopping treatment plan, the clinical status of the patient should be considered.

If SUBLOCADE is discontinued, 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.

4.2 Recommended Dose and Dosage Adjustment

Patients should first undergo induction and stabilization by initiating a transmucosal buprenorphine-containing product, delivering the equivalent of 8-24 mg/day of buprenorphine for a minimum of 7 days (see **ACTION AND CLINICAL PHARMACOLOGY (10)** and **CLINICAL TRIALS (14)**). Initiation with transmucosal buprenorphine-containing products should be based on instructions in the specific product label.

Following induction and stabilization, patients can be transitioned to SUBLOCADE starting with 300 mg/month for two months, followed by a maintenance dose of 100 mg/month. The

maintenance dose may be increased to 300 mg/month only if the patient does not demonstrate satisfactory clinical response to and can tolerate the 100 mg dose. In clinical trials, the 300 mg/month maintenance dose did not provide additional efficacy as compared to the 100 mg/month dose and was associated with a higher incidence of adverse events and study discontinuations. SUBLOCADE has a long half-life and should only be administered monthly. A minimum of 26 days is required between consecutive doses.

The clinical efficacy of starting the SUBLOCADE part of the treatment at 100 mg has not been studied.

4.3 Administration

IMPORTANT INFORMATION:

- For abdominal subcutaneous injection only.
- To be administered by a health care 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 the time of administration.

Important Information about the TERUMO SurGuard3® Safety Hypodermic Needle

Non-toxic. Non-pyrogenic. The device has no components made of natural rubber latex.

The TERUMO SurGuard3 Safety Hypodermic Needle is packaged with SUBLOCADE. No other needle should be used with SUBLOCADE. After withdrawal of the needle from the body, the attached needle safety sheath can be manually activated to cover the needle immediately after use to minimize risk of accidental needle-stick.

WARNINGS

- Handle With Care To Avoid Needle Sticks.
- Use Once and Discard Immediately In Accordance With Local Safety Standards.

CAUTIONS

- If needle is bent or damaged, do not attempt to straighten needle. Do not use the product.
- Do not attempt to deactivate the safety device by forcing the needle out of the safety sheath.
- For single use only. Do not reuse. Do not resterilize.

PRECAUTIONS

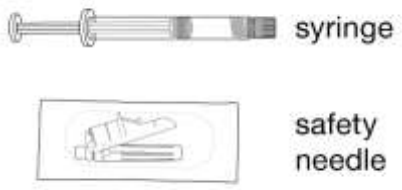
- Keep hands behind needle at all times during use and disposal.
- Observe universal precautions on all patients.
- Do not use if the unit package or product has been damaged or contaminated.
- Do not store at extreme temperature and humidity. Avoid direct sunlight.

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.

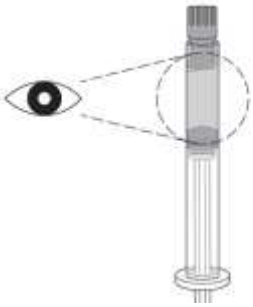
Figure 1



STEP 2 CHECK THE LIQUID CLARITY

Inspect the medication visually to make sure it does not contain contaminants or particles. SUBLOCADE ranges from colourless to yellow to amber. Variations of colour within this range do not affect the potency of the product.

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

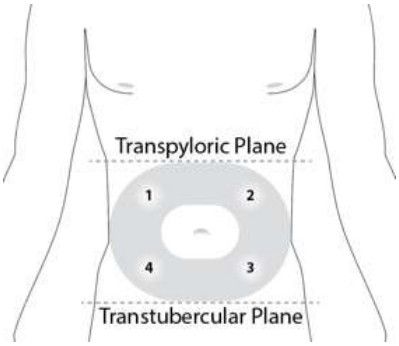
Choose an injection site on the abdomen between the transpyloric and transtubercular planes with adequate subcutaneous tissue that is free of skin conditions (e.g. nodules, lesions, excessive pigment). It is recommended that the patient is in the supine position.

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

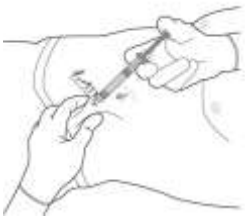
STEP 7 INJECT THE MEDICATION

SUBLOCADE is for subcutaneous injection only. Do not inject intravenously OR intramuscularly.

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 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.

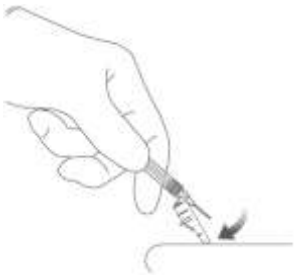
Figure 8

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.

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 that could cause irritation of the injection site.

4.4 Reconstitution

Not Applicable.

4.5 Missed Dose

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. Unavoidable occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.

4.6 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. The residual plasma concentrations from previous injections will decrease gradually over subsequent months (see **ACTION AND CLINICAL PHARMACOLOGY (10)**). Patients who have the depot removed should be monitored for signs and symptoms of withdrawal and treated appropriately (see **WARNINGS AND PRECAUTIONS (7)**).

5 OVERDOSAGE

The manifestations of acute overdose include pinpoint pupils, blue or purple lips, sedation, slow heart rate, hypotension, respiratory depression, and death. Nausea and vomiting may also be observed.

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 of naloxone 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.

In an individual physically dependent on opioids, administration of naloxone may precipitate an acute opioid withdrawal syndrome. The severity of the withdrawal will depend on the degree of physical dependence and the dose of the naloxone administered. If a serious respiratory depression in the physically dependent patient is treated, naloxone should be administered with caution.

Acute neonatal opioid withdrawal syndrome (acute NOWS), unlike acute opioid withdrawal syndrome in adults, may be life-threatening in the neonate. Naloxone dosing should be very cautious to avoid triggering iatrogenic acute NOWS in the neonate (see **WARNINGS AND PRECAUTIONS (7)**, **Neonatal Opioid Withdrawal Syndrome**).

For management of a suspected drug overdose, contact your regional poison control center.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Extended-release solution for injection, 100 mg / 0.5 mL and 300 mg / 1.5 mL	*N*-methyl-2-pyrrolidone (NMP) 50:50 Poly(DL-lactide-co-glycolide) (PLGH)

SUBLOCADE is a clear, viscous, colourless 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 (see **ACTION AND CLINICAL PHARMACOLOGY (10), Mechanism of Action**).

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. Each dose is provided in a sterile prefilled syringe with a 19 G 5/8-inch (16 mm) needle.

The following Table 2 presents the delivered amounts of the raw materials and the approximate delivered volume for the two dosage strengths.

Table 2 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
50:50 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
Size of Syringe	1 mL	2.25 mL

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General Precautions

SUBLOCADE is indicated for the management of moderate to severe opioid use disorder in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product, and should be used as part of a complete treatment plan that includes counseling and psychosocial support (For the full wording, see **INDICATIONS (1)**).

Risk of Serious Harm or Death with Intravenous Administration

Intravenous injection presents significant risk of serious harm or death as SUBLOCADE forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life-threatening pulmonary emboli, could result if administered intravenously. **Do not administer intravenously OR intramuscularly**.

Addiction, Abuse and Misuse

SUBLOCADE contains buprenorphine, a schedule I controlled substance that can be abused similar to other opioids. Buprenorphine is sought by people with opioid use disorders and is subject to criminal diversion. This should be considered when prescribing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines. Consider these risks and the patient's stability in treatment for opioid use disorder when determining whether SUBLOCADE is appropriate for the patient.

Proper assessment of the patient, periodic re-evaluation of therapy, and proper handling and storage of SUBLOCADE are appropriate measures that help to limit misuse, abuse, and diversion of opioid drugs.

Monitor all patients receiving SUBLOCADE and refer patients who have conditions indicative of diversion or progression of opioid dependence and addictive behaviors to more intensive and structured treatment plans for substance use.

SUBLOCADE is supplied in sterile prefilled syringes and is intended for administration only by subcutaneous injection in an abdominal region by a healthcare provider. The entire contents of the sterile 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 disposed of in an appropriate manner (see **STORAGE, STABILITY AND DISPOSAL (11)**).

SUBLOCADE is injected as a solution, and the subsequent precipitation of the poly (DL-lactide-co-glycolide) polymer creates a mass which contains buprenorphine. After initial formation of the depot, buprenorphine is released via diffusion from, and the biodegradation of, the mass. Clinical monitoring for evidence at the injection site of tampering or attempting to remove the mass 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.

Abuse Deterrence Studies

SUBLOCADE has physiochemical properties designed for extended-release after the subcutaneous injection. It utilizes a drug delivery system that forms a mass after subcutaneous injection.

In Vitro Testing

Results of *in vitro* testing suggest that it would be difficult to prepare a powder suitable for insufflation or inhalation from either SUBLOCADE or the excised depot. However, in vitro testing showed that buprenorphine can be extracted from SUBLOCADE at levels that could potentially be abused.

In vitro testing also suggests attempts to abuse either SUBLOCADE or the excised depots via intravenous injection without manipulation would not be successful. SUBLOCADE forms a solid mass upon contact with body fluids. Therefore, intravenous injection presents significant risk of serious harm or death. Intramuscular injection presents risk of tissue damage (see **WARNINGS AND PRECAUTIONS (7), DOSAGE AND ADMINISTRATION (4)**).

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following long-term 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.

Carcinogenesis and Mutagenesis

See **NON-CLINICAL TOXICOLOGY (16), Carcinogenesis, Mutagenesis, Impairment of Fertility**.

Cardiovascular

Like other opioids, SUBLOCADE may produce orthostatic hypotension in ambulatory patients.

QTc prolongation

Products containing buprenorphine have been shown to be associated with QTc prolongation (see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology (10)**). SUBLOCADE has been observed to prolong the QTc interval in some subjects participating in clinical trials.

SUBLOCADE should not be used 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), Class IC antiarrhythmic medications (e.g., flecainide, propafenone) or Class III antiarrhythmic medications (e.g. amiodarone).

QTc prolongation may lead to an increased risk of ventricular arrhythmias including torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death. Particular care should be exercised when administrating SUBLOCADE to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug (see **DRUG INTERACTIONS (9)**).

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age ≥65 years; baseline prolongation of the QTc interval; presence of pathological genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug. Patients should be advised to contact their healthcare provider immediately to report any new chest pain or discomfort, changes in heartbeat, palpitations, dizziness, lightheadedness, fainting, or changes in or new use of other medications.

The use of SUBLOCADE in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Dependence

Dependence and Risk of Opioid Withdrawal with Discontinuation of SUBLOCADE

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset.

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

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 **ACTION AND CLINICAL PHARMACOLOGY (10)**). Based on observed plasma levels at steady-state and given the long plasma terminal half-life of SUBLOCADE (43-60 days), therapeutic levels are expected to remain for approximately 2 to 5 months depending on the dosage administered (100 or 300 mg, respectively).

Patients who elect to discontinue SUBLOCADE should be monitored for withdrawal signs and symptoms.

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy (see **WARNINGS AND PRECAUTIONS (7)**).

Driving and Operating Machinery

Buprenorphine 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. Patients should be cautioned about driving or operating hazardous machinery until they are reasonably certain that SUBLOCADE therapy does not adversely affect their ability to engage in such activities.

Elevation of Cerebrospinal Fluid Pressure

Buprenorphine, like other opioids, 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, or changes in the perception of pain as a symptom of disease and may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease. As buprenorphine is an opioid, pain as a symptom of disease may be attenuated.

Gastrointestinal Effects

Effects in Acute Abdominal Conditions

As with other opioids, buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

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.

Hepatic/Biliary/Pancreatic

Hepatitis, Hepatic Events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing 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 the controlled clinical trial of SUBLOCADE, frequency of adverse events associated with hepatic disorders was 7.1% in SUBLOCADE arms vs 1% in placebo. A total of 9 patients (4.5%) in 300/100 mg arm and 16 patients (7.9%) in SUBLOCADE 300/300 mg arm experienced ALT and AST levels ≥3 X ULN (Placebo: 3 patients or 3%). In the same study, 3 patients (1.5%) in SUBLOCADE 300/300 mg arm discontinued the trial due to adverse event of hepatic injury vs 0% in SUBLOCADE 300/100 mg or placebo (see **ADVERSE REACTIONS (8), Liver Enzyme Abnormalities**).

Prior to initiation of SUBLOCADE, liver function tests should be conducted, to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. An etiological evaluation should be performed when a hepatic event is suspected.

Use in Patients with Impaired Hepatic Function

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

Because of the long-acting nature of the product, adjustments to SUBLOCADE dosing are not rapidly reflected in plasma buprenorphine levels. Because buprenorphine levels cannot be rapidly decreased, caution should be exercised in treating patients with pre-existing moderate hepatic impairment with SUBLOCADE. SUBLOCADE should not be given to patients with pre-existing severe hepatic impairment (see **CONTRAINDICATIONS (2)**).

Patients with moderate hepatic impairment or those who develop moderate 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. Patients who develop severe hepatic impairment while receiving SUBLOCADE should be discontinued and additional doses should not be administered (see **ACTION AND CLINICAL PHARMACOLOGY (10)**, **Pharmacokinetics**, **Special Populations and Conditions**).

Use in Patients with Impaired Renal Function

Clinical studies of SUBLOCADE did not include patients with severe renal impairment. Following intravenous administration, less than 1% of buprenorphine is excreted in urine as unchanged drug. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following intravenous administration of 0.3 mg buprenorphine (see **ACTION AND CLINICAL PHARMACOLOGY (10), Renal Impairment**).

Immune

Allergic Reactions

Cases of hypersensitivity to buprenorphine-containing products have been reported both in clinical trials and in the post-marketing experience. Cases of bronchospasm, angioneurotic oedema, 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 (2)**).

Monitoring and Laboratory Tests

Baseline liver function tests and documentation of viral hepatitis status should be performed prior to commencing therapy. Regular monitoring of liver function is also recommended. Patients who are positive for viral hepatitis, on concomitant medicinal products and/or have existing liver dysfunction are at greater risk of liver injury.

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 **WARNINGS AND PRECAUTIONS (7), Special Populations**, **Pregnant Women**).

Advise pregnant women receiving SUBLOCADE of the risk of NOWS and ensure that appropriate treatment will be available (see **WARNINGS AND PRECAUTIONS (7), Special Populations**, **Pregnant Women**). 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, with their patients, the importance of management of opioid addiction throughout pregnancy.

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol)

Buprenorphine should be used with caution during concomitant administration of other opioids, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active antiemetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

Alcohol should not be consumed with SUBLOCADE as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS (2)**, **ADVERSE REACTIONS (8)** and **DRUG INTERACTIONS (9)**).

Peri-Operative Considerations

Pain Management

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.

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

Respiratory

Risk of Respiratory and Central Nervous System (CNS) Depression

Buprenorphine, particularly when taken by the intravenous route, in combination with benzodiazepines or other CNS depressants (including alcohol), has been associated with significant respiratory depression and death. Many, but not all, post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines involved misuse by self-injection. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other CNS depressant drugs.

SUBLOCADE should be prescribed with caution to patients taking benzodiazepines or other drugs that act on the CNS, regardless of whether these drugs are taken on the advice of a healthcare provider or are being abused/misused. If it is anticipated that patients will begin taking benzodiazepines or other drugs after beginning treatment with SUBLOCADE, healthcare providers should assess the risks and benefits of initiating SUBLOCADE for those patients and should consider starting treatment with a lower dose of benzodiazepines or CNS depressants. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with SUBLOCADE (see **DRUG INTERACTIONS (9)**).

SUBLOCADE should be used 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).

Patients receiving buprenorphine in the presence of opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics, or other CNS depressants (including alcohol) may exhibit increased CNS depression.

If SUBLOCADE is discontinued, its extended-release characteristics should be considered, and the patient should be monitored for several months.

Serotonin Syndrome:

Buprenorphine could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. antidepressants, migraine medications). Treatment with the serotoninergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Buprenorphine should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS (9)**).

Sexual Health

Reproduction/Function/Fertility

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS (8)**, **Post-Market Adverse Reactions**).

Chronic use of opioids may also cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible (see **ADVERSE REACTIONS (8)**).

General Precautions

As with other opioids, SUBLOCADE should be administered with caution in debilitated patients and those with myxedema or hypothyroidism; adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

Unintentional Pediatric Exposure

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

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 should not be administered to opioid naïve patients.

7.1 Special Populations

7.1.1 Pregnant Women

Reproductive and developmental toxicity studies in animals have demonstrated a range of adverse effects on embryo-fetal, fetal, pre- and postnatal development with SUBLOCADE, buprenorphine, and most notably with the excipient *N*-methyl-2-pyrrolidone (NMP). Studies with animals exposed to NMP via inhalation have demonstrated fetotoxic effects at equivalent doses of NMP delivered by SUBLOCADE. Fetal malformations and resorptions have also been reported following oral administration of 3 times the human maximum daily dose (MDD) of NMP via SUBLOCADE based on body surface area comparison. In humans, it has not been established whether SUBLOCADE or its active or inactive components can affect reproductive capacity or cause developmental toxicity as there are no adequate and well-controlled studies of use in pregnant women. (see **NON-CLINICAL TOXICOLOGY (16)**).

Buprenorphine can cross the placental barrier and be life-threatening to the fetus if administered to the mother. In addition, there is evidence from animal studies that NMP may also cross the placental barrier.

Given the high degree of uncertainty in terms of safety to both the mother and unborn child, SUBLOCADE use should be avoided in women of childbearing potential who are not using an effective and reliable method of contraception or are judged not able to comply with contraceptive methods. If SUBLOCADE is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus and if necessary, alternative treatments should be considered (see **SERIOUS WARNINGS AND PRECAUTIONS BOX** (**3**)).

Untreated opioid addiction in pregnancy is associated with adverse obstetrical outcomes such as low birth weight, preterm birth, and fetal death. In addition, untreated opioid addiction often results in continued or relapsing illicit opioid use.

Neonatal opioid withdrawal syndrome (NOWS) may occur in newborn infants of mothers who are receiving treatment with SUBLOCADE. It presents as irritability, hyperactivity and abnormal

sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and/or failure to gain weight. Signs of (NOWS) usually occur in the first days after birth. The duration and severity of NOWS may vary. Based on the currently available data, the incidence of NOWS is not clear and there does not appear to be a dose-response relationship. Observe newborns for signs of NOWS and manage accordingly (see **WARNINGS AND PRECAUTIONS (7).**

Studies have been conducted to evaluate neonatal outcomes in women exposed to buprenorphine during pregnancy. Limited data on malformations from trials, observational studies, case series, and case reports on buprenorphine use in pregnancy do not indicate an increased risk of major malformations specifically due to buprenorphine. Pregnancy in an opioid dependent woman poses challenges to treating physicians and potential hazards for the fetus including control of illicit drug, nicotine and alcohol use, infections, premature birth, abortion, low birth weight, toxaemia, third trimester bleeding, malpresentation, puerperal morbidity, fetal distress, meconium aspiration, narcotic withdrawal, postnatal growth deficiency, microcephaly, (neuro-) developmental disorders and increased neonatal mortality.

Labour or Delivery

Life-threatening respiratory depression may occur in the newborn if any opioid is administered to the mother during pregnancy. This risk is further increased if another opioid is administered during labour and delivery. Closely monitor neonates for signs of respiratory depression. An opioid antagonist such as naloxone should be available for reversal of opioid induced respiratory depression in the neonate. Naloxone dosing in neonates should be conducted with caution to avoid triggering an iatrogenic acute NOWS (see **WARNINGS AND PRECAUTIONS (7)**). In addition, the effect of NMP exposure to the mother or neonate during labour or delivery has not been established. Therefore, the benefits to the mother and/or neonate of SUBLOCADE use during labour and delivery should be weighed carefully against the risk of potential NMP-mediated adverse effects.

7.1.2 Breastfeeding

Buprenorphine and its metabolite norbuprenorphine are excreted in human milk and infant urine. Life-threatening respiratory depression may occur in the neonate if opioids are administered to the nursing mother.

It is not known whether NMP is transferred to the neonate via breastfeeding. However, several studies in rats have demonstrated that daily maternal exposure to NMP during the post-natal period may contribute to decreased pup weight and survival. In a pre-and postnatal development study in rats, SUBLOCADE was administered subcutaneously to pregnant animals once during implantation (on Gestation Day 7) and once during weaning (on Lactation Day 7). There were no major adverse effects in terms of offspring survival, sexual maturation, behavioral assessment, or reproductive performance at up to 300 mg/kg (approximately 10 times the human recommended dose). A reduction in F1 body weights was observed in the two groups administered higher doses of buprenorphine (150 and 300 mg/kg buprenorphine) throughout the lactation and early post-weaning periods, however, body weights returned to saline control levels during the F1 growth phase.

It is therefore advised that serious caution be exercised when SUBLOCADE is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBLOCADE and any potential adverse effects on the breastfed child from the drug; including the excipient NMP, or from the underlying maternal condition. Limited data from published literature have not reported adverse reactions in

breastfed infants exposed to buprenorphine through breast milk, however nursing mothers taking SUBLOCADE should be advised to monitor the infant for increased drowsiness and breathing difficulties and infants should be regularly monitored by a health care professional.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available in pediatrics. SUBLOCADE is not indicated in pediatrics.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): There were no patients ≥ 65 years of age in the controlled clinical trial of SUBLOCADE. In general, drug use for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, respiratory and/or cardiac function, concomitant disease or other drug therapies. If the decision is made to prescribe SUBLOCADE to individuals 65 years of age or older, patients should be monitored for signs and symptoms of toxicity or overdose.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Clinically significant respiratory depression and death may occur in patients receiving SUBLOCADE, particularly when used in combination with benzodiazepines and other CNS depressants such as other opioids or alcohol (see **WARNINGS AND PRECAUTIONS (7)**).

The most commonly reported treatment related adverse reactions reported during the pivotal clinical studies (≥5% of subjects) were constipation, nausea, vomiting, headache, fatigue, insomnia, hepatic enzymes increased, and injection site pain and pruritus.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of SUBLOCADE was evaluated in a total of 1083 opioid dependent subjects who received at least 1 dose of SUBLOCADE (948 of whom received at least 1 dose of 300 mg) during the clinical development program, with 404 subjects in the pivotal Phase 3 study and 679 in the Phase 1, Phase 2 and Phase 3 long term safety studies. In these studies, there were a total of 570 subjects who received at least 6 injections of SUBLOCADE and 395 subjects who received 12 injections.

Table 3 shows the adverse drug reactions (ADRs) reported for the groups receiving SUBLOCADE and placebo following administration in the 6-month, double-blind, placebo-controlled study. Both dosing regimens of SUBLOCADE (300 mg for 2 months then either 100 mg or 300 mg for 4 months) were combined because there were no clinically important differences in ADRs between these groups. The safety profile for SUBLOCADE is consistent with the known safety profile of transmucosal buprenorphine.

Adverse drug reactions [by MedDRA Preferred Terms] reported in at least 1% of subjects receiving SUBLOCADE are grouped by System Organ Class.

Table 3 Adverse Drug Reactions for Phase 3 Double-Blind Study: ≥1% of Subjects Receiving SUBLOCADE

System Organ Class Preferred Term	**Placebo (N=100) n (%)**	**SUBLOCADE (N=404) n (%)**
Gastrointestinal disorders		
Constipation	0	35 (8.7)
Nausea	5 (5.0)	34 (8.4)
Vomiting	4 (4.0)	30 (7.4)
Abdominal pain upper	1 (1.0)	7 (1.7)
General disorders and administration site conditions		
Injection site pruritus	4 (4.0)	32 (7.9)
Injection site pain	3 (3.0)	22 (5.4)
Fatigue	3 (3.0)	20 (5.0)
Injection site erythema	0	15 (3.7)
Injection site bruising	0	4 (1.0)
Injection site induration/nodule	0	4 (1.0)
Injection site swelling/oedema	0	4 (1.0)
Investigations / Hepatobiliary disorders		
Hepatic enzyme increased*	1 (1.0)	29 (7.2)
Nervous system disorders		
Headache	6 (6.0)	36 (8.9)
Somnolence	0	14 (3.5)
Sedation	0	10 (2.5)
Dizziness	2 (2.0)	8 (2.0)
Lethargy	1 (1.0)	4 (1.0)
Skin and subcutaneous tissue disorders		
Pruritus	0	7 (1.7)
Rash	0	7 (1.7)

*Includes Hepatic enzyme increased, Liver function test abnormal, and elevations of ALT, AST, GGT, Alkaline phosphatase and/or bilirubin. There were no cases of severe drug-induced liver injury (Hy's Law).

Similar ADRs and frequencies were reported in subjects treated with SUBLOCADE in the 12-month long-term safety study and other Phase 1 and 2 studies, with the exception of constipation reported in greater than 10% of subjects and abdominal pain reported in greater than 1% of subjects.

8.3 Less Common Clinical Trial Adverse Reactions

Treatment-emergent adverse reactions reported as less common (<1%) during the pivotal phase 3 double-blind study and the Phase 3 long term safety study of SUBLOCADE included:

Eye disorders: Vision blurred

General disorders and administration site conditions: Injection site discomfort, injection site

reaction, injection site ulcer

Hepatobiliary disorders: Hepatic function abnormal

Infections and infestations: Injection site cellulitis, injection site infection

Nervous system disorders: Dizziness postural, syncope

Psychiatric disorders: Euphoric mood, libido decreased

Reproductive system and breast disorders: Erectile dysfunction

Vascular disorders: Hypotension

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Liver Enzyme Abnormalities

In the pooled Phase 3 study data, 7 subjects (0.8%) had total bilirubin elevated above 2 x upper limits of normal (ULN) post-baseline: 6 subjects had maximal total bilirubin > 2 x ULN to < 5 x ULN and 1 had an elevation ≥ 5 x ULN. A total of 98 subjects (11.6%) had alanine aminotransaminase (ALT) > 3 x ULN and 98 subjects (11.6%) had aspartate aminotransferase (AST) > 3 x ULN. The large majority of these cases had confounding factors for liver enzyme elevation such as hepatitis C, chronic alcohol use or history of alcoholic hepatitis/pancreatitis, or elevated liver enzymes at screening and/or baseline. No subject in any treatment group met the criteria for severe drug-induced liver injury or Hy's Law (see **WARNINGS AND PRECAUTIONS (7), Hepatic/Biliary/Pancreatic**).

Injection Site Reactions

In the pivotal phase 3 study, 16% of SUBLOCADE-treated patients reported an injection site reaction (Placebo: 9%). Most reactions were mild to moderate except one case of severe injection site pruritus. None of the cases were serious. There was one case of discontinuation due to injection site ulcer (Table 4).

Table 4 Injection Site Adverse Drug Reactions Reported by ≥2 Subjects in the Phase 3 Double-Blind Study

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%)

8.5 Clinical Trial Adverse Reactions (Pediatrics)

Not Applicable.

8.6 Post-Market Adverse Reactions

The following post-marketing events were seen with other buprenorphine-containing products.

Nausea: Nausea is a common side effect with opioids and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment.

Constipation: Constipation is a known and common side effect of opioids, including buprenorphine. In some patients, particularly the elderly or bedridden, faecal impaction may result. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As faecal impaction may present as overflow diarrhoea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhoea.

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.

Buprenorphine used alone: Buprenorphine used alone for treatment of opioid dependence has been associated with the following signs and symptoms (> 1 %): constipation, headache, insomnia, asthenia, drowsiness, nausea and vomiting, fainting and dizziness, orthostatic hypotension, and sweating. Other adverse events (< 0.1 %) have been reported in association with buprenorphine alone. These are:

- respiratory depression (see **WARNINGS AND PRECAUTIONS (7) and DRUG INTERACTIONS (9)**);
- hepatic necrosis and hepatitis (see **WARNINGS AND PRECAUTIONS (7)**); and
- hallucinations.

Cases of bronchospasm, angioneurotic oedema and anaphylactic shock have also been reported.

In cases of drug abuse or intentional drug misuse, some adverse experiences attributed to the act of misuse rather than the medicinal product have included: local reactions, such as cellulitis or abscess that are sometimes septic, potentially serious acute hepatitis, pneumonia, endocarditis, and other serious infections. (see **WARNINGS AND PRECAUTIONS (7)**).

In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

NOWS has been reported among newborns of women who have received buprenorphine products during pregnancy. The syndrome may be milder and more protracted than that from short acting full mu-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history (see **WARNINGS AND PRECAUTIONS (7)**).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions Box

Serious Drug Interactions

- Patients taking SUBLOCADE together with alcohol or other CNS depressants may exhibit signs of increased CNS depression, e.g. respiratory depression, hypotension, profound sedation, coma or death.

- Risks from concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS).

  - Reserve concomitant prescribing of SUBLOCADE and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.

  - Consider dose reduction of CNS depressants in situations of concomitant prescribing.

  - Follow patients for signs and symptoms of respiratory depression and sedation.

9.2 Overview

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants:

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS (7)**). SUBLOCADE should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

QTc Interval-Prolonging Drugs

QTc Interval-Prolonging Drugs: The concomitant use of SUBLOCADE with other QTc interval-prolonging drugs should be avoided (see **WARNINGS AND PRECAUTIONS (7), Cardiovascular; ACTION AND CLINICAL PHARMACOLOGY (10), Cardiac Electrophysiology**). Drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc interval prolongation and/or torsade de pointes: Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide), Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone), Class 1C antiarrhythmics (e.g., flecainide, propafenone), antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol,

ziprasidone, risperidone), antidepressants (e.g., fluoxetine, citalopram, tricyclic/tetracyclic antidepressants [e.g., amitriptyline, imipramine, maprotiline]), opioids (e.g., methadone), macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, azithromycin, tacrolimus), quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin), pentamidine, antimalarials (e.g., quinine, chloroquine), azole antifungals (e.g., ketoconazole, fluconazole, voriconazole), domperidone, angrelide, ivabradine, 5-hydroxytryptamine (5-HT)3 receptor antagonists (e.g., ondansetron), tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, ceritinib, vandetanib), arsenic trioxide, histone deacetylase inhibitors (e.g., vorinostat), beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

Drugs that Affect Electrolytes: The use of SUBLOCADE with drugs that can disrupt electrolyte levels should be avoided. Drugs that can disrupt electrolyte levels include, but are not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high-dose corticosteroids; proton pump inhibitors (see **DRUG-DRUG INTERACTIONS**, Table 5).

9.3 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5 Clinically significant drug interactions with SUBLOCADE.

Drug	Source of Evidence	Clinical Impact	Intervention
Benzodiazepines	C, CT	There have been a number of reports regarding coma and death associated with the misuse and abuse of the combination of buprenorphine and benzodiazepines. In many, but not all of these cases, buprenorphine was misused by self-injection of crushed buprenorphine tablets. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists.	Closely monitor patients with concurrent use of SUBLOCADE and benzodiazepines. Warn patients that it is extremely dangerous to self-administer benzodiazepines while taking SUBLOCADE and warn patients to use benzodiazepines concurrently with SUBLOCADE only as directed by their healthcare provider.
Non-Benzodiazepine Central Nervous System (CNS) Depressants Alcohol, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids.	C, CT	Due to additive pharmacologic effects, the concomitant use of non-benzodiazepine CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS (7)**).
Naltrexone	CT, T	Naltrexone is an opioid antagonist that can block the pharmacological effects of buprenorphine.	For opioid dependent patients currently receiving SUBLOCADE, the antagonist naltrexone may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms. For patients currently receiving naltrexone, the intended

Drug	Source of Evidence	Clinical Impact	Intervention
			therapeutic effects of SUBLOCADE administration may be blocked by the naltrexone antagonist.
Inhibitors of CYP3A4 Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)	CT, T	The effects of co-administered CYP3A4 inhibitors on buprenorphine exposure in subjects treated with SUBLOCADE have not been studied; however, such interactions have been established in studies using sublingual buprenorphine. 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, particularly when an inhibitor is added after a stable dose of sublingual buprenorphine is achieved. The increase in exposure seen with sublingual buprenorphine is mainly attributed to the inhibition of first-pass metabolism as a fraction of the sublingually administered drug is swallowed. Buprenorphine does not undergo first-pass metabolism following subcutaneous injection of SUBLOCADE, resulting in a much lower norbuprenorphine-to-buprenorphine AUC ratio (0.20 to 0.40) compared to sublingual buprenorphine (0.70 to 2.11).	Monitor patients for respiratory depression and sedation at frequent intervals.
CYP3A4 Inducers Rifampin, carbamazepine, phenytoin, phenobarbital	T	The effects of co-administered CYP3A4 inducers on buprenorphine exposure in subjects treated with SUBLOCADE have not been studied. CYP3A4 inducers may induce the metabolism of buprenorphine and, therefore, may cause increased clearance of the drug which could lead to a decrease in buprenorphine plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome. Thus, monitor patients starting or ending the use of	If patients stabilized on SUBLOCADE require treatment with CYP3A4 inducers, they should be monitored for opioid withdrawal signs and symptoms.

Drug	Source of Evidence	Clinical Impact	Intervention
		CYP3A4 inducers for potential under-dosing of SUBLOCADE.	
Serotonergic Drugs Selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol, lithium, St. John's Wort and tapentadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).	C, CT	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome, a potentially life-threatening condition.	If concomitant use is warranted, carefully monitor the patient for signs and symptoms of serotonin syndrome, particularly during treatment initiation, and during dose adjustment of the serotonergic drug.

Drug	Source of Evidence	Clinical Impact	Intervention
Monoamine Oxidase Inhibitors (MAOIs) Phenelzine, tranylcypromine, linezolid	C, CT	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma).	The use of SUBLOCADE is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Diuretics	T	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.	Monitor patients for signs of diminished diuretics and/or effects on blood pressure and increase the dosage of the diuretic, as needed.
Anticholinergics	T	Concomitant use of anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.	Monitor patients for signs of urinary retention or reduced gastric motility.
Antiretrovirals	CT	Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine, and etravirine are known CYP3A4 inducers, whereas delaviridine is a CYP3A4 inhibitor. Significant pharmacokinetic interactions between NNRTIs and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects.	Exercise caution. Therapeutic concentration monitoring is recommended.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.4 Drug-Food Interactions

Interactions with food has not been studied.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been studied.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9.7 Drug-Lifestyle Interactions

Alcohol can increase the sedative effect of opioids. Alcoholic beverages should be avoided while taking SUBLOCADE.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

SUBLOCADE injection contains buprenorphine. Buprenorphine is a partial agonist at the mu-opioid receptor and the ORL-1 (nociceptin) receptor. It is also an antagonist at the kappa and delta-opioid receptors. Buprenorphine's activity in opioid maintenance treatment is attributed to its slowly reversible link with the mu-opioid receptors in the brain, which prolongs activity at the receptor, leading to reduced opioid withdrawal symptoms.

10.2 Pharmacodynamics

Mu-Opioid Receptor Occupancy and Association with Opioid Blockade

As demonstrated previously with sublingual administration of buprenorphine in opioid dependent individuals, at least 70% brain mu-opioid receptor occupancy by buprenorphine is required to block the subjective effects (opioid blockade) of full agonist-induced responses. An analysis of brain mu-opioid receptor occupancy and buprenorphine plasma concentrations demonstrated that opioid blockade requires buprenorphine plasma concentrations of $\geq$ 2 ng/mL on average.

Mu-Opioid Receptor Occupancy Study
In a Positron Emission Tomography study with SUBLOCADE in 2 patients with opioid use disorder, one patient received four 200 mg subcutaneously SUBLOCADE injections and the other received six 300 mg subcutaneously injections of SUBLOCADE. Results show that, in these two patients, 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.

Opioid Receptor Blockade Study
This study assessed the ability of SUBLOCADE to block the subjective drug-liking effects of 6 and 18 mg hydromorphone versus placebo in non-treatment-seeking patients with moderate to severe opioid use disorder. A total of 39 subjects were inducted and stabilized over 13-14 days on a sublingual buprenorphine product to reach a final buprenorphine dose between 8 and 24 mg/day. Subjects then received a subcutaneous injection of SUBLOCADE 300 mg on Day 1 (N=39) and a second injection on Day 29 (N=30). Using the Drug-Liking Visual Analog Scale

(VAS), challenges with placebo, 6 mg hydromorphone, or 18 mg hydromorphone were evaluated prior to the first injection of SUBLOCADE and then weekly for 4 weeks each after the first injection and for 8 weeks after the second injection.

Results indicate that SUBLOCADE blocked the subjective Drug Liking effects of both 6 mg and 18-mg hydromorphone doses for most VAS parameters over the 12-week course of the trial.

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 subjects had an increase from baseline QTc greater than 60 msec at any time [2/203 subjects (1.0%) in the 300 mg/100 mg group and 5/201 subjects (2.0%) in the 300 mg/300 mg group] and one subject in the 300 mg/300 mg group was found to have a QTc greater than 500 msec.

Physiological Effects

Buprenorphine in intravenous (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. In these studies, 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.

Limited data from clinical studies conducted with SUBLOCADE (50 to 300 mg) showed no incidences of temperature elevations, or clinically significant lowering of oxygen saturation.

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.

Cardiovascular System

Opioids may induce the release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Central Nervous System:

Opioids produce respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem centers to increases in CO_2 tension and to electrical stimulation.

Opioids depress the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Opioids cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone overdose.

Gastrointestinal Tract and Other Smooth Muscle:

Opioids cause a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Endocrine System:

Opioids may influence the hypothalamic-pituitary-adreno or -gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System:

In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

10.3 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 (see Table 6).

Table 6 Mean Pharmacokinetic Parameters Between of SUBLOCADE

Pharmacokinetic parameters	**SUBLOCADE**		
Mean	**300 mg# (1st injection)**	**100 mg* (steady-state)**	**300 mg* (steady-state)**
$C_{avg,ss}$ (ng/mL)	2.19	3.21	6.54
$C_{max,ss}$ (ng/mL)	5.37	4.88	10.12
$C_{min,ss}$ (ng/mL)	1.25	2.48	5.01
$AUC_{7\text{-}28\ days}$	--	1478	3006

#Exposure after 1 injection of 300 mg SUBLOCADE following 24 mg transmucosal buprenorphine stabilization
*Steady-state exposure after 4 injections of 100 mg or 300 mg SUBLOCADE, following 2 injections of 300 mg SUBLOCADE. $AUC_{7\text{-}28\ days}$ is a partial area under the plasma concentration-time curve from day 7 to day 28 post-injection.

Distribution:

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin. Once absorbed, it distributes extensively into the body, as evidenced by a large apparent volume of distribution.

Metabolism:

Buprenorphine is metabolized to its major metabolite, norbuprenorphine, primarily by CYP3A4 and to a lesser extent by CYP2C8. 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 very low compared to buprenorphine (AUC norbuprenorphine/buprenorphine ratio of 0.20 to 0.40).

Elimination:

Buprenorphine is 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. The apparent clearance of buprenorphine was between 80 to 103 L/h over the dose range of 50-300 mg.

Excretion:

A mass balance study of buprenorphine administered by intravenous 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).

Special Populations and Conditions

Based on population pharmacokinetic analyses, age, sex and race do not have a clinically meaningful effect on pharmacokinetics of SUBLOCADE. Clinical trials of SUBLOCADE included patients aged 18 - 63 years.

Pediatrics (<18 years of age): No data are available in pediatrics. SUBLOCADE is not indicated in pediatrics.

Geriatrics (≥65 years of age): There were no patients ≥65 years of age in the controlled clinical trial of SUBLOCADE. In general, drug use for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, respiratory and/or cardiac function, concomitant disease or other drug therapies. If the decision is made to prescribe SUBLOCADE to individuals 65 years of age or older, patients should be monitored for signs and symptoms of toxicity or overdose.

Hepatic Impairment:

Buprenorphine does not undergo first-pass metabolism following subcutaneous injection of SUBLOCADE.

The effect of hepatic impairment on the PK of SUBLOCADE has not been evaluated in a dedicated Phase I study. 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 score. Compared to healthy subjects, no clinically relevant changes in plasma buprenorphine levels were observed in subjects with mild hepatic impairment. However, buprenorphine plasma exposure was increased by 64% and 181% in subjects with moderate and severe hepatic impairment, respectively.

Therefore, SUBLOCADE should not be used in subjects with severe hepatic impairment (see **CONTRAINDICATIONS (2)**). Caution should be exercised when SUBLOCADE is administered to patients with moderate hepatic impairment. Patients who develop moderate hepatic impairment while being treated with SUBLOCADE should be monitored for signs and symptoms of toxicity or overdose caused by the increased levels of buprenorphine. Patients who develop severe hepatic impairment during SUBLOCADE treatment should be discontinued (see **CONTRAINDICATIONS (2)**, **WARNINGS AND PRECAUTIONS (7), Use in Patients with Impaired Hepatic Function**).

Renal Impairment:

Clinical studies of SUBLOCADE did not include subjects with severe renal impairment. Systemic clearance of buprenorphine is not significantly related to renal function, as buprenorphine clearance occurs primarily by hepatic extraction and metabolism. Less than 1% is excreted as unchanged buprenorphine in urine following intravenous buprenorphine administration. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following intravenous administration of 0.3 mg buprenorphine.

11 STORAGE, STABILITY AND DISPOSAL

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

Store at 2 - 8°C (35.6 - 46.4°F).

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

Discard SUBLOCADE if left at room temperature for longer than 7 days.

12 SPECIAL HANDLING INSTRUCTIONS

Handle SUBLOCADE with adequate security and accountability. After administration, syringes should be properly disposed per facility procedure.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

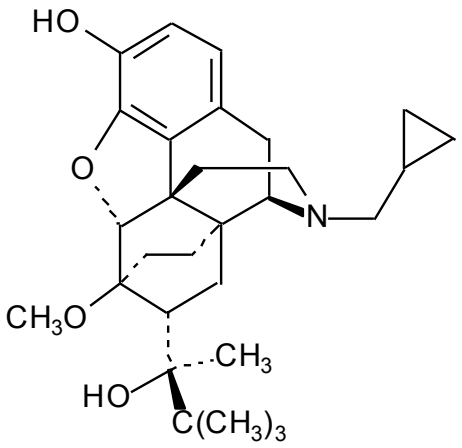
Drug Substance

Proper name: buprenorphine

Chemical name: (2S)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol

Molecular formula and molecular mass: $C_{29}H_{41}NO_4$; 467.6

Structural formula:



Physicochemical properties:

Physical Form:	Powder
Solubility:	6.95 µg/mL intrinsic (aqueous)
pKa:	9.8 and 8.6
Partition: Coefficient:	5.38
Melting Point:	218°C

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The key study from the SUBLOCADE clinical development program that supports its use in opioid use disorder is a Phase 3 efficacy and safety study.

This was a 24-week, randomized, double-blind, placebo-controlled, multicenter trial in treatment-seeking subjects who met the DSM-5 criteria for moderate or severe opioid use disorder. Subjects were randomized to one of following dosing regimens: 6 once-monthly 300 mg doses, 2 once-monthly 300 mg doses followed by 4 once-monthly 100 mg doses, or 6 once-monthly subcutaneous injections of placebo. All doses were administered in-clinic by a physician or suitably-qualified designee and were separated by 28 ± 2 days.

Prior to the first dose of SUBLOCADE, subjects were inducted and dose-stabilized on a transmucosal buprenorphine-containing product for a minimum of 7 days. Subjects were considered dose-stabilized when cravings and withdrawal symptoms were clinically controlled (≤20 on a 100-point Opioid Craving VAS and ≤12 on a 48-point COWS scale) for a minimum of 24 hours. In addition to study medication, all subjects received manual-guided psychosocial support at least once a week (Individual Drug Counselling = IDC). After randomization, supplemental dosing with the transmucosal buprenorphine-containing product was not permitted during SUBLOCADE use.

The primary endpoint was the cumulative distribution function of the percentage of urine samples negative for illicit opioids combined with self-reports negative for illicit opioid use collected weekly from Week 5 through Week 24 (% abstinence). A "grace period" was applied for Weeks 1 through 4 to allow subjects to stabilize on SUBLOCADE treatment. Missing urine drug screen samples and/or self-reports were counted as positive for illicit opioids.

The key secondary endpoint was treatment success (% responders), defined as any subject with ≥80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use (opioid-free weeks) from Week 5 through Week 24.

A total of 504 subjects were randomized into treatment arms, as follows: 203 subjects in the 300 mg/100 mg group, 201 subjects in the 300 mg/300 mg group and 100 subjects in the placebo group (2 groups of volume-matched placebo). Nearly two-thirds of the patients were between 30 and 44 years of age. There were no elderly patients in this trial. Some subject demographics and baseline characteristics are provided in Table 7.

Table 7 Subject Demographics and Baseline Characteristics

	Placebo %	**SUBLOCADE 300/100 mg %**	**SUBLOCADE 300/300 mg %**
Mean Age (years)	39.2	40.4	39.3
Median Age (range) in years	38 (20-63)	39 (20–64)	38 (20–63)
Sex			
Male	64.6	66.0	67.3
Female	35.4	34.0	32.7
Substance Use at Screening			
Opioid Use - Injectable Route	50.5	43.3	40.8
Tobacco	92.9	91.8	92.3
Alcohol	80.8	78.4	79.1
Drug Use History			
Cannabinoids	52.5	54.6	47.4
Cocaine	42.4	47.4	39.8
Amphetamine/Methamphetamine	19.2	25.3	14.8

14.2 Study Results

Based on the primary efficacy end-point, both doses of SUBLOCADE were significantly better than placebo.

The key secondary end-point, proportion of patients achieving treatment success (defined as patients with ≥80% opioid-free weeks) was also statistically significantly higher in both SUBLOCADE arms versus placebo (Table 8).

Table 8 Percentage abstinence and Treatment success/Responder rate (Full Analysis Set).

	Placebo	**SUBLOCADE 300 mg/100 mg**	**SUBLOCADE 300 mg/300 mg**
% Abstinence (Opioid-free Weeks)			
Mean (SD)	5 (17)	43 (39)	41(40)
p-value	-	< 0.0001	< 0.0001
Median	0	33	30
Treatment Success (%)	2	28	29
100% Abstinence n (%)	1 (1)	25 (13)	23 (12)
p-value	-	< 0.0001	< 0.0001

*Treatment success/Responder rate or % responders was defined as any subject with ≥80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 5 and Week 24.

Weekly assessments of other markers of clinical efficacy were also collected, including Opioid Craving VAS and Clinical Opiate Withdrawal Scale (COWS). Results were supportive of both primary and key secondary endpoints.

14.3 Comparative Bioavailability Studies

Not Applicable

15 MICROBIOLOGY

Not Applicable

16 NON-CLINICAL TOXICOLOGY

General Toxicology

SUBLOCADE*:* Repeat dose toxicity studies were carried out with SUBLOCADE and the vehicle (ATRIGEL Delivery System). Notable findings in rats included increased severity and incidence of injection site granulomas, pancreatic acinar cell apoptosis and alveolar macrophage infiltrates in the lungs of rats administered the two higher doses of SUBLOCADE (25 and 100 mg buprenorphine). The safety margins at the rat NOAEL (10 mg/kg) based on C_{max} and AUC_{0-24} were 7-15 and 3-4-fold, respectively over exposure at the maximum SUBLOCADE dose in humans (300 mg buprenorphine). Additionally, the rat 28-day exposure (AUC_{0-672h}) was compared to the 28-day exposure in humans; the NOAEL demonstrated a 2.5- to 4.3-fold safety margin following the first dose and 1.4- to 1.8-fold for the last dose.

Injection site reactions were confirmed at both the macroscopic and microscopic level in dogs when SUBLOCADE was administered subcutaneously once a month for 9 months. These effects were also observed in animals receiving the ATRIGEL Delivery System alone. The local reaction observed in these groups persisted over time and included oedema/swelling, raised areas, masses, erythema/reddening, abrasion, eschar formation, ulceration, desquamation and blanching. Histopathological findings at the injection site included subcutaneous granulomas, degenerate/necrotic cell debris, mononuclear cell infiltrates, fibroplasias, and/or haemorrhage.
The safety margin at the dog NOAEL (>40 mg/kg) was 8- to 13-fold based on C_{max} over exposure at the maximum SUBLOCADE dose in humans; the exposure margin based on $AUC_{0\text{-}24h}$ was 6-fold. Additionally, the dog 28-day exposure ($AUC_{0\text{-}672h}$) was compared to the 28-day exposure in humans; the NOAEL demonstrated a 12- to 13-fold safety margin following the first dose and 6.4- to 7.8-fold for the last dose (see also **NON-CLINICAL TOXICOLOGY (16), Local Irritation**).

Buprenorphine*:* No consistent target organ toxicity was identified in animals following a 28-day exposure period to buprenorphine, which included high oral doses.

No consistent pattern of undesirable effects was apparent in the subacute studies conducted, aside from a sedative effect which is consistent with the pharmacological action of buprenorphine.

Minimal to moderate hyperplasia of the bile duct with associated peribiliary fibrosis occurred in dogs following 52 weeks oral dosing of buprenorphine at 75 mg/kg/day.

NMP*:* There is no clear toxicity profile of NMP after repeat-dose administration. In a 28-day dietary study in rats, a decrease in body weight gain was observed in males at 1234 mg/kg body weight and in females at 2268 mg/kg body weight. Testicular degeneration and atrophy in males and thymic atrophy in females were also observed at these dose levels. The NOAEL was 429 mg/kg body weight in males and 1548 mg/kg body weight in females. In a 28-day intubation study in rats, a dose-dependent increase in relative liver and kidney weights was observed along with a decrease in lymphocyte count in both sexes at 1028 mg/kg body weight. The NOAEL was 514 mg/kg body weight. In another rat study, daily dietary administration for 90 days caused decreased body weight in males and females at doses of 433 and 565 mg/kg body weight, respectively. Neurobehavioral effects were also detected at these dose levels. NOAELs based on body weight changes and neurobehavioral parameters in males and females were established as 169 and 217 mg/kg body weight, respectively.

Long-term Toxicity/Carcinogenicity

SUBLOCADE: No long-term carcinogenicity studies have been performed in animals to evaluate the carcinogenic potential of SUBLOCADE.

Buprenorphine*:* The carcinogenic potential of 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 subcutaneous 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 subcutaneous dose of 300 mg of buprenorphine).

NMP: Long-term toxicity of NMP has been investigated in two studies with rats and one with mice. No evidence of carcinogenicity was identified in 2-year inhalation and dietary studies in rats. The primary toxic effect observed in rats was chronic nephropathy, most notably in males. The dietary study in mice demonstrated an increase in hepatocellular adenomas and carcinomas in both males and females 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.

Given the paucity of data, very little is known in terms of the effects of chronic, subcutaneous administration of NMP in animals.

Mutagenicity

SUBLOCADE*:* No evidence of mutagenic potential for subcutaneous SUBLOCADE was found in an *in vivo* subcutaneous micronucleus test using rats' bone marrow erythrocytes when tested to the maximum tolerated dose equivalent to 500 mg buprenorphine/kg (or approximately 16 times the recommended human monthly subcutaneous dose of 300 mg of buprenorphine). No evidence of mutagenic potential for subcutaneous ATRIGEL Delivery System was found in this *in vivo* subcutaneous micronucleus test in rats, when tested at 2000 mg/kg which represents approximately 14 times the maximum dose of buprenorphine in SUBLOCADE at the recommended human monthly subcutaneous dose (300 mg).

Buprenorphine: 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 (*Saccharomyces. 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. coli*) survival test, positive in a DNA synthesis inhibition test with testicular tissue from mice, for both *in vivo* and *in vitro* incorporation of [3H] thymidine, and positive in unscheduled DNA synthesis test using testicular cells from mice.

NMP*:* Evidence supporting mutagenic potential of NMP is weak. A slight increase in the number of revertant was observed when NMP was tested in a Salmonella assay with base-pair substitution strains. NMP has been shown to induce aneuploidy in yeast *S. cerevisiae* cells, without any genetic effects. However, an *in vivo* micronucleus test in yeast was negative and Chinese hamsters exposed to six weeks of NMP inhalation did not display any chromosome damage in the bone marrow.

Reproductive Toxicity and Teratogenicity

SUBLOCADE*:* Reproductive and developmental toxicity studies were conducted in rats and rabbits with subcutaneously administered SUBLOCADE or the ATRIGEL Delivery System alone. Collectively, these studies demonstrated adverse non-reproductive as well as reproductive effects on the maternal and paternal generation, as well as toxic effects on the fetus at high doses. The majority of toxicity observed was attributed to NMP exposure and correlates with published NMP studies in rodents (see **NON-CLINICAL TOXICOLOGY (16), Reproductive Toxicity and Teratogenicity,** *NMP*).

Maternal Toxicity/Fertility
Fertility and fecundity indices were unaffected by subcutaneous administration of SUBLOCADE (up to 900 mg/kg buprenorphine) or the ATRIGEL Delivery System alone (up to 4244 mg/kg ATRIGEL) in rats. However, maternal toxicity was observed in the highest dose SUBLOCADE and ATRIGEL groups and included lower body weight, body weight gain and food consumption. This was attributed to exposure to high levels of ATRIGEL, and likely NMP (29 times the recommended human monthly subcutaneous dose of 300 mg buprenorphine). Similar results were confirmed in a study with rabbits, along with high numbers of abortions and total litter resorptions. Higher mean post-implantation loss was observed in rabbits at the highest dose of SUBLOCADE and ATRIGEL, which correlated with a higher mean number of resorptions, and accordingly, a reduction in the mean number of viable fetuses/litter size (25 times recommended human monthly subcutaneous dose of 300 mg buprenorphine). Lower fetal body weights were also observed in these groups. In rats, the NOAEL for female fertility and reproductive parameters was 600 mg/kg buprenorphine (approximately 20 times the recommended human monthly subcutaneous dose of 300 mg buprenorphine) and the maternal and developmental toxicity NOAEL was 300 mg/kg buprenorphine (approximately 10 times the recommended human monthly SC dose of SUBLOCADE). In rabbits, the NOAEL for maternal and developmental toxicity was the lowest dose (78 mg/kg buprenorphine, approximately 5-fold over the exposure of the maximum SUBLOCADE dose in humans).

Paternal Toxicity
Male toxicity was observed in rats at all doses of SUBLOCADE following three once-monthly subcutaneous doses, including morbundity/mortality in the highest dose group (900 mg/kg buprenorphine), and lower body weight, body weight gain and food consumption at all doses of buprenorphine. The NOAEL for male general toxicity could not be determined as effects were observed in all doses. Decreases in male fertility and reproduction indices observed in both SUBLOCADE and ATRIGEL Delivery System high dose groups included abnormal sperm parameters (low motility, low mean number of sperm, and higher percentage of abnormal sperm). Abnormal sperm parameters were also observed in the mid-ATRIGEL and SUBLOCADE dose groups. These differences were attributed to high NMP exposure. The NOAEL for male reproductive and fertility parameters, including sperm analysis, was 300 mg/kg buprenorphine in SUBLOCADE (10 times recommended human monthly subcutaneous dose of 300 mg buprenorphine). The NOAEL for male reproductive and fertility parameters was 2829 mg/kg ATRIGEL (20 times recommended human monthly subcutaneous dose of SUBLOCADE). However, the NOAEL for sperm parameters was 1415 mg/kg ATRIGEL, which is 10 times the recommended human monthly subcutaneous dose of SUBLOCADE.

Fetal Toxicity
SUBLOCADE administered subcutaneously to pregnant rats and rabbits during the period of organogenesis at a buprenorphine dose equivalent to 38 and 15 times, respectively, the maximum recommended human dose (MRHD) of 300 mg caused embryolethality.

In rabbits, exposure to the highest doses of SUBLOCADE and the ATRIGEL Delivery System resulted in a significant reduction in mean number of viable fetuses/litter size and a statistical reduction in mean fetal body weight. In addition, a statistically increased litter incidence of total external malformations, visceral malformations and variations and skeletal variations were also observed in both of these groups. The NOAEL for maternal and developmental toxicity was established as the low dose of SUBLOCADE, corresponding to a dose of 78 mg/kg buprenorphine. The safety margin established was approximately 5-fold over exposure at the maximum SUBLOCADE dose in humans (300 mg buprenorphine); based on C_{max} and AUC_{0-24h}.The NOAEL for the ATRIGEL Delivery System was the mid dose of 713 mg/kg, containing

435 mg/kg NMP, or 10 times the recommended human monthly subcutaneous dose of 1366 mg ATRIGEL. Additionally, when the rabbit 28-day exposure ($AUC_{0\text{-}672h}$) was compared to the 28-day exposure in humans from the clinical Study RB-US-12-0005; the NOAEL demonstrated a 2.4-fold safety margin.

Fetotoxic effects such as reduction in mean fetal body weight and malformations were also confirmed in rat studies in the mid and/or high dose groups of SUBLOCADE (600 and 900 mg/kg buprenorphine) and ATRIGEL Delivery System alone. These consisted predominately of malformations of the head which also correlated with skeletal malformations of the skull in these same dose groups. Adverse visceral malformations were also observed in the high dose groups. These effects were attributed to high levels of buprenorphine and/or NMP exposure.

Post-natal Development
Post-natal development was assessed in a single SUBLOCADE study in rats, in which dams were administered SUBLOCADE or ATRIGEL Delivery System on Gestation Day 7 and again on Lactation Day 7 and the pups were evaluated through sexual maturity and mating. No significant effects were observed at 300 mg/kg buprenorphine, the high dose, (10 times the recommend monthly human dose) beyond a transient effect on body weight during the weaning and post-weaning periods which is consistent with the pharmacological action of buprenorphine.

Buprenorphine: Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant doses following intramuscular or subcutaneous administration. Embryo-fetal death was observed in both rats and rabbits administered buprenorphine during the period of organogenesis at doses approximately 6 and 0.3 times, respectively, the human sublingual dose of 16 mg/day of buprenorphine. Pre-and postnatal development studies in rats demonstrated increased neonatal deaths and dystocia, at approximately 0.3 and 3 times greater the human sublingual dose at 16 mg/day of buprenorphine. Increases in skeletal abnormalities were noted in rats and rabbits administered buprenorphine daily during organogenesis at a dose of approximately 0.6 and 6 times the human sublingual dose of 16 mg/day of buprenorphine, respectively. In a few studies, some events such as acephalous and omphalocele were observed but these findings were not clearly treatment-related. Embryo-fetal death was also observed in both rats and rabbits.

Dietary administration of buprenorphine in the rat at dose levels equivalent to approximately 47 mg/kg/day or greater produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose equivalent to approximately 10 mg/kg/day had no adverse effect on fertility. Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg/day or up to 5 mg/kg/day intramuscularly or subcutaneously.

NMP: Previously published animal studies indicate that NMP is a reproductive toxin that can be harmful to the fetus at high doses.

Subchronic, oral exposure of male rats to NMP resulted in adverse effects on testes and male fertility at greater than 11.6 times the MDD. Male-mediated toxicity on offspring (decreased pup weight and survival) was also observed at daily doses 3.5 times the MDD of NMP delivered by SUBLOCADE. Intragastric exposure of female rats to NMP before pregnancy and during gestation significantly impaired female fertility and intrauterine mortality rates.

NMP-driven developmental toxicity has been widely demonstrated in animal studies and includes embryolethal, teratogenic, and fetotoxic effects after oral (gavage) and dermal

administration in rats, after oral (gavage) treatment in rabbits, and intraperitoneal (IP) injection in mice. Increased preimplantation losses, delayed ossification, reduced fetal weight, postnatal developmental delays and reduced cognitive function were reported in rats at doses equivalent to the doses of NMP via SUBLOCADE. Decreased pup survival at 2 times the dose of NMP and malformation and post-implantation losses were reported at 3 times the dose of NMP via SUBLOCADE. NMP induced skeletal and visceral malformations in rat fetuses prenatally exposed orally at doses toxic to the mothers; and was also fetotoxic at lower doses, which were nontoxic to pregnant females. Similarly, in rabbits exposed, dermally to NMP during the gestation period, there was a significant increase in the incidence of fetuses with skeletal alterations in the absence of any signs of maternal toxicity.

Local Irritation

SUBLOCADE*:* Single-dose toxicity, repeat-dose toxicity and local tolerance studies carried out in rats, dogs and rabbits, demonstrated injection site reactions such as swelling, abrasion, reddening and raised areas or masses, and dermal observations including oedema, superficial/dermal irritation and erythema. Gross findings at injection sites in animals treated with SUBLOCADE or the ATRIGEL Delivery System alone consisted of firm, dark or pale area/foci in the subcutaneous tissue, which correlated histologically in the single and repeat-dose toxicity studies with subcutaneous granulomas, degenerate/necrotic cell debris, mononuclear cell infiltrates, fibroplasia and/or haemorrhage. Generally, the duration, frequency and severity of clinical signs and injection site observations correlated with increasing volume of the ATRIGEL Delivery System administered.

NMP**:** Slight or moderate skin irritations have been reported in rabbits and guinea-pigs.

17 SUPPORTING PRODUCT MONOGRAPHS

1. [N]SUBOXONE® (Sublingual Tablets, 2 mg / 0.5 mg ,8 mg / 2 mg, 12 mg / 3 mg, 16 mg / 4 mg)), submission control 200964, Product Monograph, Indivior UK Ltd. (August 31, 2017).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[N]**SUBLOCADE**™

Buprenorphine extended-release Injection

Read this carefully before you are given **SUBLOCADE** and each time you receive an injection. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SUBLOCADE**.

Serious Warnings and Precautions

Administration

SUBLOCADE is **ONLY** to be given to you:

- by a healthcare professional
- as an injection just under the skin (subcutaneously) of the stomach area (abdomen). **It is NOT to be given to you any other way.**

SUBLOCADE is injected as a liquid. After the injection it forms a solid mass (called a depot). It must not be given to you through a vein (intravenously) or into a muscle (intramuscularly). **Serious harm or death could result if it is given to you intravenously.**

Use During Pregnancy

You should not use SUBLOCADE if you are:

- pregnant. Your doctor will decide whether the benefit of giving you SUBLOCADE outweighs the risk to your unborn baby.
- of childbearing age and are not using an effective and reliable method of birth control.

QTc Prolongation:

Medicines containing buprenorphine have been known to cause problems with how your heart beats (abnormal heart rhythm) in some people. Tell your health care professional if you have problems with your heart.

SUBLOCADE contains buprenorphine and belongs to the opioid class of drugs. The warnings and precautions below apply to all medicines in this class including SUBLOCADE.

Addiction, Abuse, and Misuse

Even if you use SUBLOCADE as prescribed you are at risk for abuse and misuse. To understand your risk of abuse and misuse you should speak to your healthcare professional. Your healthcare professional should also monitor you to see if you develop these behaviours.

Neonatal Opioid Withdrawal Syndrome

Life-threatening breathing problems can happen while taking SUBLOCADE, especially if not used as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.

- If you took SUBLOCADE while you were pregnant, whether for short or long periods of time, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:
  - has changes in their breathing (such as weak, difficult or fast breathing)
  - is not feeding well
  - is unusually difficult to comfort
  - has tremors (shakiness)
  - has stiffness
  - has increased stools or diarrhea,
  - has sneezing, yawning, vomiting, or fever

Get medical help right away for your baby.

What is SUBLOCADE used for?

SUBLOCADE is:

- used to treat patients (18 years of age and older) who have moderate to severe opioid use disorder.
- for patients who are currently taking a transmucosal buprenorphine-containing product for at least 7 days.
- a drug treatment plan that should be used along with counselling and psychosocial support.

How does SUBLOCADE work?

SUBLOCADE contains buprenorphine. It works in a similar way as other opioid drugs that are used in the treatment of pain. When you stop taking opioid drugs, you can experience withdrawal. SUBLOCADE helps control the symptoms you feel when you are in withdrawal.

What are the ingredients in SUBLOCADE?

Medicinal ingredients: Buprenorphine
Non-medicinal ingredients: *N*-methyl-2-pyrrolidone (NMP) and 50:50 Poly(DL-lactide-co-glycolide) (PLGH).

SUBLOCADE comes in the following dosage forms:

Extended-release solution for injection available in pre-filled syringes: 100 mg / 0.5 mL and 300 mg / 1.5 mL.

Do not use SUBLOCADE if you:

- are allergic to buprenorphine or any of the ingredients in this product, including the ATRIGEL Delivery System (see above for the complete listing of non-medicinal ingredients).
- have severe asthma, trouble breathing, or other breathing problems.
- have serious problems with your liver.
- suffer from or have a history of alcoholism.
- have any heart problems.
- have bowel blockage or narrowing of the stomach or intestines.
- have severe pain in your abdomen.
- have a head injury.
- suffer from convulsive or seizure disorder.
- are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOI) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline).
- are going to have a planned surgery.
- are pregnant or planning to become pregnant.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive SUBLOCADE. Talk about any health conditions or problems you may have, including if you:

- have never used opioid medications before. You should not be given SUBLOCADE.
- have a history of illicit or prescription drug or alcohol abuse,
- have asthma, other breathing problems, or lung problems,
- have problems with your liver,
- have problems with your kidneys,
- have heart disease,
- have low or decreased in blood pressure,
- suffer from chronic or severe constipation,
- have problems with your brain or recent head injury,
- have problems with your gallbladder,
- have problems with your pancreas,
- have adrenal gland problems, such as Addison's disease,
- have low thyroid hormone levels (hypothyroidism),
- have problems urinating,
- have a curve in your spine that affects your breathing,
- have severe mental problems or hallucinations (seeing or hearing things that are not really there),
- suffer from migraines,
- are going to have a planned surgery.

Other warnings you should know about:

Pregnancy, breastfeeding and women of childbearing age: Tell your healthcare professional if you are:

- pregnant or planning to become pregnant
- breastfeeding or planning on breastfeeding your baby, or
- are a woman of childbearing age who is not using a proper method of birth control

Your healthcare professional will decide if you should use SUBLOCADE.

Studies in animals have shown that one of the non-medical ingredients in SUBLOCADE, (NMP) may cross the placental barrier and can harm the development of the embryo and the fetus. It is not known whether NMP has this effect in humans.

The active ingredient in SUBLOCADE (buprenorphine) can also be transferred to your baby through breast milk, or while still in the womb. It can then cause life-threatening breathing problems in your unborn baby or nursing infant. SUBLOCADE should only be used when the potential benefit justifies the potential risks to the fetus or baby.

It is important that you talk to your healthcare professional.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your healthcare professional may do tests, give you another medication, and take you off SUBLOCADE, if this happens.

Serotonin Syndrome: SUBLOCADE can cause serotonin syndrome, a rare but potentially life- threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin syndrome if you take certain antidepressants or migraine medications while on SUBLOCADE treatment.
Symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, feeling restless, hallucinations, mood changes, unconsciousness and coma.

Treatment of short-term pain: When you are on SUBLOCADE treatment, there may be times when you need to take other medicines, including other opioids, to treat short-term pain. Since SUBLOCADE may make it difficult to get full pain relief from other opioids, you should tell your healthcare professional that you are on SUBLOCADE if they are treating you for pain.

Sexual Function / Reproduction: Long-term use of opioids may lead to a decrease in your sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Monitoring and Laboratory Tests: Your healthcare professional should do liver functions tests before you start treatment and during your treatment with SUBLOCADE.

Driving and using machines: Before you do tasks, which may require special attention, you should wait until you know how you react to SUBLOCADE. SUBLOCADE can cause:

- drowsiness
- dizziness or
- lightheadedness

These effects may happen more often in the first few days after your injection.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

<u>Interaction with Alcohol and other Central Nervous System Depressants</u>

Taking the following medications while you are on SUBLOCADE can cause **severe drowsiness, decreased awareness, unusually slow or weak breathing, coma and death:**

- other opioid medication (used to treat pain)
- benzodiazepines (used to treat anxiety or to help you sleep)
- alcohol (this includes prescription and non-prescription medications that contain alcohol)
- other central nervous system depressants, such as
    - street drugs
    - drugs used during surgery
    - muscle relaxants
    - drugs to treat depression
    - drugs used to treat nausea and vomiting
    - drugs used to treat serious mental or emotional disorders (such as schizophrenia)

The following may interact with SUBLOCADE:

- Monoamine Oxidase Inhibitors (MAOIs) (such as phenelzine, tranylcypromine and linezolid). **Do not** take SUBLOCADE with MAOIs or if you have taken MAOIs in the last 14 days.
- antihistamines (drugs used to treat allergies)
- drugs used to treat epilepsy (such as carbamazepine, phenytoin and phenobarbital)
- warfarin (such as coumadin) and other anticoagulants (used for prevention or treatment of blood clots)
- antiretroviral drugs (used to treat certain viral infections)
- antifungal drugs (used to treat fungal infections)
- antibiotic drugs (used to treat bacterial infections)
- diuretics (used to treat high blood pressure - also known as “water pills”)
- some heart medication (such as beta blockers)
- grapefruit juice
- drugs used to treat migraines (such as triptans)

How SUBLOCADE is given to you:
You can only get SUBLOCADE from your healthcare professional.

It will be given to you:

- once a month
- by your healthcare professional
- as an injection just under the skin (subcutaneously) of the stomach area (abdomen). It is NOT to be given to you any other way.

SUBLOCADE is injected as a liquid. After the injection it forms a solid mass (called a depot). It must not be given to you through a vein (intravenously) or into a muscle (intramuscularly). **Serious harm or death could result if it is given to you intravenously.**

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 rub or massage the injection site and be aware of any belts or clothing waistbands that could cause irritation of the injection site.

Initial treatment: (before you start treatment with SUBLOCADE)

- Your healthcare professional will start you on a transmucosal buprenorphine-containing product (8 mg – 24 mg buprenorphine a day) for at least 7 days.

Usual Adult Dose: Following initial treatment, you will be transitioned to SUBLOCADE starting with 300 mg / 1.5 mL for 2 months, followed by a maintenance dose of 100 mg / 0.5 mL. Your healthcare professional may increase your maintenance dose if needed.

You should tell your family members that you are using SUBLOCADE to treat your opioid use disorder.

Discontinuing treatment: Once you stop taking SUBLOCADE, your healthcare professional should monitor you for several months for the signs and symptoms of withdrawal. If you experience withdrawal, your healthcare professional may give you other medication to treat it.

Overdose:

If you think you have taken too much SUBLOCADE, contact your healthcare professional, hospital emergency department or regional poison control center **immediately**, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- pinpoint pupils (pupils that are abnormally small under normal lighting conditions)
- dizziness
- confusion
- extreme drowsiness
- blue or purple lips
- slow heart rate
- nausea and vomiting

Missed Dose:

If you miss a dose of SUBLOCADE, see your healthcare professional right away.

What are possible side effects from using SUBLOCADE?

These are not all the possible side effects you may feel when taking SUBLOCADE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Pain or itching where you got the shot
- Drowsiness
- Insomnia
- Dizziness
- Fainting or feeling faint
- Feeling tired
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness
- Itching
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using SUBLOCADE.

Side effects that may occur at the injection site include:

- Itching
- Pain
- Redness
- Bruising
- Swelling

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Allergic Reaction**:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Itching	√		
Nausea	√		
Stomach pain	√		
UNCOMMON			
Dark urine		√	
Decreased blood pressure (dizziness, fainting, light-headedness)		√	
Fainting		√	
Hallucination (seeing or hearing things that are not really there)		√	
Jaundice (your skin or the white part of your eyes look yellow)		√	
Light coloured stools		√	
Loss of appetite	√		
RARE			
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			√
Respiratory Depression: Slow, shallow or weak breathing.			√
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			√
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		√	
Fast, Slow or Irregular Heartbeat: heart palpitations.		√	
Low Blood Pressure: dizziness, fainting, light-headedness.	√		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

SUBLOCADE will be stored by your healthcare professional.

If you want more information about SUBLOCADE:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this consumer medication information by visiting the Health Canada website, by e-mail at PatientSafetyNA@indivior.com, or by calling 1-877-782-6966.

This leaflet was prepared by Indivior UK Limited.

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