AUSTRALIAN PRODUCT INFORMATION

SUBLOCADE (BUPRENORPHINE)

WARNINGS:

Risk of serious harm or death with intravenous administration

Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage and thrombo-embolic events, including life threatening pulmonary emboli, if administered intravenously. (see section 4.4).

Hazardous and harmful use

Although SUBLOCADE is indicated for the treatment of opioid dependence it still poses risks of hazardous and harmful use which can lead to overdose and death. Monitor the patient's ongoing risk of hazardous and harmful use regularly during opioid substitution therapy with SUBLOCADE (see section 4.4. Special Warnings and Precautions for Use).

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of SUBLOCADE. Be aware of situations which increase the risk of respiratory depression, and monitor patients closely, especially on initiation or following a dose increase (see section 4.4 Special Warnings and Precautions for Use).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Patients and their caregivers should be made aware of the symptoms of respiratory depression. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while receiving SUBLOCADE.

1 NAME OF THE MEDICINE

SUBLOCADE 100 mg/0.5 mL buprenorphine modified release solution for injection.

SUBLOCADE 300 mg/1.5 mL buprenorphine modified release solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Buprenorphine is dissolved in Indivior's proprietary buprenorphine gel depot delivery system (Indivior's delivery system) at 18% by weight.

0.5 mL modified release injection solution in a prefilled syringe contains 100 mg buprenorphine (as buprenorphine base).

1.5 mL modified release injection solution in a prefilled syringe contains 300 mg buprenorphine (as buprenorphine base).

Buprenorphine is a white to cream, crystalline powder, very slightly soluble in water (<1 mg/mL). Chemically, buprenorphine is (2*S*)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol.

Buprenorphine has the molecular formula C_{29} H_{41} NO_4 and the molecular weight is 467.6.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

SUBLOCADE is a modified release solution for injection.

SUBLOCADE is a clear colourless to yellow to amber sterile solution for **subcutaneous injection only**. It forms a depot upon administration which is designed to deliver buprenorphine at a controlled rate over a one-month period.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SUBLOCADE is indicated for treatment of opioid dependence, within a framework of medical, social and psychological treatment.

4.2 DOSE AND METHOD OF ADMINISTRATION

SUBLOCADE IS FOR SUBCUTANEOUS INJECTION ONLY AND MUST NOT BE ADMINISTERED INTRAVENOUSLY, INTRAMUSCULARLY OR INTRADERMALLY (See Section 4.4 Special Warnings And Precautions For Use).

- Patients appropriate for SUBLOCADE are adults.
- Only healthcare providers should prepare and administer SUBLOCADE.
- SUBLOCADE should be injected into the subcutaneous tissue of the abdomen, thigh, buttock or back of the upper arm. Initiating treatment with SUBLOCADE as the first buprenorphine product has not been studied. Initiate SUBLOCADE treatment only after establishing tolerability with at least one dose of a buprenorphine-containing product.
- Administer each injection only using the syringe and safety needle included with the product.
- Do not administer part of a dose.

Precautions to be taken before starting treatment

Because of its partial opioid agonist properties, buprenorphine may precipitate opioid withdrawal signs and symptoms in persons who are currently physically dependent on full opioid agonists if administered before the effects of the full opioid agonist have subsided, generally 6 hours for short-acting opioids (e.g., heroin, morphine) and 24 hours for long-acting opioids (e.g., methadone, fentanyl). Verify that patients have tolerated transmucosal buprenorphine before administrating the first injection of SUBLOCADE.

Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medicinal products (See Section 4.5 Interactions with other Medicines and other forms of Interactions) and/or who have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of the liver function is recommended.

Recommended dosing

Initiation in patients not already receiving buprenorphine

Treatment with buprenorphine should be initiated when objective and clear signs of opioid withdrawal are evident in order to minimise the risk of precipitating withdrawal.

Standard dosing procedure
Prior to SUBLOCADE injection, patients who do not meet the criteria for high-risk opioid use (See under heading 'modified dosing procedure' and section 5.1 Pharmacodynamic Properties under heading 'Induction Substudy INDV-6000-401') are recommended to undergo induction and stabilization by initiating a buprenorphine-containing product, delivering the equivalent of at least 8 mg/day of transmucosal buprenorphine for at least 7 days. Transferring patients stabilised on doses over 24 mg/day buprenorphine to SUBLOCADE has not been studied in clinical trials. Dosing and induction of buprenorphine-containing products should be based on instructions in their Product Information.

The recommended dose of SUBLOCADE is 300 mg for the first two injections. The second injection may be administered as early as 1 week and up to 1 month after the initial injection, based on patient need.

Modified dosing procedure (Rapid induction dosing procedure)
Physicians are encouraged to discuss with their local specialist addiction treatment service before considering prescribing the Modified dosing procedure (Rapid induction dosing procedure).

Patients with high risk opioid use (e.g., patients who for an average of 5 or more days per week in the last 4 weeks meet one of the following criteria: using opioids via intravenous injection, using high dose of opioids [≥ 500 mg intravenous heroin equivalent daily] and /or using highly potent synthetic opioids [e.g fentanyl]; see section 5.1 Pharmacodynamic Properties under heading 'Induction Substudy INDV-6000-401) may receive SUBLOCADE injection after one initial dose (e.g. 4 mg) of transmucosal buprenorphine and be observed for one hour to confirm tolerability (allergic/hypersensitivity reaction, precipitated withdrawal symptoms, or sedation) before administering the first injection of SUBLOCADE. The recommended starting dose of SUBLOCADE is 300 mg. On initiation day, additional transmucosal buprenorphine may be administered as needed to manage withdrawal symptoms.

The recommended dose for the second injection is 300 mg. The second injection may be administered as early as 1 week and up to 1 month after the initial injection, based on patient need.

Initiation in patients already receiving buprenorphine
Patients who are on a buprenorphine-containing product, delivering the equivalent of 8 mg to 24 mg daily of transmucosal buprenorphine may be transitioned directly to the recommended starting dose of 300 mg of SUBLOCADE. Withdrawal signs and symptoms should be suppressed (COWS ≤12) before transitioning to SUBLOCADE. The recommended dose for the second injection is 300 mg. The second injection may be administered as early as 1 week and up to 1 month after the initial injection, based on patient need.

Maintenance dosage
After the first two injections, the recommended maintenance dosage of SUBLOCADE is 100 mg monthly. In clinical trials, randomisation to the 300 mg/month maintenance dose did not provide additional efficacy as compared to randomisation to the 100 mg/month maintenance dose and the 300 mg/month maintenance dose was associated with a higher incidence of adverse events, including those leading to study discontinuation. However, a monthly maintenance dosage of 300 mg may be considered in patients who tolerate SUBLOCADE, but do not demonstrate a satisfactory clinical response. Maintenance doses should be administered with at least 26 days between injections.

Buprenorphine plasma levels in the month following the second 300 mg dose are maintained with 100 mg maintenance dosing. The 300 mg maintenance dose achieves higher levels at steady-state (See Section 5.2 Pharmacokinetic Properties).

Periodic assessment
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.

Missed doses
A patient who misses a maintenance dose should receive the next dose as soon as possible, with the following dose given no less than 26 days later. Occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.

Termination of treatment
Due to the chronic nature of opioid use disorder, the need for continuing medication-assisted treatment should be re-evaluated periodically. There is no maximum recommended duration of maintenance treatment. For some patients, treatment may continue indefinitely. If considering stopping treatment, the clinical status of the patient should be considered.

If SUBLOCADE is discontinued, its modified-release characteristics should be considered and the patient should be monitored for several months for signs and symptoms of withdrawal or buprenorphine effects and treated appropriately.

After steady-state has been achieved (4-6 months), patients discontinuing SUBLOCADE may have detectable plasma and urine levels of buprenorphine for twelve months or longer (see section 5.2 Pharmacokinetic Properties).

INSTRUCTIONS FOR USE

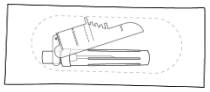
IMPORTANT INFORMATION:

- For subcutaneous injection only. Do not inject intravenously, intramuscularly or intradermally.
- **To be administered by a healthcare professional only.**
- Read the instructions carefully before handling the product.
- 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.
- SUBLOCADE should be injected into the subcutaneous tissue of the abdomen, thigh, buttock or back of the upper arm.
- Product is for single use in one patient only. Discard any residue.
- Discard SUBLOCADE if left at room temperature (below 25°C) for longer than 12 weeks.
- Do not attach the needle until time of administration.

STEP 1: GETTING READY

Remove the foil pouch and safety needle from the carton. Open the pouch and remove the syringe. Discard the oxygen absorber pack. It is not needed.

Figure 1

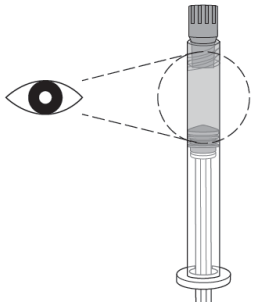


STEP 2: CHECK THE LIQUID CLARITY

Check that the medication for particulate matter and discolouration. SUBLOCADE can range from clear colourless to yellow to amber. **Variations of colour within this range do not affect the potency of the product.**

If the medication is discoloured or contains particulate matter it should not be used.

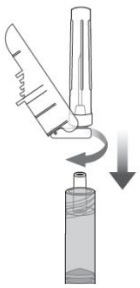
Figure 2



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 INJECTION SITE

Choose one of the following body regions for injection (see Figure 4):

- Abdomen between the transpyloric and transtubercular planes
- Back of the upper arm
- Buttock
- Thigh

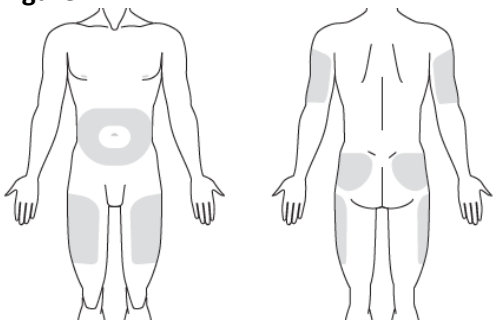
Ensure that the selected site has adequate subcutaneous tissue that is free of skin conditions (e.g. nodules, lesions, excessive pigment). It is suggested that the patient is lying down.

Do not inject into an area where the skin is irritated, reddened, bruised, infected or scarred in any way.

If injecting in the same body region as the last injection, use a different injection site to avoid irritation.

Clean the injection site well with an alcohol swab.

Figure 4



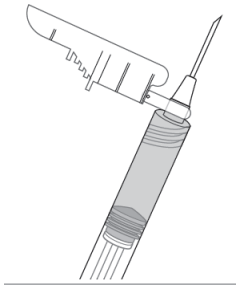
STEP 5: REMOVE EXCESS AIR FROM SYRINGE

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 minimised 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

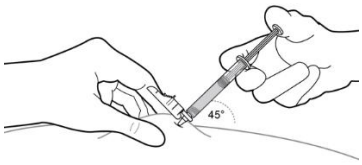
STEP 7: INJECT THE MEDICATION

SUBLOCADE is for subcutaneous injection only. Do not inject intravenously, intramuscularly or intradermally (See Section 4.4 Special Warnings and Precautions for Use).

Insert needle fully into the subcutaneous tissue. The actual angle of injection will depend on the amount of subcutaneous tissue.

Use a slow, steady push to inject the medication. Continue pushing until all of the medication is given.

Figure 7

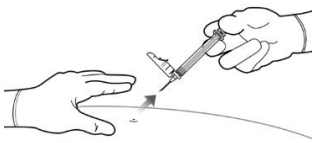


STEP 8: WITHDRAW THE NEEDLE

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

Do not rub the injection area after the injection. There may be a small amount of blood or fluid at the injection site; wipe with a cotton ball or gauze before applying a gauze pad or bandage using minimal pressure.

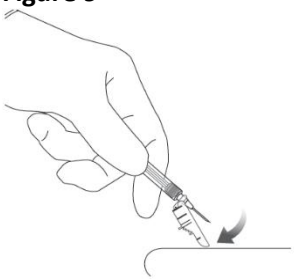
Figure 8



STEP 9: LOCK THE NEEDLE GUARD AND DISCARD THE SYRINGE

Lock the needle guard into place by pushing it against a hard surface such as a table (**Figure 9**).
Dispose of all syringe components in a secure sharps disposal container.

Figure 9



STEP 10: INSTRUCT THE PATIENT

Advise the patient that they may have a lump for several weeks that will decrease in size over time. Instruct the patient not to rub or massage the injection site and to be aware of the placement of any restrictive clothing such as belts, waistbands or sleeves.

Removal of the Depot

In the event a depot must be removed, it can be surgically excised by a healthcare professional under local anaesthesia within 14 days of injection. The removed depot should be disposed of carefully. Patients who have a depot removed should be monitored for signs and symptoms of withdrawal and treated appropriately.

4.3 CONTRAINDICATIONS

Hypersensitivity to buprenorphine or any other component of Indivior's delivery system.
Severe hepatic insufficiency (Child -Pugh C).
Subjects less than 18 years of age.
Severe respiratory insufficiency.
Acute intoxication with alcohol or other CNS depressants.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

Incorrect administration

Do not administer intravenously, intramuscularly or intradermally. Inadvertent intramuscular or intradermal administration may increase the likelihood of serious injection site reactions. In some post-marketing case reports injection site reactions have involved abscess, ulceration, and necrosis. Some cases resulted in surgical depot removal, debridement, antibiotic administration, and SUBLOCADE discontinuation. Evaluate and treat serious injection site reactions as appropriate. Carefully review injection techniques (see section 4.2 Dose and method of administration).

General

SUBLOCADE should be administered with caution in debilitated patients and those with severe impairment of hepatic, pulmonary, or renal function; myxoedema or hypothyroidism, adrenal cortical insufficiency (e.g. Addison's disease); CNS depression or coma; toxic psychoses; acute alcoholism; or delirium tremens.

Buprenorphine increases intracholedochal pressure as do other opioids. Therefore, caution should be exercised when buprenorphine is to be administered to patients with dysfunction of the biliary tract.

As with other opioids, caution is advised in patients using buprenorphine and having hypotension, prostatic hypertrophy or urethral stenosis.

Opioids may produce orthostatic hypotension in ambulatory patients.

As with other mu-opioid receptor agonists, the administration of SUBLOCADE may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Misuse, abuse and diversion

Although SUBLOCADE is indicated for the treatment of opioid dependence it still poses risks of hazardous and harmful use which can lead to overdose and death. Monitor the patient's ongoing risk of hazardous and harmful use regularly during opioid substitution therapy with SUBLOCADE.

Buprenorphine can be misused or abused in a manner similar to other opioids, legal or illicit. Some risks of misuse and abuse include overdose, spread of blood borne viral infections, respiratory depression and hepatic injury. SUBLOCADE misuse by someone other than the intended patient poses the additional risk of new opioid dependent individuals using buprenorphine as the primary opioid of abuse and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicine is not safeguarded against theft. Sub-optimal treatment with buprenorphine may prompt medication misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with buprenorphine may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines. To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and patient follow-up visits with clinical monitoring appropriate to the patient's level of stability should be conducted.

SUBLOCADE is injected as a liquid and the subsequent precipitation of the poly (D,L-lactide-co-glycolide) polymer creates a depot which contains buprenorphine. The entire contents of the prefilled syringe should be administered. After administration, a small amount (approximately 0.1 mL) of SUBLOCADE will remain in the needle and syringe and should be properly disposed of.

After initial formation of the depot, buprenorphine is released via diffusion from, and the biodegradation of, the depot. Clinical monitoring for evidence at the injection site of tampering or attempting to remove the depot should be ongoing throughout treatment. No accounts of subjects removing or attempting to remove the depot after SUBLOCADE administration were reported in clinical studies.

Intravenous injection presents significant risk of serious harm or death as SUBLOCADE forms a mass upon contact with body fluids. Intramuscular injection presents risk of tissue damage.

Abuse Deterrence Studies

SUBLOCADE has physicochemical properties designed for modified-release after subcutaneous injection. These properties make both SUBLOCADE and excised depot difficult to misuse and abuse. To evaluate the ability of these physiochemical properties to reduce the potential for abuse of SUBLOCADE, a series of *in vitro* laboratory studies were conducted.

In Vitro Testing

Results of *in vitro* testing suggest that it would be difficult to prepare a powder from either SUBLOCADE or the excised depot.

Attempts to abuse either SUBLOCADE or the excised depots via intravenous injection would result in serious harm.

Risk of Respiratory and Central Nervous System (CNS) Depression

Serious, life-threatening or fatal respiratory depression may occur with the use of SUBLOCADE. Be aware of situations which increase the risk of respiratory depression and monitor patients closely, especially on initiation or following a dose increase.

Buprenorphine has been associated with life-threatening respiratory depression and death. Many, but not all, post-marketing reports regarding coma and death involved misuse by self-injection or were associated with the concomitant use of buprenorphine and benzodiazepines or other CNS depressants

including alcohol. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants at the same time as receiving SUBLOCADE.

In the event of depression of respiratory or cardiac function, see Section 4.9 Overdose.

SUBLOCADE may cause severe, possibly fatal, respiratory depression in children. Protect children against exposure.

SUBLOCADE should be used with caution in patients with compromised respiratory function (e.g. chronic obstructive pulmonary disease, sleep apnoea, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression or kyphoscoliosis).

Due to its modified-release characteristics, if SUBLOCADE is discontinued as a result of compromised respiratory function monitor patients for ongoing buprenorphine effects for several months.

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see section 4.5 Interactions with other medicines and other forms of interaction). Patients and their caregivers should be made aware of the symptoms of respiratory depression. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while receiving SUBLOCADE.

Head Injury and Increased Intracranial Pressure

Buprenorphine, like other potent opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased, or history of seizure. Buprenorphine can produce miosis and changes in the level of consciousness, or changes in the perception of pain as a symptom of disease may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease.

Dependence and Risk of Opioid Withdrawal

Buprenorphine is a partial agonist at the μ (mu)-opioid receptor and studies in animals, as well as clinical experience, have shown that buprenorphine may produce dependence but at a lower level than a full agonist (e.g. morphine).

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. Model simulations indicate that steady-state buprenorphine plasma concentrations decreased slowly over time following the last injection and remained at therapeutic levels for 2 to 5 months on average, depending on the dosage administered (100 mg or 300 mg, respectively).

Patients who elect to discontinue treatment with SUBLOCADE should be monitored for withdrawal signs and symptoms. Consider transmucosal buprenorphine if needed to treat withdrawal after discontinuing SUBLOCADE.

Neonatal Abstinence Syndrome

Chronic use of buprenorphine by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, convulsions, apnoea or bradycardia) in the neonate. In many reported cases the withdrawal was serious and required treatment. The syndrome is generally delayed for several hours to several days after birth (see *Use in*

Pregnancy). Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Allergic Reactions

Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic oedema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine is a contraindication to SUBLOCADE.

Use in Opioid Naïve Patients

There have been reported deaths of opioid naive individuals who received doses as low as 2 mg of buprenorphine sublingual tablet for analgesia. SUBLOCADE is not appropriate as an analgesic.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Adrenal insufficiency

Adrenal insufficiency has been reported with opioid use, more often following long-term use. Symptoms may include nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure. If adrenal insufficiency is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with SUBLOCADE should be considered.

Endocrine effects

Opioids, such as SUBLOCADE, may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Hormonal disturbances that have been observed include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

Androgen deficiency may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility.

Hepatobiliary disorders

Opioids may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis. Therefore, SUBLOCADE has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Gastrointestinal Toxicity

Reports of significant oesophageal dysfunction have been observed via high-resolution manometry in patients taking opioid medicines on a long-term basis. Discontinuation or weaning of opioids should be considered in patients presenting with oesophageal complaints including but not limited to dysphagia, regurgitation, or non-cardiac chest pain.

Hepatitis, Hepatic Events

Cases of acute hepatic injury have been reported in opioid-dependent patients, both in clinical trials and post-marketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy and death. Serious cases of acute hepatic injury have also been reported in a context of misuse, especially by the intravenous route. These hepatic injuries were dose-related and could be due to mitochondrial toxicity. Pre-existing or acquired mitochondrial impairment (genetic diseases, viral infections particularly chronic hepatitis C, liver enzyme abnormalities, alcohol abuse, anorexia, associated mitochondrial toxins, e.g.

aspirin, isoniazid, valproate, amiodarone, antiviral nucleoside analogues, or drug misuse by injection) could promote the occurrence of such hepatic injuries.

These co-factors must be taken into account before prescribing SUBLOCADE and during treatment monitoring. Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medicines (See Section 4.5 Interactions with other medicines and other forms of interactions) and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending upon the findings, the medicine may be discontinued. If treatment is continued, hepatic function should be monitored closely.

Use in hepatic impairment

Buprenorphine is extensively metabolised by the liver. The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a post-marketing study, in which a buprenorphine/naloxone 2.0 mg/0.5 mg sublingual tablet was administered to healthy subjects and subjects with varying degrees of hepatic impairment. Plasma levels were found to be elevated for buprenorphine in patients with moderate to severe hepatic impairment (Table 1). Buprenorphine plasma exposure increased approximately 3-fold in patients with severely impaired hepatic function.

Table 1. Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine following buprenorphine/naloxone administration (change relative to healthy subjects)

PK parameter	Mild Hepatic Impairment (Child-Pugh Class A) (n=9)	Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)	Severe Hepatic Impairment (Child-Pugh Class C) (n=8)
BUPRENORPHINE			
Cmax	**1.2 fold increase**	**1.1 fold increase**	**1.7 fold increase**
AUC_{last}	**Similar to control**	**1.6 fold increase**	**2.8 fold increase**

In the same study, changes in C_{max} and AUC_{last} in subjects with HCV infection without hepatic impairment were not clinically significant in comparison to the healthy subjects.

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

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

Patients who develop moderate to severe hepatic impairment while being treated with SUBLOCADE should be monitored for several months for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

Use in renal impairment

Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine and metabolites. Therefore, no dose modification based on renal function is generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CL_{cr} <30 mL/min), which may require dose adjustment.

Clinical studies of SUBLOCADE did not include subjects with renal impairment.

Use in Patients at Risk for Arrhythmia

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

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

Use in the elderly

The safety and efficacy of buprenorphine in elderly patients over 65 years have not been established.

Risks associated with Treatment of Emergent Acute Pain

While on SUBLOCADE, situations may arise where patients need acute pain management, or may require anaesthesia. 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 sedation or opioid therapy is required, e.g. as part of anaesthesia, patients should be continuously monitored in an anaesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure. The sedation or opioid therapy should be provided by individuals specifically trained in the use of anaesthetic 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 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.

Paediatric use

SUBLOCADE is not recommended for use in children. The safety and effectiveness of SUBLOCADE in subjects below the age of 18 has not been established.

Effects on laboratory tests

Athletes should be aware that this medicine may cause a positive reaction to “anti-doping” tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The table below includes clinically significant drug interactions with SUBLOCADE.

Table 2. Clinically Significant Drug Interactions

Benzodiazepines and other Central Nervous System depressants	
Examples	Alcohol, Benzodiazepines, Non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, antipsychotics, gabapentinoids, cannabis, other opioids (e.g. methadone, analgesics, and antitussives), antihistamines (e.g. sedating H1-receptor antagonists), clonidine (see section 4.4 Special Warnings and Precautions for Use).
Clinical Impact:	Due to additive pharmacologic effects, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention	Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate. Similarly, cessation of other CNS depressants is preferred when possible. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments. This combination with benzodiazepines may result in death due to respiratory depression of central origin; therefore, patients must be closely monitored when prescribed this combination, and this combination should be avoided in cases where there is a risk of misuse. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking this product and should also be cautioned to use benzodiazepines concurrently with this product only as prescribed. Use caution with medicines containing alcohol.
Other Opioid Analgesics	
Clinical Impact:	The analgesic properties of other opioids may be reduced in patients receiving treatment with buprenorphine for opioid dependence. Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine. Conversely, the potential for overdose should be considered with higher than usual doses of full agonist opioids, such as methadone or level III analgesics, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining.
Intervention	Patients with a need for analgesia and opioid dependence treatment may be best managed by multidisciplinary teams that include both pain and opioid dependence treatment specialists (see Section 4.4 Special Warnings and Precautions for Use).

Naltrexone and other opioid antagonists	
Clinical Impact:	Since buprenorphine is a partial mu-opioid agonist, concomitantly administered opioid antagonists such as naltrexone can reduce or completely block the effects of SUBLOCADE. Patients maintained on buprenorphine may experience a sudden onset of prolonged and intense opioid withdrawal symptoms if dosed with opioid antagonists that achieve pharmacologically relevant systemic concentrations.
CYP3A4 inhibitors	
Examples	Protease inhibitors (like ritonavir, saquinavir or indinavir), azole antifungals like ketoconazole or itraconazole, calcium channel antagonists and macrolide antibiotics like erythromycin.
Clinical Impact:	The effects of co-administered CYP3A4 inhibitors on buprenorphine exposure in subjects treated with SUBLOCADE have not been studied and the effects may be dependent on the route of administration; however, such interactions have been established in studies using transmucosal buprenorphine. Buprenorphine is metabolized to norbuprenorphine primarily by CYP3A4, therefore potential interactions may occur when SUBLOCADE is given concurrently with agents that affect CYP3A4 activity. The concomitant use of sublingual buprenorphine and CYP3A4 inhibitors can increase the plasma concentration of buprenorphine, resulting in increased or prolonged opioid effects.
Intervention:	Patients who transfer to SUBLOCADE treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inhibitors should be monitored to ensure that the plasma buprenorphine level provided by SUBLOCADE is adequate. If patients already on SUBLOCADE require newly-initiated treatment with CYP3A4 inhibitors, patients should be monitored for signs and symptoms of over-medication. Within 2 weeks of SUBLOCADE administration, if signs and symptoms of buprenorphine toxicity or overdose occur but the concomitant medication cannot be reduced or discontinued, it may be necessary to remove the depot and treat the patient with a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilised on SUBLOCADE in the setting of concomitant medication that is a CYP3A4 inhibitor, and the concomitant medication is discontinued, the patient should be monitored for withdrawal. If the dose of SUBLOCADE is not adequate in the absence of the concomitant medication, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments.
CYP3A4 inducers	
Examples	Rifampicin, phenobarbital, carbamazepine, phenytoin.

Clinical Impact:	The effects of co-administered CYP3A4 inducers on buprenorphine exposure in subjects treated with SUBLOCADE have not been studied. Buprenorphine is metabolized to norbuprenorphine primarily by CYP3A4; therefore, potential interactions may occur when SUBLOCADE is given concurrently with agents that affect CYP3A4 activity. 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.
Intervention:	Patients who transfer to SUBLOCADE treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inducers should be monitored to ensure that the plasma buprenorphine level provided by SUBLOCADE is adequate. If patients already on SUBLOCADE require newly-initiated treatment with CYP3A4 inducers, the patients should be monitored for withdrawal. If the dose of SUBLOCADE is not adequate and the concomitant medication cannot be reduced or discontinued, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilised on SUBLOCADE in the setting of concomitant medication that is a CYP3A4 inducer, and the concomitant medication is discontinued, the patient should be monitored for signs and symptoms of over-medication. Within 2 weeks of SUBLOCADE administration, if the dose provided by SUBLOCADE is excessive in the absence of the concomitant inducer, it may be necessary to remove SUBLOCADE and treat the patient with a formulation of buprenorphine that permits dose adjustments.
Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Examples	Efavirenz, nevirapine, etravirine, delavirdine
Clinical Impact:	Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine, and etravirine are known CYP3A inducers, whereas delavirdine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g. efavirenz and delavirdine) and sublingual buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects.
Intervention:	Patients who are on chronic treatment with SUBLOCADE should be monitored for increase or decrease in therapeutic effects if NNRTIs are added to their treatment regimen.
Antiretrovirals: Protease inhibitors (PIs)	
Examples:	Atazanavir, ritonavir
Clinical Impact:	Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (lopinavir/ritonavir, ritonavir) have little effect on sublingual buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine after sublingual administration, and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients

	receiving sublingual buprenorphine and atazanavir with and without ritonavir concomitantly.
Intervention:	If treatment with atazanavir with and without ritonavir must be initiated in a patient already treated with SUBLOCADE, the patient should be monitored for signs and symptoms of over-medication. It may be necessary to remove the depot and treat the patient with a sublingual buprenorphine product that permits rapid dose adjustments.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In a fertility study in rats, female mating, fertility, and fecundity indices were unaffected by the subcutaneous (SC) administration of SUBLOCADE up to approximately 38 times the maximum recommended human dose (MRHD) of 300 mg on an AUC basis. However, higher mean post-implantation loss was observed with SUBLOCADE at 38 times the maximum recommended human dose of buprenorphine and at an equivalent level of Indivior's delivery system alone, which correlated with higher mean number of resorptions and reduced mean number of viable fetuses/litter size. Mean gravid uterine weight and mean final body weight were lower and correlated with higher mean number of resorptions and lower fetal body weights. The NOAEL (No Observed Adverse Effect Level) for female fertility was approximately 25 times the MRHD for buprenorphine (AUC).

Male fertility and reproduction indices were lower as evidenced by abnormal sperm parameters (low motility, low mean number of sperm and higher percentage of abnormal sperm) with SUBLOCADE at 600 mg/kg and with an equivalent level of Indivior's delivery system. The NOAEL for male fertility parameters, including sperm analysis, and male-mediated developmental parameters was approximately 32 times the MRHD on an AUC basis.

In a fertility study in male and female rats, there were no adverse effects on mating, fertility, and fecundity indices when N-methyl-2-pyrrolidone (NMP) an excipient in SUBLOCADE, was administered SC at up to 288 mg/kg/day. NMP was administered daily in this study (compared with the proposed clinical monthly dosing) to ensure reproductive tissue exposure throughout the critical periods of development. The NOAEL for NMP corresponded to 91-fold the once monthly maximum human NMP exposure (AUC) in SUBLOCADE.

Use in pregnancy (Category C)

In an embryofetal development study in rats, SUBLOCADE administered subcutaneously to pregnant animals before mating and again on GD 7 during the period of organogenesis resulted in increased post-implantation loss, which correlated with higher mean number of resorptions and decreased number of viable fetuses per litter, and decreased mean fetal body weights at 900 mg/kg (approximately 38 times the MRHD of 300 mg of SUBLOCADE on an AUC basis); however, similar effects were observed with an equivalent level of Indivior's delivery system alone, indicating they may be attributable to the vehicle. Dose-related increases in incidences of skeletal malformations of the head and visceral malformations were observed with SUBLOCADE with significant changes at 900 mg/kg (approximately 38 times the MRHD on an AUC basis). Similar effects were observed with equivalent levels of Indivior's delivery system. Based on these results, the NOAEL for developmental toxicity was 300 mg/kg, or approximately 15 times the MRHD for buprenorphine (on an AUC basis) and approximately 267 times the NMP exposure (AUC) at the MRHD.

In a separate embryofetal study, daily subcutaneous administration of NMP to pregnant rats during the period of organogenesis at doses greater than 86 mg/kg/day (corresponding approximately 15 times the NMP exposure (AUC) at the MRHD) was associated with reduced fetal body weight, but

there were no teratogenic effects observed at NMP doses of up to 370 mg/kg/day, nor was any maternal toxicity observed. NMP was administered daily in this study (compared with the proposed clinical monthly dosing) to ensure reproductive tissue exposure throughout the critical periods of development. The NOAEL for fetal developmental effects corresponded to approximately 15 times the NMP exposure (AUC) at the MRHD.

In an embryofetal development study in rabbits, administration of a single subcutaneous injection of SUBLOCADE to pregnant animals on Gestation Day 7 during the period of organogenesis resulted in an increased litter incidence of skeletal malformations at 155 mg/kg (approximately 6 times the MRHD on an AUC basis). There was also an increased litter incidence of external malformations, visceral, and skeletal malformations and variations at 390 mg/kg SUBLOCADE (approximately 15 times the MRHD for buprenorphine [AUC]) with similar effects observed with an equivalent level of the Indivior's delivery system, indicating they may be attributable to the vehicle. Moreover, increased post-implantation loss, which correlated with increased mean number of resorptions and decreased mean number of viable fetuses, and decreased fetal body weights were observed at the same dose. The NOAEL for developmental toxicity for SUBLOCADE was 78 mg/kg buprenorphine or approximately 2 times the maximum human buprenorphine exposure and approximately 52 times the maximum human NMP exposure (AUC).

In a separate embryofetal study, an increased incidence of brachydactyly of the forelimbs, and reduced gallbladder size was seen in fetal rabbits following daily subcutaneous administration of NMP to their dams during the period of organogenesis at doses of 356 mg/kg/day (corresponding to exposures of 89 times MRHD NMP exposure (AUC) following daily SC NMP injections). The NOAEL for these effects (133 mg/kg/day), which was also the NOAEL for maternal toxicity, corresponded to daily administration of SUBLOCADE at exposures of 15 times the MRHD NMP exposure (AUC). NMP was administered daily in this study (compared with the proposed clinical monthly dosing) to ensure reproductive tissue exposure throughout the critical periods of development.

Mean pup bodyweights were generally significantly lower than saline and Indivior's delivery system groups in both sexes in a rat pre-/postnatal development study with maternal SC administration at 150 mg/kg (administered once on GD 7 and LD7) from birth through weaning and to PND 28; however body weights returned to saline control levels during the F1 growth phase. Dosing with Indivior's delivery system or SUBLOCADE had little or no effect on the physical development, sensory response, reflex performance, and subsequent reproductive performance of F1 pups. These results suggested that lowest dose of 50 mg/kg (exposure ratio 1.5 based on body surface area) is the NOAEL for rat pre-/postnatal development.

In a separate pre/postnatal development study, daily subcutaneous administration of NMP to female rats from GD 6 through to the end of lactation (PND 20) at 288 mg/kg/day (approximately 91 times the once monthly MRHD NMP exposure (AUC)) was associated with decreased offspring body weights at birth and throughout lactation and post-weaning, and reduced fertility and fecundity in both male and female offspring, in the absence of maternal toxicity. Maternal doses of 144 mg/kg (approximately 38 times the once monthly MRHD NMP exposure (AUC)) throughout the same period had no adverse effects on pregnancy or on the physical development, sensory response, reflex performance, and subsequent reproductive performance of F1 pups. NMP was administered daily in this study (compared with the proposed clinical monthly dosing) to ensure reproductive tissue exposure throughout the critical periods of development.

Continued use of heroin during pregnancy is associated with significant risk to the mother and the fetus and neonate.

Buprenorphine readily crosses the placental barrier and may cause respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions). The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Data on the use of buprenorphine in pregnancy, and its impact on the mother and fetus, are limited. Data from randomised, controlled trials and observational studies do not indicate an increased risk of maternal or fetal adverse outcomes compared to methadone.

Buprenorphine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in lactation

Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. Decreases in postnatal survival, growth and development were also observed in animals treated with buprenorphine during lactation. In two studies of thirteen women, buprenorphine was found in low levels in human breast milk. In both studies the estimated infant dose was <1% of the maternal dose. Because buprenorphine passes into the mother's milk, the development 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 or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Buprenorphine may influence the ability to drive and use machines when administered to opioid dependent patients. This product may cause drowsiness, dizziness or impaired thinking, especially during the first few days following treatment and dose adjustment. If used with alcohol or central nervous system depressants the effect is likely to be more pronounced (See Section 4.4 Special Warnings and Precautions for Use). Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that SUBLOCADE does not adversely affect their ability to engage in such activities.

There is an increased level of buprenorphine for 3 days after each injection. Buprenorphine levels increase during the first two months and are maintained with the 100 mg dose; further accumulation occurs with the 300 mg maintenance dose, which achieves steady-state after the fourth monthly injection.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The clinical 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 848 subjects in the pivotal Phase 3 studies and 235 in the Phase 1 and 2 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.

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

Adverse events reported for the groups receiving SUBLOCADE and placebo following administration in the 6-month, double-blind, placebo-controlled study are shown in Table 3. Both dosing regimens of SUBLOCADE included treatment with 300 mg for 2 months then either 100 mg or 300 mg for 4 months. The frequency of possible side effects listed below is defined using the following convention: Very common (≥1/10), Common (≥1/100 to <1/10).

Table 3. Adverse Events during the Phase 3 Double-Blind Study: ≥1% of Total Subjects Receiving SUBLOCADE by Body System and Treatment Group in Study RB-US-13-0001

System Organ Class Preferred term	**SUBLOCADE (300/300 mg) N=201**	**SUBLOCADE (300/100 mg) N=203**	**Placebo N=100**
Gastrointestinal Disorders			
Constipation	16 (8.0%)	19 (9.4%)	0
Nausea	16 (8.0%)	18 (8.9%)	5 (5.0%)
Vomiting	11 (5.5%)	19 (9.4%)	4 (4.0%)
Toothache	5 (2.5%)	8 (3.9%)	1 (1.0%)
Diarrhoea	5 (2.5%)	5 (2.5%)	5 (5.0%)
Abdominal pain upper	3 (1.5%)	4 (2.0%)	1 (1.0%)
General Disorders and Administration Site Conditions			
Injection site pruritus	19 (9.5%)	13 (6.4%)	4 (4.0%)
Injection site pain	12 (6.0%)	10 (4.9%)	3 (3.0%)
Fatigue	12 (6.0%)	8 (3.9%)	3 (3.0%)
Drug withdrawal syndrome	7 (3.5%)	9 (4.4%)	6 (6.0%)
Injection site erythema	6 (3.0%)	9 (4.4%)	0
Pain	5 (2.5%)	3 (1.5%)	4 (4.0%)
Injection site bruising	2 (1.0%)	2 (1.0%)	0
Injection site induration	2 (1.0%)	2 (1.0%)	0
Injection site oedema/swelling	2 (1.0%)	2 (1.0%)	0
Non-cardiac chest pain	2 (1.0%)	2 (1.0%)	0
Infections and Infestations			
Upper respiratory tract infection	12 (6.0%)	15 (7.4%)	1 (1.0%)
Nasopharyngitis	10 (5.0%)	11 (5.4%)	1 (1.0%)
Tooth abscess	5 (2.5%)	8 (3.9%)	0
Urinary tract infection	5 (2.5%)	4 (2.0%)	0
Gastroenteritis viral	5 (2.5%)	3 (1.5%)	0
Sinusitis	3 (1.5%)	3 (1.5%)	1 (1.0%)
Bronchitis	1 (0.5%)	5 (2.5%)	0
Tooth infection	1 (0.5%)	5 (2.5%)	0
Cellulitis	2 (1.0%)	2 (1.0%)	1 (1.0%)
Nervous System Disorders			
Headache	17 (8.5%)	19 (9.4%)	6 (6.0%)
Somnolence	4 (2.0%)	10 (4.9%)	0
Sedation	3 (1.5%)	7 (3.4%)	0
Dizziness	3 (1.5%)	5 (2.5%)	2 (2.0%)
Migraine	3 (1.5%)	2 (1.0%)	0
Lethargy	3 (1.5%)	1 (0.5%)	0

System Organ Class Preferred term	SUBLOCADE (300/300 mg) N=201	SUBLOCADE (300/100 mg) N=203	Placebo N=100
Paraesthesia	3 (1.5%)	1 (0.5%)	0
Investigations			
Hepatic enzyme increased*	15 (7.5%)	14 (6.9%)	1 (1.0%)
Blood creatine phosphokinase increased	5 (2.5%)	11 (5.4%)	1 (1.0%)
Weight increased	7 (3.5%)	2 (1.0%)	0
Electrocardiogram QT prolonged	3 (1.5%)	2 (1.0%)	0
Lipase increased	1 (0.5%)	3 (1.5%)	1 (1.0%)
Psychiatric Disorders			
Insomnia	17 (8.5%)	13 (6.4%)	11 (11.0%)
Anxiety	8 (4.0%)	10 (4.9%)	5 (5.0%)
Musculoskeletal and Connective Tissues Disorders			
Back pain	6 (3.0%)	8 (3.9%)	3 (3.0%)
Arthralgia	3 (1.5%)	4 (2.0%)	3 (3.0%)
Pain in extremity	4 (2.0%)	1 (0.5%)	0
Muscle twitching	3 (1.5%)	1 (0.5%)	0
Skin and Subcutaneous Tissue Disorders			
Hyperhidrosis	4 (2.0%)	4 (2.0%)	0
Pruritus	3 (1.5%)	4 (2.0%)	0
Rash	1 (0.5%)	6 (3.0%)	0
Injury, Poisoning and Procedural Complications			
Ligament sprain	3 (1.5%)	2 (1.0%)	0
Limb injury	1 (0.5%)	3 (1.5%)	1 (1.0%)
Muscle strain	2 (1.0%)	2 (1.0%)	0
Road traffic accident	1 (0.5%)	3 (1.5%)	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	3 (1.5%)	2 (1.0%)	0
Dyspnoea	3 (1.5%)	1 (0.5%)	0
Vascular Disorders			
Hypertension	2 (1.0%)	3 (1.5%)	0
Hot flush	2 (1.0%)	2 (1.0%)	1 (1.0%)
Metabolism and Nutrition Disorders			
Decreased appetite	4 (2.0%)	1 (0.5%)	3 (3.0%)

* 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).

Less Common Clinical Trial Adverse Reactions

Treatment-emergent adverse reactions reported as less common (<1%) during the pivotal Phase 3 studies of the SUBLOCADE clinical development program included:

Eye disorders: Vision blurred

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

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

Post-marketing experience with buprenorphine

Post-marketing experience with buprenorphine containing products for treatment of opioid dependence has been associated with the following side effects: respiratory depression (see Precautions) and coma, hallucinations, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, fetal disorders, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, urinary retention, vertigo, drug dependence, headache, nausea, vomiting, drug withdrawal syndrome, peripheral oedema, orthostatic hypotension, heart rate and rhythm disorders, and deaths.

Respiratory disorders with a frequency not known: Central sleep apnoea syndrome.

Gastrointestinal disorders with a frequency not known: Pancreatitis

Hepatobiliary disorders with a frequency not known: Spasm of sphincter of Oddi.

Endocrine disorders with a frequency not known: Adrenal insufficiency and Androgen deficiency.

Cases of hepatitis, jaundice, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy, hepatic necrosis and elevations in hepatic transaminases have been reported (see Section 4.4 Special Warnings and Precautions for Use).

Cases of acute or chronic hypersensitivity to buprenorphine have been reported with symptoms including rashes, urticaria, pruritus and reported cases of bronchospasm, angioedema, and anaphylactic shock (see Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions for Use).

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs. As with other opioids, buprenorphine could cause serotonin syndrome with 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.

<u>*Induction Sub-study of INDV-6000-401*</u> (See Section 5.1 Pharmacodynamic Properties – Clinical trials *for further details*).

At induction 77% of patients were fentanyl positive by urine drug screen (mean usage, 7 days a week). The incidence of precipitated withdrawal was higher in patients positive for fentanyl than in patients negative for fentanyl (Table 4), with no significant differences between standard or rapid induction. Of all events, 2.2% were severe and < 1% led to discontinuation from the study.

Table 4. Number (%) of Participants with Events Assessed as Precipitated Withdrawal by the Investigator during Induction, by Fentanyl Urine Drug Screen Subpopulation, in the Induction Sub-Study (N=729)

Fentanyl Positive Subpopulation			Fentanyl Negative Subpopulation		
SoC (N=196)	RI (N=367)	Total (N=563)	SoC (N=59)	RI (N=107)	Total (N=166)
44 (22.4)	107 (29.2)	151 (26.8)	2 (3.4)	7 (6.5)	9 (5.4)

RI: rapid induction; SoC: standard induction

Fentanyl subpopulations are based on the same-day urine screen result for fentanyl at induction.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Manifestations of acute overdose include miosis, sedation, hypotension, respiratory depression and death. Nausea and vomiting may be observed.

Toxic leukoencephalopathy has been observed with opioid overdose.

The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

Treatment

In the event of depression of respiratory or cardiac function, 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 following standard intensive care measures. The patient should be transferred to an environment within which full resuscitation facilities are available. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose.

The long duration of action of buprenorphine should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose. Naloxone can be cleared more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms, so a continuing infusion may be necessary. Ongoing IV infusion rates should be titrated to patient response. If infusion is not possible, repeated dosing with naloxone may be required.
Clinical data are limited with regards to the possible surgical removal of the depot as only two cases of surgical removal were reported in premarketing clinical studies.

For further information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) for advice.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Buprenorphine is a μ (mu) opioid receptor partial agonist, κ (kappa) opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the μ receptors in the brain which reduces craving for opioids and opioid withdrawal symptoms. This minimises the need of the opioid dependent patient for illicit opioid medicines.

During clinical pharmacology studies in opioid-dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, "good effect", and respiratory depression.

An intent of buprenorphine treatment is to suppress withdrawal symptoms, cravings and opioid drug liking. These effects are achieved through sufficient receptor occupancy (receptor blockade) as described below.

Plasma concentration and Clinical Response

In Opioid blockade study (13-0002) overall the relationship of the buprenorphine plasma concentration versus the VAS scores for the subjective measures (Drug Liking, Any Drug Effect, Good Drug Effect, Bad Drug Effect, Sedation, and High,) indicate there was a reduction in VAS scores with increased buprenorphine plasma concentration.

In a Positron Emission Tomography (PET) study with SUBLOCADE in 2 subjects (one subject receiving 200 mg SC injections and one subject receiving 300 mg SC injections) with opioid use disorder, 79 to 92% occupancy of the mu-opioid receptors in the brain at day 7 following the last dose under steady-state conditions was maintained for 28 days to 75 & 81%.

The SUBLOCADE opioid blockade study evaluated the blockade of subjective opioid effects, pharmacokinetics (PK) and safety of SC injections of SUBLOCADE and the results are presented in the Clinical Trials section.

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

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

Withdrawal symptoms [Clinical Opiate Withdrawal Scale (COWS)] were clinically controlled (defined as ≤12 on a 48-point scale) in most subjects consistent with a concentration of ≥2 ng/mL, however, observed maximal response (COWS 0) was reached at approximately 4 ng/mL.

Opioid craving was clinically controlled (defined as craving ≤20 on a 100-point Opioid Craving VAS) in most subjects consistent with a concentration of ≥2 ng/mL, however, the observed plateau for maximal response (0 craving) was reached at approximately 3 ng/mL.

Clinical trials

The pivotal studies from the SUBLOCADE clinical development program are a Phase 3 double-blind efficacy and safety study (13-0001) and an opioid blockade study (13-0002). Additional information

was derived from the induction substudy (INDV-6000-401) and the Community Long-Acting Buprenorphine (CoLAB1801) study.

Opioid blockade study (13-0002)
The study evaluated the blockade of subjective opioid effects, PK and safety of SC injections of SUBLOCADE in 39 subjects with OUD (not treatment-seeking).

The primary objective of this study was to demonstrate that the "Drug Liking" visual analog scale (VAS) measured after challenge with intramuscular injections of 6 mg (Dose 1) and 18 mg (Dose 2) hydromorphone is noninferior to the "Drug Liking" visual analog scale (VAS) measured after challenge with placebo at weeks 1 through 4 following the first injection of 300 mg SUBLOCADE.

After SUBLOCADE injections at weeks 0 and 4, on average, subjective effects of both 6 and 18 mg doses of hydromorphone were blocked; however wide variability was seen across subjects. Complete blockade continued throughout the 8 weeks of observation that followed the second SUBLOCADE injection.

For comparison, stabilisation doses of SL buprenorphine in Week 0 failed to provide full blockade of subjective effects of 18 mg of hydromorphone.

Efficacy study (13-0001)
The efficacy of SUBLOCADE in the treatment of opioid use disorder was evaluated in a Phase 3, 24-week, randomised, double-blind, placebo-controlled, multicentre trial in treatment-seeking patients who met the DSM-5 criteria for moderate or severe opioid use disorder. Patients were randomised 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 SC injections of placebo. All doses were administered by a physician or suitably-qualified designee and were separated by 28 ± 2 days. In addition to study medication, all subjects received protocol specified psychosocial support at least once a week (Individual Drug Counselling = IDC).

Prior to the first dose, subjects were inducted and dose stabilised on 8/2 to 24/6 mg per day of SUBOXONE® (buprenorphine/naloxone) sublingual film (SUBOXONE SL Film) for a minimum of 7 days. Subjects were considered dose stabilised when cravings and withdrawal symptoms were clinically controlled (≤12 on a 48-point COWS scale and ≤20 on a 100-point Opioid Craving VAS) for a minimum of 24 hours. After randomisation, supplemental dosing with SUBOXONE SL Film was not permitted during the study.

Efficacy was evaluated over Weeks 5 to 24 based on weekly urine drug screens combined with self-reported use of illicit opioid use. A “grace period” was applied for Weeks 1 through 4 to allow patients to stabilise in treatment. During this period, opioid use, if it occurred, was not considered in the analysis. Missing urine drug screen samples and/or self-reports during weeks 5-24 were counted as positive for illicit opioids. The key secondary endpoint was treatment success (responder), 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 patients were randomised 4:4:1:1 [203 subjects in the 300 mg/100 mg group, 201 patients in the 300 mg/300 mg group and 100 patients in the placebo group (2 groups of volume-matched placebo)].

Based on the cumulative distribution function (CDF) of the percentage of urine samples negative for illicit opioids combined with self-reports of negative for illicit opioid is collected from week 5 through week 24 (Table 5), regardless of dose, SUBLOCADE was superior to the placebo group with statistical

significance. The proportion of patients achieving treatment success (defined as patients with ≥80% opioid-free weeks) was statistically significantly higher in both groups receiving SUBLOCADE compared to the placebo group.

Analysis of the dropout pattern in Study 13-0001 indicated that opioid craving was a major predictor of dropout. An opioid craving score >20 was associated with an increase in dropout rate of up to 3.0 and 3.6-fold in active treatment arms and placebo arm, respectively, compared to craving ≤5.

Figure 10. Subjects Achieving Varying Percentages of Opioid-Free Weeks

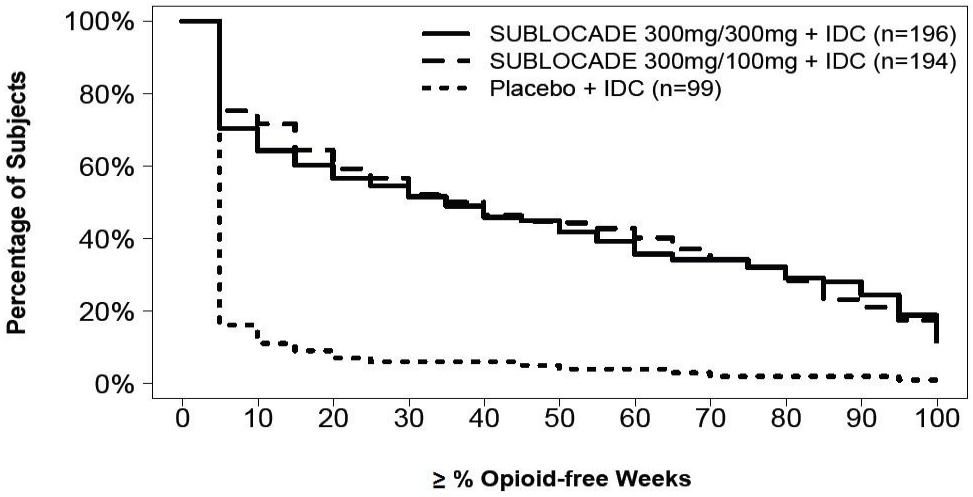


Table 5. Cumulative Distribution Function of Percentage of Opioid-Free Weeks

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

Table 6. Primary and Key Secondary Endpoints (Study 13-0001)

	SUBLOCADE 300 mg/100 mg	SUBLOCADE 300 mg/300 mg	Placebo
Percentage Abstinence (Opioid-free Weeks)			
Mean (SD)	42.7% (38.50%)	41.3% (39.66%)	5.0% (16.98%)
p-value	< 0.0001	< 0.0001	-
≥80% Abstinence (Opioid-free Weeks) (Responder)			
Treatment Success*	28.4%	29.1%	2.0%
p-value	< 0.0001	< 0.0001	-

*Treatment success 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.

Induction Substudy (INDV-6000-401)

Rapid induction on SUBLOCADE following a single dose of 4 mg transmucosal buprenorphine was compared to standard induction (minimum of 7 days of transmucosal buprenorphine) based on data from 723 treatment-seeking patients with moderate to severe OUD and high-risk opioid use. High-risk opioid use was defined as patients who for an average of 5 or more days per week in the last 4 weeks met one of the following criteria: using opioids via intravenous injection, using high doses of opioids [≥ 500 mg intravenous heroin equivalent daily], and/or using highly potent synthetic opioids [e.g fentanyl].

Patients were randomized at a 2:1 ratio to SUBLOCADE rapid induction or standard induction and stratified according to the same-day urine drug screen result for fentanyl due to the potential for fentanyl use to impact the response to induction. At induction 77% of patients were fentanyl positive and 23% were fentanyl negative by urine drug screen.

For rapid induction, patients were observed for a minimum of 1 hour after receiving a single dose of 4 mg transmucosal buprenorphine to confirm tolerability before administering the first injection of 300 mg SUBLOCADE. On initiation day, up to an additional 8 mg of transmucosal buprenorphine could be administered to manage withdrawal symptoms. In both treatment groups, the second 300 mg injection was administered at 1 week after the first SUBLOCADE injection and subsequent injections were scheduled every 4 weeks.

Rapid induction was superior to standard induction for the primary endpoint of participant retention at the second injection. The proportion of participants who received the second injection was higher in the rapid induction arm (66.4%) compared with the standard induction arm (54.5%) and the estimated treatment retention rate difference in the overall population was 11.8%.

The proportion of fentanyl-positive participants who received the second injection was 62.8% for rapid induction and 47.9% for standard induction (estimated difference: 14.8%). The proportion of fentanyl-negative participants who received the second injection was 78.8% for rapid induction and 76.3% for standard induction (estimated difference: 3.0%).

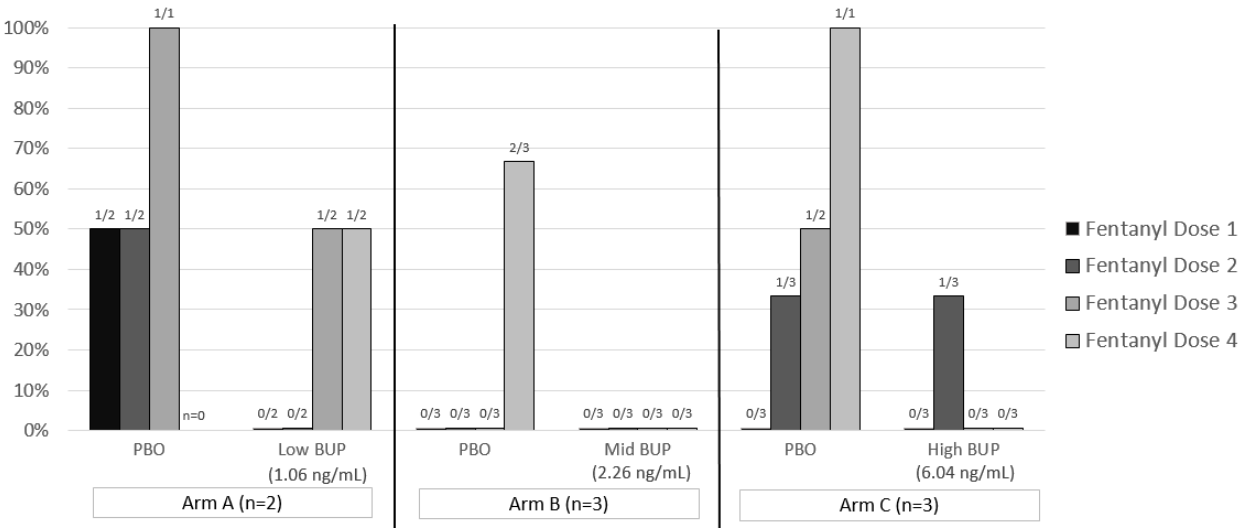
Pharmacodynamic Interaction with Fentanyl

An open-label, cross-over study was conducted in 8 opioid-tolerant subjects to assess the ability of intravenous buprenorphine to prevent respiratory depression associated with high doses of fentanyl administered in a clinical setting. Opioid-tolerant subjects were medically stable and taking oral morphine equivalents of ≥ 90 mg daily with no other CNS depressant use. Buprenorphine infusions at

three dose levels and placebo infusions were administered, followed by up to four doses of fentanyl. The three intravenous buprenorphine dose levels were designated as low (0.25 mg/70kg bolus + 0.1 mg/70kg/hr), mid (0.5 mg/70kg bolus + 0.2 mg/70kg/hr), and high (1.25 mg/70kg bolus + 0.5 mg/70kg/hr). The low, mid, and high buprenorphine dose levels produced average plasma concentrations (from 2 hours to 6 hours after infusion onset) of 1.06 ng/mL, 2.26 ng/mL, and 6.04 ng/mL, respectively. Buprenorphine concentrations of approximately 2 and 6 ng/mL are consistent with steady-state plasma levels achieved by 100 mg and 300 mg SUBLOCADE monthly injections, respectively.

Escalating intravenous fentanyl boluses of 0.25, 0.35, 0.50 and 0.70 mg/70 kg (up to a maximum cumulative dose of 1.8 mg/70 kg) were administered over 90 seconds at +2hr, +3hr, +4hr and +5hr after the start of intravenous infusion of buprenorphine or placebo. Apnoea events after each fentanyl bolus are shown in Figure 11. Four of the 8 subjects in the placebo infusion groups discontinued prior to the fourth fentanyl bolus because of apnoea (2 after the second bolus and 2 after the third bolus); 3 of the remaining 4 subjects experienced apnoea after the fourth fentanyl dose. All 8 subjects in the buprenorphine infusion groups completed the fentanyl boluses and 2 of the 8 experienced apnoea.

Figure 11. Occurrence of Apnoea Events After Fentanyl Doses in a Pharmacodynamic Interaction Study



There were 2 opioid-tolerant subjects in the low intravenous buprenorphine (BUP) group (Arm A), 3 in the mid BUP group (Arm B), and 3 in the high BUP group (Arm C). The numbers in parentheses represent the geometric mean of buprenorphine plasma concentrations in each group from 2 hours to 6 hours after infusion onset. The escalating fentanyl doses 1 to 4 were 0.25, 0.35, 0.50 and 0.70 mg/70 kg body weight. The same subject in the low BUP group had apnoea after the third and fourth fentanyl boluses.

Study CoLAB1801

An open-label, multicentre, single-arm study was conducted to evaluate monthly injections of SUBLOCADE over 48 weeks in 100 patients with opioid dependence from a diverse range of community healthcare settings. The study examined the retention rate in treatment at 48 weeks Results showed treatment retention rates of 75% with mean dosing interval between SUBLOCADE injections of 29 days.

5.2 PHARMACOKINETIC PROPERTIES

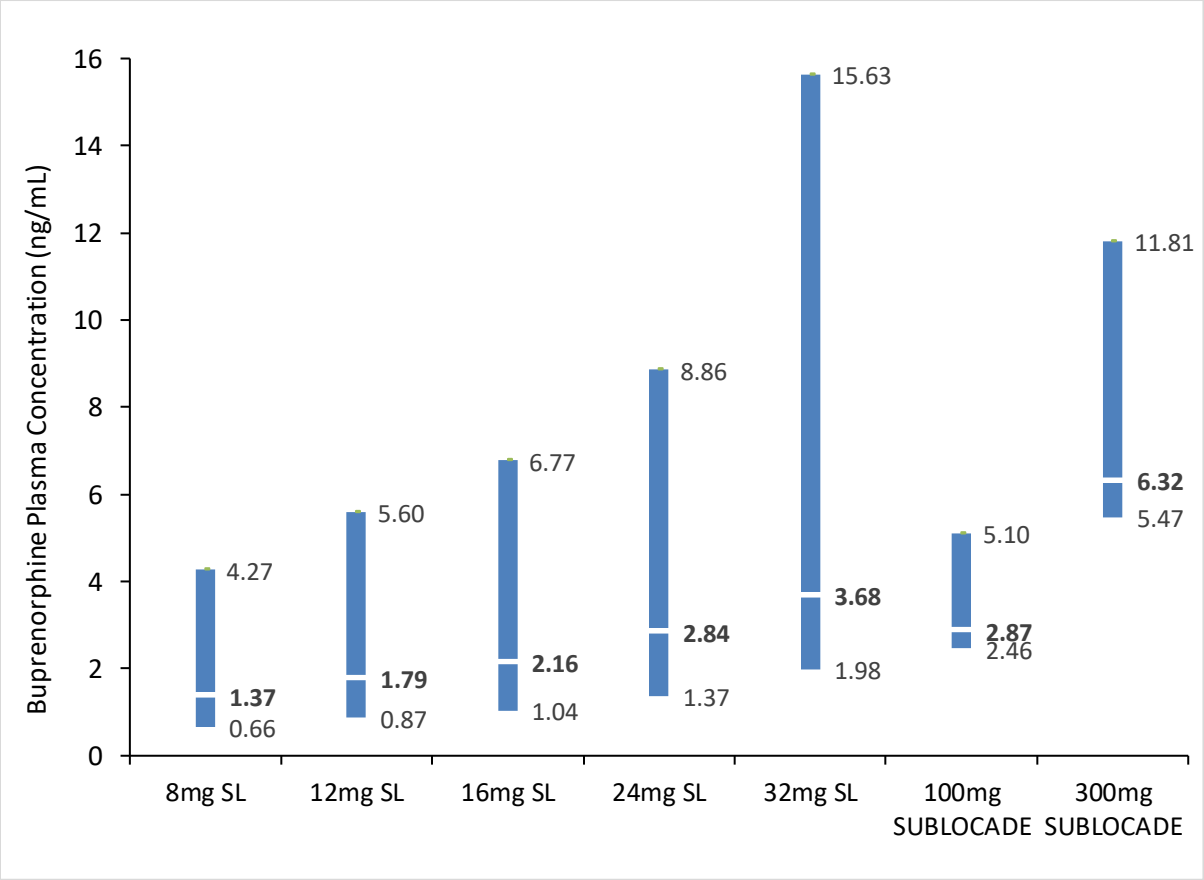
Absorption

The pharmacokinetics (PK) of buprenorphine following subcutaneous injection of SUBLOCADE was evaluated in subjects with opioid use disorder after single doses (20 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.

Buprenorphine average plasma concentration (C_{avg}) after one injection of 300 mg SUBLOCADE following 24 mg SUBUTEX stabilization was 2.19 ng/mL, with a peak concentration (C_{max}) of 5.37 ng/mL and a trough concentration (C_{trough}) of 1.86 ng/mL. Mean buprenorphine plasma concentrations levels for C_{avg}, C_{max} and C_{trough} at steady-state are presented in Figure 12 in comparison to transmucosal buprenorphine. At steady state, the plasma levels of buprenorphine reached with the maintenance dose of 100 mg are within the range obtained with transmucosal treatment: the peak concentration may be lower, while the average and trough concentration may be higher (see Figure 12).

Figure 12. Comparison of Steady-state Buprenorphine Plasma Exposure Between Daily Transmucosal Buprenorphine and Once Monthly SUBLOCADE at Trough (C_{trough}), Average (C_{avg}) and Peak (C_{max}) Levels



SL: sublingual

Each bar shows the geometric mean for buprenorphine trough concentration (bottom), average plasma concentration (white mark), and peak plasma concentration (top).

Data are based on population pharmacokinetic simulations, except for the 32 mg SL dose (observed data from an historical study)

Distribution

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

Metabolism

Buprenorphine is metabolised into its major metabolite, norbuprenorphine, primarily by CYP3A4.Norbuprenorphine can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity.

Norbuprenorphine steady-state plasma concentrations in humans after subcutaneous injection of SUBLOCADE are low compared to buprenorphine (AUC norbuprenorphine/buprenorphine ratio of 0.20 to 0.40).

Excretion

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

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70%), the rest being eliminated in urine.

A study assessing buprenorphine exposure 22 to 38 months following the last SUBLOCADE injection indicated that buprenorphine could potentially be detected in plasma and urine over that time period. When detected, buprenorphine concentrations in plasma were below levels known to control disease symptoms. Concentrations in urine were more variable than in plasma and generally higher depending on the test used. Hence, it is expected that patients will be positive for a longer time in urine than in plasma.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No evidence of clastogenic potential towards rat bone marrow cells by subcutaneous SUBLOCADE was found in an *in vivo* micronucleus test.

The conclusion from various genotoxicity assays, including Ames tests and chromosome aberration studies is that buprenorphine and N-methyl-2-pyrrolidone (NMP) are not genotoxic.

Carcinogenicity

Studies conducted in animals (rats and mice) show that buprenorphine is not carcinogenic at oral doses of up to 56 and 100 mg/kg/day, respectively, both of which equate to approximately 15-fold human exposure at the maximum recommended clinical dose of 32 mg based on body surface area.

N-methyl-2-pyrrolidone (NMP), an excipient in SUBLOCADE, produced an increase in hepatocellular adenomas and carcinomas in male and female mice at around 6 and 8 times, respectively, the maximum daily dose (MDD) of NMP delivered via SUBLOCADE. The clinical significance of these findings is unclear. No tumours were noted at 1 and 1.3 times the MDD. Exposure of rats to NMP for 2 years via inhalation (at around 0.7 x MDD) or via diet (at around 3 x MDD) was shown to be non-carcinogenic. The possible carcinogenicity of NMP from subcutaneous SUBLOCADE has not been tested.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Indivior's delivery system contains:
polyglactin
N-methyl-2-pyrrolidone

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2 – 8°C. Refrigerate. Do not freeze.

Once outside the refrigerator this product may be stored in its original packaging at room temperature (below 25°C) for up to 12 weeks prior to administration.

Discard SUBLOCADE if left at room temperature for longer than 12 consecutive weeks.

6.5 NATURE AND CONTENTS OF CONTAINER

SUBLOCADE is supplied in a single use pack.

SUBLOCADE buprenorphine 100 mg/0.5 mL modified release injection solution for subcutaneous administration is supplied as a single use dose in a 1 mL plastic syringe with a plunger stopper (bromobutyl rubber), together with a pre-packaged sterile safety needle (19 G, 16 mm with polypropylene shield).

SUBLOCADE buprenorphine 300 mg/1.5 mL modified release solution for injection for subcutaneous administration is supplied as a single-use dose in a 2.25 mL plastic syringe with a plunger stopper (bromobutyl rubber), together with a pre-packaged sterile safety needle (19 G, 16 mm with polypropylene shield).

Each assembled syringe with plastic plunger rod is supplied in an aluminium foil-laminate pouch containing an oxygen absorbing desiccant. The pouch is in a labelled paperboard carton along with a sterile safety needle and labelling.

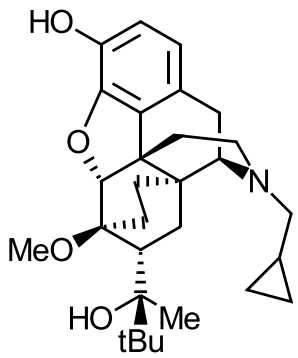
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Dispose of all syringe components in a secure sharps disposal container.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical structure of buprenorphine is:



CAS number

The CAS number is 52485-79-7.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 8

8 SPONSOR

Indivior Pty Ltd
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Macquarie Park NSW 2113
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For adverse event reporting please contact:
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Tel: +800-270-81901
PatientSafetyRoW@indivior.com

9 DATE OF FIRST APPROVAL

18 July 2019

10 DATE OF REVISION

14 January 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1	Removal of '*maintenance*'.
4.2	Updated Information on administration and dosage
4.4	Addition of Sleep-related breathing disorders (including central sleep apnoea), Adrenal insufficiency, Endocrine effects, Hepatobiliary disorders and Gastrointestinal Toxicity.
4.8	Addition of Respiratory, Gastrointestinal, Hepatobiliary and Endocrine disorders as part of post-marketing experience with buprenorphine section. Addition of induction information.
4.9	Addition of Toxic leukoencephalopathy. Deletion of New Zealand reference.
5.1	Additonal of induction and CoLAB studies – Clinical Trial section.