PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# $^{N}$pms-BUPRENORPHINE-NALOXONE

Buprenorphine and Naloxone Sublingual Tablet

Sublingual Tablet; buprenorphine (as buprenorphine hydrochloride) / naloxone (as naloxone hydrochloride dihydrate), 2 mg / 0.5 mg and 8 mg / 2 mg

USP

Partial Opioid Agonist
and
Opioid Antagonist

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## RECENT MAJOR LABEL CHANGES

| | |
|---|---|
| 4 DOSAGE AND ADMINISTRATION, 4.4 Administration | 09/2023 |
| 7 WARNINGS AND PRECAUTIONS, Gastro-intestinal | 09/2023 |

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**Sections or subsections that are not applicable at the time of authorization are not listed.**

## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

pms-BUPRENORPHINE-NALOXONE (buprenorphine and naloxone) is indicated for:

- substitution treatment in adults with problematic opioid drug dependence.

### 1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of buprenorphine/naloxone in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

### 1.2 Geriatrics

Geriatrics (> 65 years of age): The safety and efficacy of buprenorphine/naloxone have not been established in adults over 65 years of age.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, respiratory or cardiac function, concomitant disease or other drug therapy.

### 2 CONTRAINDICATIONS

- Patients who are hypersensitive to buprenorphine, naloxone, or to any ingredient in the formulation (For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**).
- Opioid naïve patients.
- 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 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.

## 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

**Serious Warnings and Precautions**

- **Limitations of Use**
  **pms-BUPRENORPHINE-NALOXONE must be dispensed daily under the supervision of a healthcare professional, until the patient has sufficient clinical stability and is able to safely store pms-BUPRENORPHINE-NALOXONE take-home doses (see 4 DOSAGE AND ADMINISTRATION).**

  **Appropriate security measures should be taken to safeguard stocks of pms-BUPRENORPHINE-NALOXONE against diversion.**

- **Addiction, Abuse, and Misuse**
  **Abuse and diversion of buprenorphine/naloxone have been reported. All patients should be monitored regularly for the development of these behaviours or conditions (see 7 WARNINGS AND PRECAUTIONS, Addiction, Abuse, and Misuse).**

- **Life-threatening Respiratory Depression: OVERDOSE**
  **Serious, life-threatening, or fatal respiratory depression may occur with use of pms-BUPRENORPHINE-NALOXONE. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed.**

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

- **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 7 WARNINGS AND PRECAUTIONS, Neurologic, and 9 DRUG INTERACTIONS).**
  - **Reserve concomitant prescribing of pms-BUPRENORPHINE-NALOXONE and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
  - **Consider dose reduction of CNS depressants, pms-BUPRENORPHINE-NALOXONE, or both in situations of concomitant prescribing.**
  - **Follow patients for signs and symptoms of respiratory depression and sedation.**

- **Accidental Exposure**
  **Accidental ingestion of even one dose of pms-BUPRENORPHINE-NALOXONE by individuals not physically dependent on opioids, especially children, can result in a fatal overdose of buprenorphine (see 4 DOSAGE AND ADMINISTRATION).**

- **Neonatal Opioid Withdrawal Syndrome**
  **Prolonged maternal use of pms-BUPRENORPHINE-NALOXONE during pregnancy can result in a neonatal opioid withdrawal syndrome, which may be life-threatening (see 7 WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome).**

- **Risk of Overdose in Opioid-Naïve Patients**
  **pms-BUPRENORPHINE-NALOXONE is not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose.**

- **Interchangeability of Dosage Forms**
  **Due to the greater bioavailability of buprenorphine-naloxone film compared to buprenorphine-naloxone tablet at certain dosage strengths, patients switching from a film formulation to a tablet should be monitored for opioid withdrawal and other symptoms of under-dosing.**

**pms-BUPRENORPHINE-NALOXONE should be placed under the tongue until completely dissolved, and patients should not swallow or consume food or drink until the tablet is completely dissolved. Altering pms-BUPRENORPHINE-NALOXONE to take it by routes other than the indicated sublingual route can lead to serious adverse events including death. Do not cut, break, crush or chew pms-BUPRENORPHINE-NALOXONE (see 7 WARNINGS AND PRECAUTIONS, Addiction, Abuse, and Misuse).**

# 4 DOSAGE AND ADMINISTRATION

## 4.1 Dosing Considerations

- Altering the tablet to take it by routes other than the indicated route can lead to serious adverse events including death. Do not cut, break, crush, swallow or chew pms-BUPRENORPHINE-NALOXONE.

**Appropriate security measures should be taken to safeguard stocks of pms-BUPRENORPHINE-NALOXONE against diversion.**

**pms-BUPRENORPHINE-NALOXONE must be dispensed on a daily basis under the supervision of a healthcare professional until the patient has sufficient clinical stability and is able to safely store pms-BUPRENORPHINE-NALOXONE take-home doses.**

- pms-BUPRENORPHINE-NALOXONE is indicated for substitution treatment in adults with problematic opioid drug dependence. Naloxone is an antagonist at mu-opioid receptors. The intention of the naloxone component is to deter injection and intranasal misuse and abuse in individuals physically dependent on mu-opioid full agonists.

- Opioid drug dependence is a chronic relapsing disease; length of treatment must be tailored

for each patient depending on his/her condition.

- Patients prescribed pms-BUPRENORPHINE-NALOXONE should be carefully monitored within a framework of medical, social, and psychological support as part of a comprehensive opioid-dependence treatment program.

- **pms-BUPRENORPHINE-NALOXONE sublingual tablets should only be prescribed by physicians who meet the following requirements:**

  1. **Experience in substitution treatment in opioid drug dependence, and**
  2. **Completion of a recognized Buprenorphine/Naloxone Education Program.**

  **The Buprenorphine/Naloxone Education Program is a risk management program that is founded on the following four core components that provide for the safe and effective use of the drug within a framework of medical, social and psychological support:**

  - **training of the prescribing physicians in the use of pms-BUPRENORPHINE-NALOXONE sublingual tablets;**
  - **maintenance of a list of Buprenorphine/Naloxone Education Program trained physicians;**
  - **daily dosing supervised by a healthcare professional, progressing to unsupervised administration as the patient's clinical stability permits;**
  - **take-home doses once the patient has sufficient clinical stability and is able to safely store pms-BUPRENORPHINE-NALOXONE. Take-home doses should be assessed and reviewed on a regular basis.**

- Physicians may obtain more information about a Buprenorphine/Naloxone Prescriber's Education Program by calling the following toll-free phone number: 1-888-550-6060.

### 4.2 Recommended Dose and Dosage Adjustment

Health Canada has not authorized an indication for pediatrics use (See 1.1 Pediatrics)

Induction

- Precautions to be taken before induction

  Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Regular monitoring of liver function is recommended.

  Prior to induction, consideration should be given to the type of opioid dependence (i.e., long- or short-acting opioid products), the time since last opioid use, and the degree or level of opioid dependence. To avoid precipitating opioid withdrawal, induction with pms-BUPRENORPHINE-NALOXONE should be undertaken when objective and clear signs of opioid withdrawal are evident.

- Patients taking heroin (or other short-acting opiates)

  For patients dependent on heroin or short-acting opioids, the first dose of pms-BUPRENORPHINE-NALOXONE should be started when objective signs of moderate opioid withdrawal appear, but not less than 6 hours after the patient last used opioids.

  A score equal to or greater than 13 on the Clinical Opiate Withdrawal Scale (COWS) may be a useful reference.

- Patients taking methadone (or long-acting opioid products)

  For patients receiving methadone, the methadone maintenance dose should be reduced to the minimum methadone daily dose that the patient can tolerate before beginning pms-BUPRENORPHINE-NALOXONE therapy. The first pms-BUPRENORPHINE-NALOXONE dose should be started only when objective signs of moderate opioid withdrawal appear (e.g. COWS score equal to or greater than 13), and generally not less than 24 hours after the patient last used methadone because of the long half-life of methadone.

- Induction dosage

  For induction, pms-BUPRENORPHINE-NALOXONE tablet should only be administered sublingually**.**

  Patients should be started with an initial dose of 2 mg or 4 mg and the dose may be titrated upwards in 2 or 4 mg increments of buprenorphine, at approximately 2-hour intervals, under supervision. The suggested total dose target on Day 1 is within the range of 8 – 12 mg.

  On Day 2, a single daily dose between 8 mg to 16 mg pms-BUPRENORPHINE-NALOXONE is recommended.

  It is recommended that an adequate treatment dose, titrated to clinical effectiveness, be achieved as rapidly as possible (e.g., over one to two days). In some studies, a too-gradual induction over several days led to a high drop-out rate of buprenorphine patients during the induction period.

  During initiation of treatment, closer dosing supervision is recommended to ensure proper sublingual placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

  Patients who have been opioid abstinent and wish to return to treatment should be initiated with a 2 mg pms-BUPRENORPHINE-NALOXONE dose and then have their dosages titrated per physician's judgement.

Maintenance

- Dosage stabilisation and maintenance therapy

  Following treatment induction, the patient should be rapidly stabilised on an adequate maintenance dose by titrating to clinical effect. Dose titration in increments or decrements of 2 - 8 mg buprenorphine to a level that holds the patient in treatment and suppresses opioid withdrawal is guided by reassessment of the clinical and psychological status of the patient.

  Clinical studies have shown that a maintenance dose of 12 mg to 16 mg of pms-BUPRENORPHINE-NALOXONE used once daily is clinically effective for most patients. Doses should not exceed a maximum single daily dose of 24 mg.

  During maintenance therapy, it may be necessary to periodically re-stabilise the patient to a new maintenance dosage in response to changing patient needs.

- Less-than-daily dosing

  Following successful induction and after the patient is receiving a stable dose, the frequency of pms-BUPRENORPHINE-NALOXONE dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient who receives a stable daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 24 mg.

  In some patients, following successful induction and after the patient is receiving a stable dose, the frequency of pms-BUPRENORPHINE-NALOXONE dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually-titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no medication on the intervening days. However, the dose given on any one day should not exceed 24 mg. Patients requiring a titrated dose greater than 8 mg/day may not find this regimen adequate.

  Patients with problematic drug dependence upon concomitant CNS-active substances, including alcohol, should not be treated with the increased doses required by the less-than-daily dosing regimen intended for use in a supervised dose setting. Patients with sporadic use of concomitant non-opioid medications should be monitored closely, and all patients dosed on a less-than-daily basis should be observed for at least 1.5 hours following the first dose administration initiating less-than-daily dosing.

- Reducing dosage and terminating treatment (medical taper)

  The decision to discontinue therapy with pms-BUPRENORPHINE-NALOXONE should be made as part of a comprehensive treatment plan. To avoid withdrawal symptoms and potential relapse to illicit drug use, the pms-BUPRENORPHINE-NALOXONE dose may be progressively

decreased over time until treatment can be discontinued. The decision to taper should be made by the prescriber, patient, and counsellor/support staff. The risk of relapse following withdrawal of treatment should be considered.

To avoid opioid overdose, patients should be informed that reducing and/or discontinuing any opioids including pms-BUPRENORPHINE-NALOXONE decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

**Dose adjustments for patients with hepatic impairment**

pms-BUPRENORPHINE-NALOXONE is contraindicated in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. Dose adjustments may be considered in cases of mild to moderate hepatic impairment, and patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and / or buprenorphine (see **10.3 Pharmacokinetics**).

**Dose adjustments for patients with renal impairment**

Caution is recommended when dosing patients with severe renal impairment ($CL_{cr}$ <30 ml/min) which may require dose adjustment.

**4.4 Administration**

It is recommended that the minimum number of tablet(s) be used to achieve the dose.

Patients should not swallow or consume food or drink until pms-BUPRENORPHINE-NALOXONE sublingual tablet is completely dissolved.

Proper administration technique should be described and demonstrated to the patient. pms-BUPRENORPHINE-NALOXONE should not be moved after placement.

Advise patients to do the following after the product has completely dissolved in the oral mucosa: take a sip of water, swish gently around the teeth and gums, and swallow. Advise patients to wait for at least one hour after taking pms-BUPRENORPHINE-NALOXONE before brushing teeth (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).

pms-BUPRENORPHINE-NALOXONE tablet should be placed under the tongue until completely dissolved.

When multiple tablets are needed to achieve the prescribed dosage, a patient may place all tablets sublingually at the same time or in two separate portions, the second portion to be placed sublingually directly after the first portion has dissolved.

**Switching From a Film Formulation**

Patients being switched from a film formulation should be started on the same dosage of the previously administered product. However, dosage adjustments may be necessary as not all strengths and combinations of the buprenorphine-naloxone tablet are bioequivalent to the buprenorphine-naloxone film. Both the 8 mg / 2 mg and the 12 mg / 3 mg tablets may result in significantly lower plasma levels of buprenorphine and naloxone compared to the same dose of film.

Patients should be monitored for symptoms related to under-dosing when switching from film to tablet.

Combining different formulations or alternating between formulations is not advised.

**Clinical Supervision**

It is recommended that treatment be initiated with supervised administration progressing to unsupervised administration as the patient's clinical stability permits. During the initiation of treatment, closer supervision of dosing is recommended to ensure proper sublingual placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

As the patient becomes stabilised in treatment, longer intervals between patient assessments may be appropriate based upon patient compliance with treatment, effectiveness of the treatment plan, and overall patient progress. It is also recommended that the prescription quantity for unsupervised administration be determined with consideration for the frequency of patient visits and the patient's ability to manage supplies of take-home medication.

### 4.5 Missed Dose

Missed doses are notable as they may contribute to a loss of tolerance to buprenorphine. The more doses a patient misses, the greater the loss of tolerance. Patients should be reassessed to ensure they are receiving an appropriate dose on resumption of pms-BUPRENORPHINE-NALOXONE treatment. The resumption dose may need to be adjusted back to levels used during pms-BUPRENORPHINE-NALOXONE induction.

If the patient has relapsed to full agonist opioids, the patient should be advised to suspend resumption of their pms-BUPRENORPHINE-NALOXONE until they are in moderate opioid withdrawal due to the risk of precipitated withdrawal.

## 5 OVERDOSAGE

- Clinical Presentation

Signs and symptoms of opioid overdose include miosis (pinpoint pupils), sedation, hypotension,

toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy, respiratory depression, and death. Nausea and vomiting may be observed.

The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death.

- Treatment of Overdose

In the event of overdose, general supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. Symptomatic treatment of respiratory depression, following standard intensive care measures, should be performed. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment where full resuscitation facilities are available.

If the patient vomits, care must be taken to prevent aspiration of the vomitus.

Due to the extremely slow dissociation of buprenorphine from opioid receptors, naloxone even at high doses of 10-35 mg/70kg may be of limited value in the management of buprenorphine overdose. Use of an opioid antagonist (e.g., naloxone) is nevertheless recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared to its effects on full agonist opioid agents.

If naloxone is used, the long duration of action of buprenorphine should be taken into consideration when determining the length of treatment and medical surveillance 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. Carefully monitor the patient until spontaneous respiration is reliably re-established. Even in the face of improvement, continued medical monitoring is required for at least 24 hours because of the possibility of extended effects of buprenorphine.

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

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 1 – Dosage Forms, Strengths, Composition and Packaging**

| **Dosage Form / Route of Administration** | **Strength / Composition** | **Packaging** | **Non-medicinal Ingredients** |
|---|---|---|---|
| pms-BUPRENORPHINE-NALOXONE Tablet / Sublingual | **2 mg / 0.5 mg tablet:**<br>2 mg buprenorphine/<br>0.5 mg naloxone | Each white to off-white, round, biconvex, uncoated tablets with a "N2" engraved on one side and a logo "↑" on the other side, contains 2 mg buprenorphine (as buprenorphine hydrochloride) and 0.5 mg naloxone (as naloxone hydrochloride dihydrate). Bottles of 30 tablets. | Acesulfame Potassium, Citric Acid Anhydrous, Corn Starch, Lactose Monohydrate, Lemon & Lime Flavour, Mannitol, Povidone K30, Sodium Citrate, and Sodium Stearyl Fumarate. |
| | **8 mg / 2 mg tablet:**<br>8 mg buprenorphine/<br>2 mg naloxone | Each white to off-white, round, biconvex, uncoated tablets with a "N8" engraved on one side and a logo "↑" on the other side, contains 8 mg buprenorphine (as buprenorphine hydrochloride) and 2 mg naloxone (as naloxone hydrochloride dihydrate). Bottles of 30 tablets. | |

## 7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

### General

pms-BUPRENORPHINE-NALOXONE is indicated for substitution treatment in adults with problematic opioid drug dependence, and, as with other opioid substitution medications, should be used within the framework of medical, social and psychological support as part of a comprehensive opioid-dependence treatment program.

As with other opioids, pms-BUPRENORPHINE-NALOXONE should be used with caution in patients with the following conditions:

- myxedema, hypothyroidism, or adrenal cortical insufficiency (e.g. Addison's disease);
- toxic psychoses;
- hypotension, prostatic hypertrophy or urethral stricture.

Opioid-induced miosis, 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. Opioids should be administered with caution to elderly or debilitated patients (see **7.1.4 Geriatrics**).

### Addiction, Abuse, and Misuse

pms-BUPRENORPHINE-NALOXONE contains buprenorphine, a substance that can be misused or abused in a manner similarly to other opioids, legal or illicit, which can lead to overdose and death. 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 pms-BUPRENORPHINE-NALOXONE is appropriate for the patient. Buprenorphine is sought by people with opioid use disorders and is subject to criminal diversion. This should be considered when prescribing pms-BUPRENORPHINE-NALOXONE in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion.

Prescribe and dispense pms-BUPRENORPHINE-NALOXONE with appropriate precautions to minimize risk of misuse, abuse, or diversion, and ensure appropriate protection from theft, including in the patient's home. Clinical monitoring appropriate to the patient's level of stability and periodic re-evaluation of therapy is essential. Multiple refills should not be prescribed early in treatment and should be given only with appropriate patient follow-up visits.

Monitor all patients receiving pms-BUPRENORPHINE-NALOXONE and refer patients who have conditions indicative of diversion or progression of opioid dependence and addictive behaviors to more intensive and structured treatments for substance use.

Sub-optimal treatment with pms-BUPRENORPHINE-NALOXONE may prompt medication misuse by

the patient, leading to overdose or treatment dropout. A patient who is under-dosed with pms-BUPRENORPHINE-NALOXONE may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or sedative-hypnotics such as benzodiazepines.

The combining of buprenorphine with naloxone in pms-BUPRENORPHINE-NALOXONE is intended to deter misuse and abuse of the buprenorphine. Intravenous or intranasal misuse of pms-BUPRENORPHINE-NALOXONE is expected to be less likely than with buprenorphine alone since the naloxone in pms-BUPRENORPHINE-NALOXONE can precipitate withdrawal in individuals dependent on heroin, methadone, or other opioid agonists.

Some risks of misuse and abuse include overdose, respiratory depression and hepatic injury, and spread of blood borne viral infections. Some adverse effects 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.

Extra precautions are required in patients dependent upon concomitant CNS-active substances, including alcohol, and patients with sporadic use of concomitant non-opioid medications.

**Carcinogenesis and Mutagenesis**

See **16 NON-CLINICAL TOXICOLOGY**.

**Cardiovascular**

- **Hypotension**

pms-BUPRENORPHINE-NALOXONE may cause orthostatic hypotension in ambulatory patients.

pms-BUPRENORPHINE-NALOXONE administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines, and other tranquilizers, sedatives/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of pms-BUPRENORPHINE-NALOXONE.

- **QTc prolongation**

Products containing buprenorphine have been shown to be associated with QTc prolongation.

pms-BUPRENORPHINE-NALOXONE 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 prescribing pms-BUPRENORPHINE-NALOXONE to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug (see **9 DRUG INTERACTIONS**).

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, light-headedness, fainting, or changes in or new use of other medications.

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

**Dependence/Tolerance**

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence with or without psychological dependence, characterized by withdrawal upon abrupt discontinuation or rapid taper. Withdrawal (abstinence) symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see 8.2 Clinical Trial Adverse Reactions). The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset.

Patients who elect to discontinue treatment with pms-BUPRENORPHINE-NALOXONE should be monitored for withdrawal signs and symptoms.

**Driving and Operating Machinery**

pms-BUPRENORPHINE-NALOXONE may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery.

Patients should be cautioned about operating hazardous machinery and automobiles, until they are reasonably certain that pms-BUPRENORPHINE-NALOXONE therapy does not adversely affect their ability to engage in such activities.

pms-BUPRENORPHINE-NALOXONE may cause orthostatic hypotension, drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If used together with alcohol or central nervous system depressants (such as benzodiazepines, tranquilizers, sedatives or hypnotics), the effect is likely to be more pronounced.

**Endocrine and Metabolism**

- **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.

**Gastrointestinal**

Buprenorphine, a component of pms-BUPRENORPHINE-NALOXONE, and other morphine-like opioids have been shown to decrease bowel motility and increase intracholedochal pressure. pms-BUPRENORPHINE-NALOXONE may obscure the diagnosis or clinical course of patients with acute abdominal conditions, and should be administered with caution to patients with dysfunction of the biliary tract.

- **Dental Adverse Events**

Cases of dental caries, some severe (i.e., tooth fracture, tooth loss), have been reported following the use of transmucosal buprenorphine-containing products. Reported events include cavities, tooth decay, dental abscesses/infection, rampant caries, tooth erosion, fillings falling out, and, in some cases, total tooth loss. Treatment for these events included tooth extraction, root canal, dental surgery, as well as other restorative procedures (i.e., fillings, crowns, implants, dentures).

Multiple cases were reported in individuals without any prior history of dental problems. However, the causality has not been established in all the cases.

Refer patients to dental care services and encourage them to have regular dental checkups while taking pms-BUPRENORPHINE-NALOXONE. Educate patients to seek dental care and strategies to maintain or improve oral health while being treated with transmucosal buprenorphine-containing products. Strategies include, but are not limited to, gently rinsing the teeth and gums with water and then swallowing after pms-BUPRENORPHINE-NALOXONE has been completely dissolved in the oral mucosa. Advise patients to wait for at least one hour after taking pms-BUPRENORPHINE-NALOXONE before brushing teeth (see 4.4 Administration).

**Hepatic/Biliary/Pancreatic**

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 hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. 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 injection 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. Liver function tests, prior to initiation of treatment are recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, pms-BUPRENORPHINE-NALOXONE may need to be carefully discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

**Immune**

- **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, urticaria, and pruritus. Cases of bronchospasm, angioedema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine or naloxone or any component of the formulation is a contraindication to pms-BUPRENORPHINE-NALOXONE use.

**Monitoring and Laboratory Tests**

Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Regular monitoring of liver function is 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 (NOWS)**

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 the opioid withdrawal syndrome in adults, the 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.

NOWS may present as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and/or failure to gain weight. Signs of neonatal withdrawal usually occur in the first days after birth. The duration and severity of NOWS may vary. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to minimize the risk of respiratory depression or withdrawal syndrome in neonates. Based on the currently available data, the incidence of NOWS is not clear and there does not appear to be a dose-response relationship.

Advise pregnant women receiving opioid addiction treatment with pms-BUPRENORPHINE-NALOXONE of the risk of a NOWS and ensure that appropriate treatment for the newborn will be available.

This risk of NOWS and the risk of exposure to pms-BUPRENORPHINE-NALOXONE during pregnancy must be balanced against the risk of untreated opioid addiction. The decision to discontinue pms-BUPRENORPHINE-NALOXONE therapy during pregnancy should be made as part of a comprehensive treatment plan (see **7.1.1 Pregnant Women**).

**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 anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioids (see **9 DRUG INTERACTIONS**). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid is

initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when pms-BUPRENORPHINE-NALOXONE is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **9 DRUG INTERACTIONS**).

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

- **Serotonin Toxicity / Serotonin Syndrome:**

Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with buprenorphine, including pms-BUPRENORPHINE-NALOXONE, particularly during combined use with other serotonergic drugs (See **9 DRUG INTERACTIONS**). Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing)and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

If concomitant treatment with pms-BUPRENORPHINE-NALOXONE and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **9 DRUG INTERACTIONS**). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

- **Elevation of Cerebrospinal Fluid Pressure**

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with a history of seizure, 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.

**Peri-Operative Considerations**

pms-BUPRENORPHINE-NALOXONE is not indicated for the treatment of pain. There have been reported deaths of opioid-naïve individuals who received a 2 mg dose of buprenorphine as a sublingual tablet for analgesia.

- **Pain Management**

While on pms-BUPRENORPHINE-NALOXONE, situations may arise where patients need acute pain management, or may require anesthesia. Treat patients receiving pms-BUPRENORPHINE-NALOXONE 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 pms-BUPRENORPHINE-NALOXONE.

**Precipitation of Opioid Withdrawal Syndrome**

Because of the partial agonist properties of buprenorphine, pms-BUPRENORPHINE-NALOXONE can precipitate withdrawal symptoms in opioid-dependent patients if administered before the agonist effects resulting from recent opioid use or misuse have subsided.

To avoid precipitating an opioid withdrawal syndrome during induction onto pms-BUPRENORPHINE-NALOXONE from short-acting or long-acting opioids, the patient should show objective signs and symptoms of at least moderate withdrawal prior to induction dosing. For example, a moderate score of withdrawal, equal or greater than 13 on the Clinical Opiate Withdrawal Scale (COWS) may be a useful reference assessment.

Withdrawal symptoms may also be associated with sub-optimal dosing.

Because it contains naloxone, pms-BUPRENORPHINE-NALOXONE may produce marked and intense withdrawal signs and symptoms if misused or abused intranasally or by injection by individuals dependent on full opioid agonists such as heroin, morphine or methadone.

**Renal**

Renal elimination plays a relatively minor role (see **10.3 Pharmacokinetics**) in the overall clearance of buprenorphine; therefore, dose modification based on renal function is not required. However, metabolites of buprenorphine accumulate in patients with advanced renal failure and caution is recommended when dosing patients with severe renal impairment ($CL_{cr}$ <30 mL/min) which may require dose adjustment.

The effects of renal failure on naloxone pharmacokinetics are unknown.

**Reproductive Health: Female and Male Potential**

- **Fertility**

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28 times the recommended human daily sublingual dose of 16 mg on a mg/$m^2$ basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/$m^2$ basis) had no adverse effect on fertility.

- **Sexual Function/Reproduction**

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

**Respiratory**

- **Life-Threatening Respiratory Depression**

Clinically significant respiratory depression and death may occur in patients receiving pms-BUPRENORPHINE-NALOXONE. A number of cases of death due to respiratory depression have been reported, particularly when buprenorphine was used by IV route and in combination with benzodiazepines, when high dose buprenorphine was administered to individuals not physically dependent on opioids, or with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Deaths have also been reported in association with concomitant administration of buprenorphine and other CNS depressants. Patients should be warned of the potential danger of the self-administration of benzodiazepines or other depressants while under treatment with pms-BUPRENORPHINE-NALOXONE, particularly when pms-BUPRENORPHINE-NALOXONE is misused or abused.

Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed (see **7.2 Special Populations**). pms-BUPRENORPHINE-NALOXONE may cause severe, possibly fatal, respiratory depression in children who accidentally

ingest it. Protect children against exposure and access (see **12 SPECIAL HANDLING INSTRUCTIONS**).

pms-BUPRENORPHINE-NALOXONE should be used with caution in patients with compromised respiratory function (e.g., decreased respiratory reserve, hypoxia, hypercapnia, or kyphoscoliosis), in the elderly and in debilitated patients. Patients with the physical and/or pharmacological risk factors above should be monitored, and dose reduction may be considered.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper (see **4 DOSAGE AND ADMINISTRATION**)**.**

**In the case of overdose, primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, as required.** In patients with respiratory depression, symptomatic treatment following standard intensive care measures should be instituted (see **5 OVERDOSAGE**).

**Information for Patients**

- Patients should be advised to keep pms-BUPRENORPHINE-NALOXONE out of reach and sight of children to prevent accidental ingestion that can result in death. Patients should be advised not to take this medicine in front of children. Patients should be advised that if a child is exposed to pms-BUPRENORPHINE-NALOXONE, medical attention should be sought immediately.

- Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines, sedatives, tranquilizers, antidepressants or alcohol while taking pms-BUPRENORPHINE-NALOXONE, which may result in serious harm or death. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed bytheir physician.

- Patients should inform their physician if other prescription medications are currently being used or are prescribed for future use.

- Patients should be cautioned to keep pms-BUPRENORPHINE-NALOXONE in a safe place, and to protect it from theft. Patients should be advised never to give pms-BUPRENORPHINE-NALOXONE to anyone else, as it may cause harm or death. Selling or giving away this medicine is against the law.

- Patients should inform their family members that, in the event of overdose, the treating physician or emergency staff should be informed that the patient is physically dependent on narcotics and is being treated with pms-BUPRENORPHINE-NALOXONE.

- Patients should be cautioned about driving a car or operating hazardous machinery,

including automobiles, until they are reasonably certain that pms-BUPRENORPHINE-NALOXONE therapy does not adversely affect their ability to engage in such activities. pms-BUPRENORPHINE-NALOXONE may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving or operating machinery, especially during drug induction and dose adjustment.

- Patients should be cautioned that, like other opioids, pms-BUPRENORPHINE-NALOXONE may cause orthostatic hypotension in ambulatory individuals.

- Patients should be advised not to change the dosage of pms-BUPRENORPHINE-NALOXONE without consulting their physician.

- Patients should be informed that pms-BUPRENORPHINE-NALOXONE can cause opioid drug dependence and that opioid withdrawal signs and symptoms may occur when the medication is discontinued. Patients seeking to discontinue treatment with buprenorphine for opioid dependence should be advised to work closely with their physician on a tapering schedule and should be apprised of the potential to relapse.

- Women of childbearing potential, who become pregnant or are planning to become pregnant, should be advised to consult their physician regarding the possible risks to their baby if they are exposed to pms-BUPRENORPHINE-NALOXONE during pregnancy. Patients who are breastfeeding should be warned to monitor the infant for drowsiness and difficulty breathing.

- Athletes should be aware that this medicine may cause a positive reaction to "anti-doping tests" and should inform the authorities that they are being treated with pms-BUPRENORPHINE-NALOXONE.

## 7.1 Special Populations

### 7.1.1 Pregnant Women

Limited published data from clinical trials, observational studies, and case reports on the use of buprenorphine in pregnancy do not indicate an increased risk of major malformations. Buprenorphine can cross the placental barrier and can be life-threatening to the fetus. There are no adequate and well-controlled studies of buprenorphine/naloxone use in pregnant women; therefore, it should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, may be life-threatening (see **7 WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome**).

Pregnant women using pms-BUPRENORPHINE-NALOXONE should not discontinue their

medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. If pms-BUPRENORPHINE-NALOXONE is discontinued, tapering should be slow and under medical supervision to avoid serious adverse events to the fetus, withdrawal symptoms in the pregnant woman and potential relapse to illicit drug use. The decision to discontinue pms-BUPRENORPHINE-NALOXONE therapy during pregnancy should be made by the prescriber, patient, and counsellor/support staff as part of a comprehensive treatment plan. The risk of relapse following withdrawal of treatment should be considered (see **7 WARNINGS AND PRECAUTIONS**). Healthcare professionals should continue to meet with patients throughout their pregnancy to monitor the management of the opioid addiction, to minimize the risk of reintroducing opioids and to reinstate pms-BUPRENORPHINE-NALOXONE at the appropriate dose if required (see **4 DOSAGE AND ADMINISTRATION**).

Dosage adjustments of buprenorphine may be required during pregnancy, even if the patient was maintained on a stable dose prior to pregnancy. Withdrawal signs and symptoms should be monitored closely, and the dose adjusted as necessary. If the pregnant woman has chosen to discontinue treatment at any point during her pregnancy or postpartum period (see Reducing dosage and terminating treatment (medical taper)), and subsequently chooses to restart treatment, the treatment should be initiated with 2 mg and then titrated per physician's judgement.

Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant doses. Pre- and post-natal development studies in rats demonstrated dystocia, increased neonatal deaths, and developmental delays. No clear teratogenic effects were seen with a range of doses equivalent to or greater than the human dose. However, in a few studies, some events such as acephalus, omphalocele, and skeletal abnormalities were observed but these findings were not clearly treatment-related. Embryo-fetal death was also observed in both rats and rabbits.

**Labor and Delivery**

Since opioids can cross the placental barrier and are excreted in breast milk, pms-BUPRENORPHINE-NALOXONE is not recommended to be used during labour and delivery unless, in the judgement of the physician, the potential benefits outweigh the risks. 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 **7 WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome**).

### 7.1.2 Breast-feeding

There are no data on the combination product buprenorphine/naloxone in breastfeeding, however oral absorption of naloxone is limited. Buprenorphine and its metabolite

norbuprenorphine are excreted in human milk and infant urine. Limited data from two published studies that included 13 lactating women in total, who were maintained on a sublingual dose of 2.4 to 24 mg/day, did not report adverse reactions in infants exposed to buprenorphine through breast milk and suggest that infant buprenorphine exposure through breast milk is less than 1% of the maternal daily dose.

Caution should be exercised when pms-BUPRENORPHINE-NALOXONE is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for pms-BUPRENORPHINE-NALOXONE and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. Nursing mothers taking pms-BUPRENORPHINE-NALOXONE should be advised to monitor the infant for increased drowsiness and breathing difficulties and infants should be regularly monitored by a health care professional.

Life-threatening respiratory depression may occur in the neonate if opioids are administered to a nursing mother.

### 7.1.3 Pediatrics

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of buprenorphine/naloxone in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

### 7.1.4 Geriatrics

The safety and efficacy of buprenorphine/naloxone have not been established in adults over 65 years of age.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrating upwards slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Patients with Hepatic Impairment:**

pms-BUPRENORPHINE-NALOXONE is contraindicated in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. If pms-BUPRENORPHINE-NALOXONE is used in this patient population, caution is advised (see **10.3 Pharmacokinetics**).

Both buprenorphine and naloxone are extensively metabolized by the liver. In patients with moderate and severe hepatic impairment, plasma levels and half-life values of both buprenorphine and naloxone were found to be markedly increased compared to healthy subjects. This effect was more pronounced in patients with severe hepatic impairment.

Hepatic impairment results in a reduced clearance of naloxone to a much greater extent than

buprenorphine, and the doses of buprenorphine and naloxone in this fixed-dose combination product cannot be individually titrated. Therefore, patients with severe hepatic impairment will be exposed to substantially higher levels of naloxone than patients with normal hepatic function. This may result in an increased risk of precipitated withdrawal at the beginning of treatment (induction) and may interfere with buprenorphine's efficacy throughout treatment. In patients with moderate hepatic impairment, the differential reduction of naloxone clearance compared to buprenorphine clearance is not as great as in patients with severe hepatic impairment. Dose adjustments may be considered in cases of mild to moderate hepatic impairment, and patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and / or buprenorphine. As with other opioids, buprenorphine has been shown to increase intracholedochal pressure and should therefore be administered with caution to patients with dysfunction of the biliary tract.

**Patients with Renal Impairment:**

Renal elimination plays a relatively minor role (see **10.3 Pharmacokinetics**) in the overall clearance of buprenorphine; therefore, dose modification based on renal function is generally not required. However, metabolites of buprenorphine accumulate in patients with advanced renal failure. Caution is recommended when dosing patients with severe renal impairment ($CL_{cr}$ <30 mL/min) which may require dose adjustment.

The effects of renal failure on naloxone pharmacokinetics are unknown.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

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

In patients with marked opioid dependence, initial administration of pms-BUPRENORPHINE-NALOXONE can produce an opioid-withdrawal effect similar to that associated with naloxone.

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, 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 may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

In the pivotal clinical studies (CR96/013 [double-blind] and CR96/014 [open label extension]), of 472 patients treated with sublingual tablets containing buprenorphine in combination with

naloxone, 334 patients were treated for 3 months, 261 patients were treated for greater than 6 months and 100 patients were treated up to one year. The most used dose was 16 mg/day. Treatment-emergent adverse events reported in the pivotal clinical study of buprenorphine/naloxone (≥ 1.0 % of buprenorphine/naloxone treated patients) are listed in Table 2.

The most commonly-reported treatment related adverse reactions reported during the pivotal clinical studies were headache and signs and symptoms commonly associated with drug withdrawal (e.g. abdominal pain, anxiety, diarrhoea, muscle aches, insomnia, headache, constipation, nausea and hyperhidrosis). Some reports of seizure, vomiting, diarrhoea, and elevated liver function tests were considered serious.

**Table 2 Treatment-Emergent Adverse Events Reported in Pivotal Clinical Study of Buprenorphine/Naloxone Tablet (≥1.0 % of Buprenorphine/Naloxone-Treated Patients)**

| **Treatment-Emergent Adverse Event** | **Number (%)**<br>N = 472 |
|---|---|
| **Body as a Whole** | |
| Headache | 202 (42.8%) |
| Pain | 197 (41.7%) |
| Withdrawal Syndrome | 194 (41.1%) |
| Infection | 149 (31.6%) |
| Pain Back | 132 (28.0%) |
| Flu Syndrome | 89 (18.9%) |
| Pain Abdominal | 77 (16.3%) |
| Injury Accidental | 72 (15.3%) |
| Asthenia | 48 (10.2 %) |
| Chills | 44 (9.3%) |
| Fever | 36 (7.6%) |
| Pain Chest | 23 (4.9%) |
| Abscess | 17 (3.6%) |
| Pain Neck | 12 (2.5%) |
| Malaise | 9 (1.9%) |
| Allergic Reaction | 8 (1.7%) |
| Edema Face | 8 (1.7%) |
| Cyst | 7 (1.5%) |
| Infection Viral | 5 (1.1%) |
| Neck Rigid | 5 (1.1%) |
| **Cardiovascular System** | |
| Vasodilation | 29 (6.1%) |
| Hypertension | 17 (3.6%) |
| Migraine | 13 (2.8%) |
| **Digestive System** | |
| Constipation | 115 (24.4%) |

| | |
|---|---|
| Nausea | 76 (16.1%) |
| Vomiting | 61 (12.9%) |
| Dyspepsia | 45 (9.5%) |
| Diarrhea | 50 (10.6%) |
| Tooth Disorder | 37 (7.8%) |
| Liver Function Abnormal | 18 (3.8%) |
| Anorexia | 16 (3.4%) |
| Nausea/Vomiting | 13 (2.8%) |
| Flatulence | 11 (2.3%) |
| Abscess Periodontal | 10 (2.1%) |
| Gastrointestinal Disorder | 7 (1.5%) |
| Ulcer Mouth | 6 (1.3%) |
| Stomatitis | 5 (1.1%) |
| **Hemic and Lymphatic System** | |
| Anemia | 7 (1.5%) |
| Ecchymosis | 6 (1.3%) |
| Lymphadenopathy | 5 (1.1%) |
| **Metabolism and Nutritional Disorders** | |
| Peripheral Edema | 24 (5.1%) |
| Weight Decreased | 15 (3.2%) |
| Hyperglycemia | 5 (1.1%) |
| **Musculoskeletal System** | |
| Myalgia | 31 (6.6%) |
| Arthralgia | 20 (4.2%) |
| Leg Cramps | 13 (2.8%) |
| Joint Disorder | 9 (1.9%) |
| Arthritis | 5 (1.1%) |
| **Nervous System** | |
| Insomnia | 138 (29.2%) |
| Depression | 70 (14.8%) |
| Anxiety | 65 (13.8%) |
| Nervousness | 42 (8.9%) |
| Somnolence | 40 (8.5%) |
| Dizziness | 33 (7.0%) |
| Paresthesia | 28 (5.9%) |
| Agitation | 10 (2.1%) |
| Dream Abnormal | 9 (1.9%) |
| Drug Dependence | 9 (1.9%) |
| Hypertonia | 9 (1.9%) |
| Libido Decreased | 9 (1.9%) |
| Tremor | 7 (1.5%) |
| Thinking Abnormal | 6 (1.3%) |
| **Respiratory System** | |
| Rhinitis | 75 (15.9%) |

| | |
|---|---|
| Pharyngitis | 64 (13.6%) |
| Cough Increased | 36 (7.6%) |
| Asthma | 21 (4.4%) |
| Pneumonia | 12 (2.5%) |
| Lung Disorder | 10 (2.1%) |
| Bronchitis | 9 (1.9%) |
| Dyspnea | 9 (1.9%) |
| Respiratory Disorder | 7 (1.5%) |
| Sinusitis | 7 (1.5%) |
| Sputum Increased | 5 (1.1%) |
| Yawning | 6 (1.3%) |
| **Skin and Appendages** | |
| Sweating | 74 (15.7%) |
| Rash | 23 (4.9%) |
| Pruritus | 11 (2.3%) |
| Dry Skin | 6 (1.3%) |
| Herpes Simplex | 6 (1.3%) |
| Nodule Skin | 6 (1.3%) |
| Urticaria | 6 (1.3%) |
| Acne | 5 (1.1%) |
| Contact Dermatitis | 5 (1.1%) |
| **Special Senses** | |
| Conjunctivitis | 14 (3.0%) |
| Lacrimation Disorder | 14 (3.0%) |
| Eye Disorder | 8 (1.7%) |
| Pain Ear | 8 (1.7%) |
| Amblyopia | 5 (1.1%) |
| **Urogenital System** | |
| Dysmenorrhea | 19 (4.0%) |
| Urinary Tract Infection | 19 (4.0%) |
| Urine Abnormal | 12 (2.5%) |
| Impotence | 11 (2.3%) |
| Vaginitis | 11 (2.3%) |
| Dysuria | 9 (1.9%) |
| Hematuria | 8 (1.7%) |

### 8.3 Less Common Clinical Trial Adverse Reactions

Treatment-emergent adverse reactions reported as less common (<1%) in the pivotal buprenorphine/naloxone clinical studies (CR96/013, CR96/014) included:

**Body as a Whole**: carcinoma, cellulitis, chills/fever, hangover, heat stroke, hernia, human immunodeficiency virus (HIV) test positive, hostility, hypothermia, infection fungal, infection parasitic, neoplasia, overdose, pain chest (substernal), pain flank, pain pelvic, photosensitivity,

pain rib and suicide attempt.

**Cardiovascular System**: angina pectoris, bradycardia, electrocardiogram abnormal, hypotension, myocardial infarction, palpitation, phlebitis, tachycardia, thrombosis, thrombophlebitis (deep), vascular disorder and varicose vein.

**Digestive System**: appetite increased, colitis, dry mouth, dysphagia, eructation, gastritis, gamma glutamyl transpeptidase increased, gingivitis, glossitis, gum hemorrhage, rectal hemorrhage, hematemesis, hepatitis C, rectal disorder, saliva increased, stomatitis/ulcer, tenesmus, tooth caries, ulcer peptic, stomach ulcer hemorrhage and tongue discoloration.

**Endocrine System**: sexual function abnormal.

**Hemic and Lymphatic System**: leukocytosis, leucopenia, methemoglobin, thrombocythemia, thrombocytopenia and white blood cells abnormal.

**Metabolism and Nutritional Disorders**: alanine aminotransferase increased, albuminuria, alkaline phosphatase increased, aspartate aminotransferase increased, blood urea nitrogen increased, creatinine increased, edema, electrolytes abnormal, hypercholesteremia, hyperlipidemia, hypoglycemia, hypokalemia, lactate dehydrogenase increased, weight increased.

**Musculoskeletal System**: bursitis, myasthenia, pain bone, spasm general, tendon disorder and tenosynovitis.

**Nervous System**: amnesia, apathy, convulsion, depersonalization, emotional lability, euphoric mood, hallucination, hyperkinesia, miosis, neuralgia, neuropathy, paralysis facial, speech disorder, stupor, twitch, urinary retention and vertigo.

**Respiratory System**: emphysema, epistaxis, hemoptysis, hiccup, laryngitis, pleural disorder and voice alteration.

**Skin and Appendages**: alopecia, exfoliative dermatitis, fungus dermatitis, hair disorder, lichen dermatitis, melanoma skin, neoplasia skin, psoriasis, rash maculopapular, rash vesiculobullous, skin disorder and ulcer skin

**Special Senses**: corneal lesion, deafness, ear disorder, otitis media, pain eye, tinnitus.

**Urogenital System**: amenorrhea, ejaculation abnormal, fibrocystic breast, leukorrhea, mastitis, menorrhagia, menstrual disorder, metrorrhagia, neoplasia breast, nephrolithiasis, orchitis, pain breast, pain kidney, papanikolaou smear suspicious, unintended pregnancy, prostate disorder, salpingitis, testis disorder, urethritis, urination impaired, urinary frequency, and urinary urgency.

### 8.5 Post-Market Adverse Reactions

Table 3 lists adverse drug reactions reported during post-marketing surveillance, not reported

elsewhere in the label, some of which may have only been observed with buprenorphine alone in the treatment of opioid dependence. Adverse drug reactions are presented by MedDRA System Organ Class in order by preferred term.

**Table 3 Adverse Drug Reactions Collected Through Post-Marketing Surveillance**

| System Organ Class | Preferred Term |
|---|---|
| Hepatobiliary disorders | Cytolytic hepatitis<br>Hepatorenal syndrome<br>Jaundice |
| Investigations | Transaminases increased |
| Nervous system disorders | Hepatic encephalopathy<br>Syncope |

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:** Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal 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.

## 9 DRUG INTERACTIONS

### 9.1 Serious Drug Interactions

**Serious Drug Interactions**

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 7 WARNINGS AND PRECAUTIONS).

- Reserve concomitant prescribing of pms-BUPRENORPHINE-NALOXONE and benzodiazepines or other CNS depressants for use in patients treated with pms-BUPRENORPHINE-NALOXONE 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 Drug Interactions 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, gabapentin, pregabalin, baclofen, 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 7 WARNINGS AND PRECAUTIONS). pms-BUPRENORPHINE-NALOXONE should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.**

### 9.3 Drug-Behavioural Interactions

Alcohol can increase the sedative effect of opioids. Alcoholic beverages should be avoided while taking pms-BUPRENORPHINE-NALOXONE.

### 9.4 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 4 Established or Potential Drug-Drug Interactions**

| Proper / Common name | Source of Evidence | Effect | Clinical comment |
|---|---|---|---|
| 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 pms-BUPRENORPHINE-NALOXONE and benzodiazepines. Warn patients that it is extremely dangerous to self-administer benzodiazepines while taking pms-BUPRENORPHINE-NALOXONE and warn patients to use benzodiazepines concurrently with pms-BUPRENORPHINE-NALOXONE only as directed by their healthcare provider. |
| Non-Benzodiazepine Central Nervous System (CNS) Depressants<br><br>Alcohol, non-benzodiazepine sedatives/hypnotics, | 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. |

| Proper / Common name | Source of Evidence | Effect | Clinical comment |
|---|---|---|---|
| anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids. | | | |
| Naltrexone | CT, T | Naltrexone is an opioid antagonist that can block the pharmacological effects of buprenorphine. | For opioid-dependent patients currently receiving pms-BUPRENORPHINE-NALOXONE treatment, the antagonist naltrexone may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms. For patients currently receiving naltrexone treatment, the intended therapeutic effects of pms-BUPRENORPHINE-NALOXONE administration may be blocked by the naltrexone antagonist. |
| Inhibitors of CYP3A4<br><br>Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir) | CT, T | The concomitant use of buprenorphine and CYP3A4 inhibitors 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 pms-BUPRENORPHINE-NALOXONE is achieved.<br><br>After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the buprenorphine plasma concentration will decrease, potentially resulting in | Monitor patients for respiratory depression and sedation at frequent intervals. |

| Proper / Common name | Source of Evidence | Effect | Clinical comment |
|---|---|---|---|
| | | decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to buprenorphine. | |
| CYP3A4 Inducers<br><br>Rifampin, carbamazepine, phenytoin, phenobarbital | T | The concomitant use of buprenorphine and CYP3A4 inducers can decrease the plasma concentration of buprenorphine, potentially resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence on buprenorphine.<br><br>After stopping a CYP3A4 inducer, as the effects of the inducer decline, the buprenorphine plasma concentration will increase, which could increase or prolong both therapeutic effects and adverse reactions and may cause serious respiratory depression. | If patients stabilized on pms-BUPRENORPHINE-NALOXONE require treatment with CYP3A4 inducers, they should be monitored for opioid withdrawal signs and symptoms. |
| Serotonergic Drugs<br><br>Selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin | C, CT | The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. | 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. |

| Proper / Common name | Source of Evidence | Effect | Clinical comment |
|---|---|---|---|
| neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). | | | |
| Monoamine Oxidase Inhibitors (MAOIs)<br><br>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 pms-BUPRENORPHINE-NALOXONE is not recommended for patients taking MAOIs or within 14 days of stopping such treatment. |
| QTc interval-prolonging drugs* | T | Opioid use with QTc interval-prolonging drugs may increase the risk of QTc interval prolongation and/or torsade de pointes | Concomitant use with other QTc interval-prolonging drugs should be avoided. |
| 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 | Exercise caution. Therapeutic concentration monitoring is recommended. |

| Proper / Common name | Source of Evidence | Effect | Clinical comment |
|---|---|---|---|
| | | 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. | |

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

* 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).

### 9.5 Drug-Food Interactions

Interactions with food have not been studied.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been studied.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa opioid receptor. Buprenorphine has a high affinity for mu-opioid receptors, therefore reducing the binding ability, and thus the activity, of other opioids on these 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.

Naloxone is an antagonist at mu, delta, and kappa-opioid receptors. Because of its almost complete first-pass metabolism and low sublingual bioavailability, naloxone administered orally or sublingually has no detectable pharmacological activity. However, if misused or abused intranasally or by injection by a person dependent upon a full opioid agonist, the presence of naloxone in pms-BUPRENORPHINE-NALOXONE can produce marked opioid antagonist effects that can prompt the immediate onset of opioid withdrawal symptoms as a deterrent to misuse and abuse.

### 10.2 Pharmacodynamics

**Subjective Effects**

Comparison of buprenorphine with full agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opiate agonist effects, which are limited by a ceiling effect.

Buprenorphine 16 mg had opioid agonist effects similar to 4 mg intramuscular hydromorphone, and equivalent to about 30 mg intramuscular morphine.

Opioid agonist ceiling effects were also observed in a double-blind parallel group, dose ranging

comparison of single doses of 1, 2, 4, 8, 16 or 32 mg buprenorphine sublingual solution (comparable approximately to 1.5 mg, 3 mg, 6 mg, 12 mg, 24 mg and 48 mg, respectively, of the tablet form), oral methadone (15, 30, 45 or 60 mg) and placebo. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced, male subjects who were not physically dependent. Both drugs produced typical opioid agonist effects. For all measures for which drugs produced an effect, buprenorphine produced a dose-related response but, in each case, there was a dose which produced no further effects. In contrast, the highest dose of methadone (60 mg) always produced the greatest effects.

**Physiologic Effects**

Buprenorphine effects were assessed in opioid-experienced subjects administered 12 mg sublingually or up to 16 mg by IV injection to examine cardiovascular, respiratory and subjective effects at doses comparable to those used for treatment of opioid dependence.

Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, $O_2$ saturation or skin temperature across time. Systolic blood pressure was higher for the 8 mg buprenorphine IV 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 solution (1, 2, 4, 8, 16 or 32 mg) were compared to those of oral methadone (15, 30, 45 or 60 mg) in non-dependent, opioid experienced healthy male volunteers. In this study, hypoventilation not requiring mechanical intervention was reported more frequently after buprenorphine sublingual solution doses of 4 mg and higher (4 mg solution comparable approximately to a 6 mg tablet dose) than after methadone at these doses tested. Both drugs decreased $O_2$ saturation to the same degree.

Effect of Naloxone

Naloxone had no clinically significant effect when administered by the sublingual route; plasma concentrations are low and decline rapidly. Buprenorphine/Naloxone, when administered sublingually even to an opioid-dependent population, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similarly to naloxone. In methadone-maintained patients and heroin-dependent subjects, IV administration of buprenorphine/naloxone combinations precipitated opioid withdrawal and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal effects that were ratio-dependent; the most intense withdrawal effects were produced by 2:1 and 4:1 ratio, less intense by an 8:1 ratio.

**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 produce 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**

When taken orally, buprenorphine undergoes first-pass hepatic metabolism with N-dealkylation and glucuroconjugation in the small intestine. The use of this medication by the oral route is therefore ineffective.

When buprenorphine/naloxone tablet was administered sublingually, there was wide inter-subject variability in the absorption of buprenorphine but within-subject variability was low. Plasma levels of buprenorphine increased linearly with the dose in the range of 2 mg to 16 mg, although the increase was not directly dose proportional. Mean $C_{max}$ for sublingual tablet doses of 2 mg, 8 mg, 12 mg and 16 mg were, respectively, 0.780, 2.58, 4.60 and 5.51 (ng/mL). Mean $AUC_{0\text{-}inf}$ for sublingual tablet doses of 2 mg, 8 mg, 12 mg and 16 mg were, respectively, 7.65, 25.3, 43.9 and 54.7 (h*ng/mL).

Naloxone mean peak plasma concentrations were achieved at approximately 1 hr post-dose. Plasma levels of naloxone increased linearly with the dose in the range of 0.5 mg to 4 mg, although the increase was not directly dose proportional.

Naloxone has not been found to affect the pharmacokinetics of buprenorphine, and both buprenorphine alone and buprenorphine/naloxone sublingual tablets deliver similar plasma concentrations of buprenorphine.

**Distribution**

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to albumin.

**Metabolism**

Buprenorphine is primarily metabolized through *N*-dealkylation by liver microsomal CYP3A4. The parent molecule and the primary dealkylated metabolite, norbuprenorphine, undergo subsequent glucuronidation.

Norbuprenorphine binds to opioid receptors in vitro; however, it is not known whether norbuprenorphine contributes to the overall effect of buprenorphine/naloxone. Naloxone is metabolized in the liver, primarily by glucuronide conjugation. Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide, as well as N-dealkylation, and reduction of the 6-oxo group.

**Elimination**

Buprenorphine is eliminated in the feces (~70%), the rest (~30%) being eliminated in the urine. In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 4.8% conjugated; norbuprenorphine, 21% free and 2.1% conjugated). In urine, most of buprenorphine and norbuprenorphine were conjugated (buprenorphine, 1% free and 8.4% conjugated; norbuprenorphine, 2.7% free and 8.8% conjugated).

Based on studies performed with buprenorphine/naloxone tablet, buprenorphine has a mean elimination half-life from plasma ranging from 24 to 42 hours and naloxone has a mean elimination half-life from plasma ranging from 2 to 12 hours.

**Drug Interactions Studies**

CYP3A4 Inhibitors and Inducers
Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in in vitro studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

**Special Populations and Conditions**

- **Pediatrics** Individuals under 18 years of age should not take pms-BUPRENORPHINE-NALOXONE.

- **Geriatrics** The safety and efficacy of buprenorphine/naloxone have not been established in adults over 65 years of age.

  In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrating upwards slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

- **Hepatic Insufficiency** pms-BUPRENORPHINE-NALOXONE is contraindicated in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. If pms-BUPRENORPHINE-NALOXONE is used in this patient population, caution is advised.

  Both buprenorphine and naloxone are extensively metabolized by the liver. In a pharmacokinetic study, the disposition of buprenorphine and naloxone were determined after administering a 2 mg/ 0.5 mg buprenorphine/naloxone tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine and naloxone in patients with hepatic impairment were compared to disposition in subjects with normal hepatic function.

In subjects with mild hepatic impairment, the changes in mean $C_{max}$, $AUC_{0\text{-last}}$, and half-life values of both buprenorphine and naloxone were not clinically significant. No dosing adjustment should be required in patients with mild hepatic impairment but close monitoring is advised.

For subjects with moderate and severe hepatic impairment, mean $C_{max}$, $AUC_{0\text{-last}}$, and half-life values of both buprenorphine and naloxone were increased; the effects on naloxone are greater than that on buprenorphine (Table 5).

**Table 5 Changes in Pharmacokinetic Parameters in Subjects with Moderate and Severe Hepatic Impairment**

| Hepatic Impairment | PK Parameters | Increase in buprenorphine compared to healthy subjects | Increase in naloxone compared to healthy subjects |
|---|---|---|---|
| Moderate | $C_{max}$ | 8% | 170% |
| | $AUC_{0\text{-last}}$ | 64% | 218% |
| | Half-life | 35% | 165% |
| Severe | $C_{max}$ | 72% | 1030% |
| | $AUC_{0\text{-last}}$ | 181% | 1302% |
| | Half-life | 57% | 122% |

** Single dose of a buprenorphine/naloxone 2.0 / 0.5 mg tablet administered.*

The difference in magnitude of the effects on naloxone and buprenorphine are greater in subjects with severe hepatic impairment than subjects with moderate hepatic impairment.

Hepatic impairment results in a reduced clearance of naloxone to a much greater extent than buprenorphine, and the doses of buprenorphine and naloxone in this fixed-dose combination product cannot be individually titrated. Therefore, patients with severe hepatic impairment will be exposed to substantially higher levels of naloxone than patients with normal hepatic function. This may result in an increased risk of precipitated withdrawal at the beginning of treatment (induction) and may interfere with buprenorphine's efficacy throughout treatment. In patients with moderate hepatic impairment, the differential reduction of naloxone clearance compared to buprenorphine clearance is not as great as in patient with severe hepatic impairment. Dose adjustments may be considered in cases of mild to moderate hepatic impairment, and patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and / or buprenorphine.

As with other opioids, buprenorphine has been shown to increase intracholedochal pressure and should therefore be administered with caution to patients with dysfunction of the biliary tract.

*HCV infection*

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

- **Renal Insufficiency** Renal elimination plays a relatively minor role (~ 30%) in the overall clearance of buprenorphine/naloxone. No dose modification based on renal function is required but caution is recommended when dosing subjects with severe renal impairment.

  No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following a single IV administration of 0.3 mg buprenorphine. The effects of renal failure on naloxone pharmacokinetics are unknown. Buprenorphine plasma concentrations and buprenorphine clearance following continuous infusion at a median infusion rate of 161 µg/h (range 36-230 µg/h) for a median duration of 30 h (2-565 h) were similar in patients with normal and impaired renal functions. In patients with renal failure, plasma concentrations of norbuprenorphine were increased by a median of four times, and buprenorphine-3-glucoronide concentrations by a median of 15 times.

## 11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C to 30°C. Protect from light and moisture.

Advise patients to store pms-BUPRENORPHINE-NALOXONE safely and out of sight and reach of children and to destroy any unused medication appropriately to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

**pms-BUPRENORPHINE-NALOXONE should never be disposed of in household trash**. Disposal via a pharmacy take back program is recommended. Consult with a pharmacist and/or consult with www.healthsteward.ca for information on responsible pharmaceutical disposal options.

## 12 SPECIAL HANDLING INSTRUCTIONS

pms-BUPRENORPHINE-NALOXONE should be kept in a safe place out of the sight and reach of children before, during and after use. pms-BUPRENORPHINE-NALOXONE should not be used in front of children, since they may copy these actions. Do not give to others.

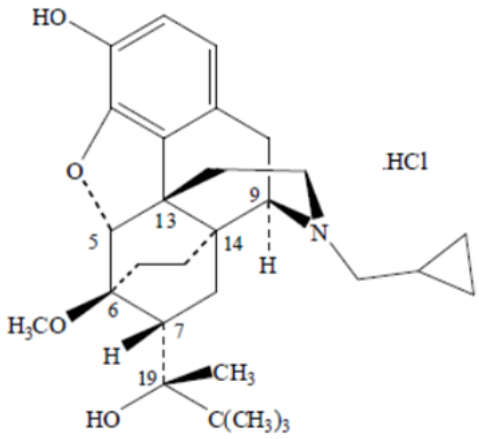
**PART II: SCIENTIFIC INFORMATION**

## 13 PHARMACEUTICAL INFORMATION

### Drug Substance

**Buprenorphine**

| | |
|---|---|
| Proper name: | buprenorphine hydrochloride |
| Chemical name: | 21-cyclopropyl-7α-[(S)-1-hydroxy-1,2,2-trimethyl-propyl]-6,14-*endo*-ethano-6,7,8,14-tetrahydrooripavine hydrochloride |
| Molecular Formula: | $C_{29}H_{41}NO_4 \bullet HCl$ |
| Molecular mass: | 504.1 g/mol |
| Structural formula: | |



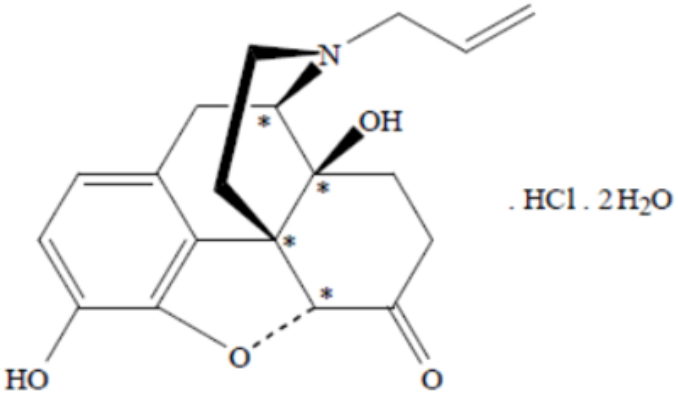

Physicochemical properties:

| | |
|---|---|
| Physical Form: | White to off-white crystalline powder |
| Solubility: | Sparingly soluble in water, freely soluble in methanol, soluble in alcohol, practically insoluble in cyclohexane |
| pKa: | Amine function 8.5 ($3.16 \times 10^{-9}$)<br>Phenol function 10.0 ($1 \times 10^{-10}$) |
| pH: | The pH of a 1% w/v solution in freshly distilled water is between 4.0 and 6.0. |
| Partition: Coefficient: | Log P = 4.98 |
| Melting Point: | 272°C |

**Naloxone**

| | |
|---|---|
| Proper Name: | naloxone hydrochloride dihydrate |
| Chemical Name: | 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate |
| Molecular Formula: | $C_{19}H_{21}NO_4 \bullet HCl \bullet 2H_2O$ |
| Molecular Mass: | 399.87 g/mol |

Structural formula:




Physicochemical properties:

| | |
|---|---|
| Physical Form: | White to slightly off-white powder |
| Solubility: | Soluble in water, in dilute acids and in strong alkali; slightly soluble in alcohol, practically insoluble in ether and chloroform. |
| pKa: | 7.9 |
| Melting Point: | 200 to 205°C |

## 14 CLINICAL TRIALS

### 14.1 Clinical Trials by Indication

- Substitution treatment in adults with problematic opioid drug dependence.

**Buprenorphine/naloxone Tablet Trial Design and Study Demographics**

**Efficacy and safety data of the combination of buprenorphine and naloxone (Studies CR96/013 + CR96/014)**

This was a one-year multicenter, placebo-controlled study comprising a 4-week randomized double-blind comparison of buprenorphine/naloxone, buprenorphine and placebo tablets followed by a 48-week open-label safety study of buprenorphine/naloxone. In the first 4-week double-blind phase, 323 heroin-addicted subjects received either placebo, buprenorphine 16 mg/day, or combination treatment of 16 mg buprenorphine + 4 mg naloxone (combination tablet) per day. For subjects randomized to active treatment dosing began with one 8 mg tablet of buprenorphine on day 1, followed by 16 mg (two 8 mg tablets) of buprenorphine on day 2. Subjects continued on 16 mg/day for four weeks. On day 3, subjects randomized to buprenorphine + naloxone were switched to the combination tablet. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Subjects received one hour of individual counselling per week and a single session of HIV education. Outcome measures were % of urine samples negative for opioids and self-reported craving for opioids.

**Comparative efficacy of buprenorphine and methadone (Study CR88/130)**

This was a double-blind, double-dummy, parallel group, randomized study comparing buprenorphine ethanolic solution to methadone. One hundred sixty-two heroin dependent subjects age 21-50 years received sublingual buprenorphine (8 mg/day) or methadone (20 mg/day and 60 mg/day), during a 3-10 day induction phase, a 16-week maintenance phase and a 7 week detoxification phase. Buprenorphine was titrated to the maintenance dose by day 3; methadone doses were titrated more gradually. Maintenance dosing continued through week 17. Study drugs were tapered by approximately 70-80% per week over weeks 18-to-24, with placebo dosing for the last two weeks. Subjects received individual and/or group counselling weekly. Outcome measures were retention time in treatment, urine samples negative for opioids, and failure to maintain abstinence.

**Study Results**

**Efficacy and safety data of the combination of buprenorphine and naloxone (Studies CR96/013 + CR96/014)**

The percentage of thrice-weekly urine samples that were negative for opioids was higher for subjects treated with buprenorphine (20.7%) or the combination tablet (17.8%) than for those who received placebo (both at $p<0.001$). Both active treatment buprenorphine treated groups reported significantly less craving than placebo ($p<0.001$).

**Comparative efficacy of buprenorphine and methadone (Study CR88/130)**

Buprenorphine was as effective as methadone, 60 mg/day, and both were superior to methadone, 20 mg/day, in reducing illicit opioid use and maintaining participants in treatment for 25 weeks.

## 14.2 Comparative Bioavailability Studies

A blinded, single dose, randomized, two-period, two-treatment, two-sequence, cross-over comparative bioavailability study of pms-BUPRENORPHINE-NALOXONE 1 X 8 mg/2 mg (buprenorphine/naloxone) Sublingual Tablets (Pharmascience Inc.) and Suboxone™ 1 X 8 mg/2 mg (buprenorphine/naloxone) Sublingual Tablets (RB Pharmaceuticals Limited) in 63 healthy male and female volunteers was conducted under fasting conditions. Summaries of results for buprenorphine and naloxone are presented in the following tables.

| Buprenorphine<br>(1 x 8 mg)<br>From measured data<br>Geometric Mean<br>Arithmetic Mean (CV %) | | | | |
|---|---|---|---|---|
| Parameter | Test* | Reference† | % Ratio of Geometric Means | Confidence Interval, 90% |
| $AUC_{72}$<br>(ng*h/mL) | 23.9788<br>25.3042 (33) | 23.3516<br>24.4826 (32) | 102.69 | 97.61 - 108.03 |
| $AUC_I$<br>(ng*h/mL) | 28.1053<br>29.3389 (30) | 27.0249<br>28.2483 (33) | N/A | N/A |
| $C_{max}$<br>(ng/mL) | 3.1234<br>3.3359 (35) | 2.8575<br>3.0081 (32) | 109.31 | 101.29 - 117.96 |
| $T_{max}$§<br>(h) | 1.53 (35) | 1.42 (33) | | |
| $T_{½}$§<br>(h) | 35.40 (48) | 32.91 (42) | | |

* pms-BUPRENORPHINE-NALOXONE 8 mg/2 mg sublingual tablets (Pharmascience Inc., Canada)
† Suboxone™ 8 mg/2 mg sublingual tablets, RB Pharmaceuticals Limited, were purchased in Canada
§ Expressed as the arithmetic mean (CV%) only

| Unconjugated Naloxone<br>(1 x 2 mg)<br>From measured data<br>Geometric Mean<br>Arithmetic Mean (CV %) | | | | |
|---|---|---|---|---|
| Parameter | Test* | Reference† | % Ratio of Geometric Means | Confidence Interval, 90 % |
| $AUC_T$<br>(ng*h/mL) | 0.27873<br>0.31597 (60) | 0.27920<br>0.31249 (56) | 99.83 | 93.11 - 107.04 |
| $AUC_I$<br>(ng*h/mL) | 0.31905<br>0.34858 (43) | 0.30335<br>0.32939 (43) | N/A | |
| $C_{max}$<br>(ng/mL) | 0.11770<br>0.14028 (65) | 0.11649<br>0.12580 (41) | 101.04 | 91.79 - 111.22 |
| $T_{max}$§<br>(h) | 1.10 (88) | 1.09 (109) | | |
| $T_{½}$§<br>(h) | 4.20 (60) | 3.86 (45) | | |

* pms-BUPRENORPHINE-NALOXONE 8 mg/2 mg sublingual tablets (Pharmascience Inc.)
† Suboxone™ 8 mg/2 mg sublingual tablets, RB Pharmaceuticals Limited, were purchased in Canada
§ Expressed as the arithmetic mean (CV%) only

## 15 MICROBIOLOGY

Not Applicable

## 16 NON-CLINICAL TOXICOLOGY

The non-clinical studies below were all conducted with buprenorphine/naloxone tablets or with a combination of buprenorphine/naloxone at a ratio of 4:1.

Pre-clinical and clinical doses or exposures are compared based on the clinical dose of 16 mg / 4 mg buprenorphine / naloxone, or 16 mg buprenorphine. Preclinical doses or exposures are expressed as multiples of the corresponding clinical counterpart.

**General Toxicology:** The toxicity profiles of buprenorphine and buprenorphine with naloxone in animals after a 28- day exposure period are similar in that no consistent target organ was identified, even at high oral doses.

No consistent pattern of undesirable effects was apparent in the subacute studies conducted, other than a sedative effect which is a direct consequence of the pharmacological activity of the test substance mixture.

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

**Carcinogenicity:** A carcinogenicity study of buprenorphine/naloxone (4:1 ratio) in rats at dietary levels yielding doses of approximately 7, 31, and 123 mg/kg/day (4-, 18-, and 44- fold clinical exposure) showed statistically significant increases in benign testicular Leydig cell adenomas in all dose groups. No other drug-related tumours were noted.

**Genotoxicity:** Buprenorphine/naloxone (4:1 ratio) was not mutagenic in a bacterial mutation assay (Ames test) using four strains of S. typhimurium and two strains of E. coli, in an in vitro cytogenetic assay in human lymphocytes or in an IV micronucleus test in rats.

**Reproductive and Developmental Toxicology:** Administration of buprenorphine/naloxone (4:1 ratio) to rats at 500 ppm or greater in the diet resulted in reduction in female fertility, however, there were no adverse effects on fertility in females at clinically relevant dose levels.

## 17 SUPPORTING PRODUCT MONOGRAPHS

[N]SUBOXONE® (Sublingual Tablets, 2 mg / 0.5 mg, 8 mg / 2 mg, 12 mg / 3 mg, 16 mg / 4 mg), submission control 269182, Product Monograph, Indivior UK Ltd. (March 16, 2023).

**PATIENT MEDICATION INFORMATION**

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**$^{N}$pms-BUPRENORPHINE-NALOXONE**
Buprenorphine and Naloxone Sublingual Tablets
2 mg / 0.5 mg and 8 mg / 2 mg

Read this carefully before you start taking **pms-BUPRENORPHINE-NALOXONE** and each time you get a refill. 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 **pms-BUPRENORPHINE-NALOXONE**.

**Serious Warnings and Precautions**

- You will take pms-BUPRENORPHINE-NALOXONE with healthcare professional supervision until you are clinically stable and able to safely store pms-BUPRENORPHINE-NALOXONE take-home doses.
- Even if you take pms-BUPRENORPHINE-NALOXONE as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.
- Life-threatening breathing problems can happen while taking pms-BUPRENORPHINE-NALOXONE, especially if not taken as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.
- You should never give anyone your pms-BUPRENORPHINE-NALOXONE. They could die from taking it. If a person has not been prescribed pms-BUPRENORPHINE-NALOXONE, taking even one dose can cause a fatal overdose. This is especially true for children.
- Taking pms-BUPRENORPHINE-NALOXONE with other opioids, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- If you took pms-BUPRENORPHINE-NALOXONE at any time while you were pregnant, 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. Seek immediate help for your baby if it has any of the following symptoms:
  - has changes in their breathing (such as weak, difficult or fast breathing)
  - is unusually difficult to comfort
  - is not feeding well
  - has tremors (shakiness) or stiffness
  - has increased sneezing, yawning, vomiting, fever, stools, or diarrhea.
- While taking pms-BUPRENORPHINE-NALOXONE, alcohol should be avoided. Drinking alcohol

while you are on pms-BUPRENORPHINE-NALOXONE may result in you feeling stronger effects from the drug than usual such as increased drowsiness, reduced breathing and loss of consciousness. This can possibly lead to an accidental overdose that can be fatal.

- Keep pms-BUPRENORPHINE-NALOXONE in a safe place away from children.
- Accidental use by a child is a medical emergency and may result in death. Never take your medicine in front of children as they will want to copy you. If a child accidentally comes in contact with pms-BUPRENORPHINE-NALOXONE, get emergency help right away.
- Prevent theft and misuse. Never give pms-BUPRENORPHINE-NALOXONE to anyone else. Selling or giving away this medicine is against the law.
- Do not use pms-BUPRENORPHINE-NALOXONE to treat acute or chronic pain.
- Do not switch between buprenorphine-naloxone tablets and films unless directed by your doctor.
- When you take pms-BUPRENORPHINE-NALOXONE it must be placed under the tongue (sublingually) until completely dissolved. Do not cut, break, crush, chew or swallow pms-BUPRENORPHINE-NALOXONE or take it any other way than directed by your doctor as this can seriously harm you, can lead to death or can result in very unpleasant opioid withdrawal effects.

**What is pms-BUPRENORPHINE-NALOXONE used for?**

- pms-BUPRENORPHINE-NALOXONE is part of a medical, social and psychological treatment program for adults undergoing substitution treatment for problematic opioid drug dependence.

Treatment with pms-BUPRENORPHINE-NALOXONE is intended for use in adults (18 years of age or older) and is voluntary.

Only a qualified doctor can prescribe pms-BUPRENORPHINE-NALOXONE. The dose of pms-BUPRENORPHINE-NALOXONE needs to be taken under the daily supervision of a healthcare professional until you are clinically stable and able to safely store pms-BUPRENORPHINE-NALOXONE take-home doses.

**How does pms-BUPRENORPHINE-NALOXONE work?**

Buprenorphine, a component of pms-BUPRENORPHINE-NALOXONE, works in the brain as other opioid drugs (e.g. morphine, methadone). If you are in withdrawal from opioid drugs, pms-BUPRENORPHINE-NALOXONE will stop the feelings of withdrawal.

pms-BUPRENORPHINE-NALOXONE also contains naloxone. When naloxone is injected, it blocks the effects of medicines and drugs like methadone, heroin, and morphine. Naloxone is added to pms-BUPRENORPHINE-NALOXONE to stop people from injecting (“shooting-up”) pms-BUPRENORPHINE-NALOXONE. When you use pms-BUPRENORPHINE-NALOXONE under

your tongue, as prescribed, the naloxone in pms-BUPRENORPHINE-NALOXONE should not stop the medicine's effects. However, if you inject pms-BUPRENORPHINE-NALOXONE, the naloxone can give you withdrawal symptoms.

**What are the ingredients in pms-BUPRENORPHINE-NALOXONE?**
Medicinal ingredients: buprenorphine / naloxone

Non-medicinal ingredients: Acesulfame Potassium, Citric Acid Anhydrous, Corn Starch, Lactose Monohydrate, Lemon & Lime Flavor, Mannitol, Povidone K30, Sodium Citrate, and Sodium Stearyl Fumarate.

**pms-BUPRENORPHINE-NALOXONE comes in the following dosage form:**
2 mg buprenorphine / 0.5 mg naloxone and 8 mg buprenorphine / 2 mg naloxone sublingual tablets.

**Do not use pms-BUPRENORPHINE-NALOXONE if:**

- your doctor did not prescribe it for you
- you are allergic to buprenorphine, naloxone, or to any of the ingredients in pms-BUPRENORPHINE-NALOXONE (see above for the complete listing of non-medicinal ingredients)
- you have never taken opioids before
- you have severe asthma, trouble breathing, or other lung problems
- you have serious problems with your liver
- you suffer from alcoholism or alcohol withdrawal
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have increased pressure in your skull or a head injury
- you suffer from convulsive or seizure disorder
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase Inhibitor (MAOI) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you recently had or you are going to have planned surgery

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-BUPRENORPHINE-NALOXONE. Talk about any health conditions or problems you may have, including if you:**

- have a history of illicit or prescription drug or alcohol abuse
- have asthma, other breathing problems, or lung problems
- have severe kidney, liver, or lung disease
- have a history or a family history of heart problems
- have low or decrease in blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have gallbladder or pancreas problems
- have adrenal gland problems, such as Addison's disease

- have low thyroid hormone levels (hypothyroidism)
- are a man and have urinary disorders (especially linked to enlarged prostate)
- are pregnant/breastfeeding or are planning to become pregnant or to breastfeed
- have difficulty 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

**Other warnings you should know about:**

**Driving and using machines:** pms-BUPRENORPHINE-NALOXONE can cause you to feel drowsy, dizzy, or light-headed. This usually occurs after you take your first dose, or when your dose is increased. Before you do tasks which require special attention, you should wait until you know how you react to pms-BUPRENORPHINE-NALOXONE.

**Drug testing for sport events:** Athletes should be aware that this medicine, due to its active substance, may cause a positive reaction to "anti-doping tests".

**Dependence**: pms-BUPRENORPHINE-NALOXONE can cause opioid drug dependence and opioid withdrawal signs and symptoms may occur when the medication is discontinued. You should discuss with your doctor if you want to stop taking pms-BUPRENORPHINE-NALOXONE.

**Pregnancy, nursing, labour and delivery:** Opioids can be transferred to your baby through breast milk, or while still in the womb. pms-BUPRENORPHINE-NALOXONE can then cause life-threatening breathing problems in your unborn baby or nursing infant. Your doctor will determine if the benefits of using pms-BUPRENORPHINE-NALOXONE, outweigh the risks to your unborn baby or nursing infant.

If you are pregnant and are taking pms-BUPRENORPHINE-NALOXONE, it is important that you don't stop taking your medication suddenly. If you do, it can cause a miscarriage or a still-birth. If you choose to stop pms-BUPRENORPHINE-NALOXONE treatment while pregnant, talk to your doctor for guidance. Your doctor will monitor and guide you on how to slowly stop taking pms-BUPRENORPHINE-NALOXONE. This may help avoid serious harm to your unborn baby. It is important that you continue to see the healthcare professional that prescribed you pms-BUPRENORPHINE-NALOXONE in order to prevent relapse to opioid use and to reinstate pms-BUPRENORPHINE-NALOXONE at an adjusted dose if required. pms-BUPRENORPHINE-NALOXONE should not be restarted at the same dose if it has been stopped for some time. This could cause harm to you or your baby and you could overdose. Speak to your doctor first for help restarting pms-BUPRENORPHINE-NALOXONE at a safe dose.

**Disorder of the adrenal gland:** You may develop 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 doctor may do tests, give you another medication, and slowly take you off pms-BUPRENORPHINE-NALOXONE.

**Serotonin Toxicity (also known as Serotonin Syndrome):** pms-BUPRENORPHINE-NALOXONE can cause serotonin toxicity, 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 toxicity if you take pms-BUPRENORPHINE-NALOXONE with certain anti-depressants or migraine medications.

Serotonin toxicity 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, restlessness, hallucinations, mood changes, unconsciousness, and coma.

**Sexual Function and Reproduction:** Long term use of opioids may lead to a decrease in 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 function tests before you start treatment and during your treatment with pms-BUPRENORPHINE-NALOXONE.

**Heart problems:** pms-BUPRENORPHINE-NALOXONE can cause problems with your heart rhythm called QTc prolongation. You may have no symptoms, or you may have dizziness, feeling like your heart has skipped or added a beat, fainting or seizures. If these symptoms continue, they can lead to sudden death. You may be more at risk if you have had or have:

- a heart attack
- congestive heart failure
- an irregular heartbeat or heart rhythm
- a blockage in one or more of your arteries that affects blood flow to your heart
- an abnormally rapid heart rate
- heart palpitations (feeling like your heart has skipped a beat or added an extra beat)
- a family history of sudden cardiac death at less than 50 years of age
- problems of electrocardiogram (ECG) abnormality called “Long QT syndrome”
- diabetes
- imbalances in the electrolytes in your body (potassium, magnesium and calcium)

**Dental Problems:** Some people taking pms-BUPRENORPHINE-NALOXONE have experienced dental problems such as cavities, tooth decay, dental infection, fillings falling out and/or tooth loss. You should have regular dental check-ups. If you have any problems with your teeth tell your healthcare professional and schedule an appointment with a dentist right away. Tell your dentist that you are taking pms-BUPRENORPHINE-NALOXONE.

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

**Serious Drug Interactions**

**Taking:**

- **benzodiazepines (drugs used to help you sleep or that help reduce anxiety);**
- **alcohol or other sedative drugs. This includes prescription and non-prescription medications that contain alcohol;**
- **or other central nervous system depressants (including street drugs)**

**while you are on pms-BUPRENORPHINE-NALOXONE treatment can cause severe drowsiness, breathing problems, coma, and death.**

**The following may interact with pms-BUPRENORPHINE-NALOXONE:**

- opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- antidepressants (for depression and mood disorders). **Do not** take pms-BUPRENORPHINE-NALOXONE with (MAOI) or if you have taken MAOIs in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention or treatment of vomiting)
- drugs used to treat muscle spasms and back pain (e.g., baclofen)
- pregabalin, used to treat nerve pain
- gabapentin, used to prevent and control seizures in the treatment of epilepsy
- anti-retroviral drugs (used to treat certain viral infections)
- anti-fungal drugs (used to treat fungal infections)
- antibiotic drugs (used to treat bacterial infections)
- drugs used to treat high blood pressure
- some heart medication (such as beta blockers)
- grapefruit juice
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

Taking pms-BUPRENORPHINE-NALOXONE may make it difficult to get full pain relief from other opioid drugs. Make sure you tell your doctor that you are taking pms-BUPRENORPHINE-NALOXONE if they are treating you for pain.

**How to take pms-BUPRENORPHINE-NALOXONE:**

**Take exactly as directed and follow the instructions below. As with other narcotics, serious harm or death can result from misusing pms-BUPRENORPHINE-NALOXONE.**

**The tablet must be placed under the tongue until dissolved. Do not cut, break, crush, chew or**

**swallow pms-BUPRENORPHINE-NALOXONE or take it any other way than directed by your doctor as this can seriously harm you, can lead to death or can result in very unpleasant opioid withdrawal effects.**

**You should tell your family members that you are using pms-BUPRENORPHINE-NALOXONE to treat your opioid dependence.**

- Place the appropriate number of pms-BUPRENORPHINE-NALOXONE tablets under your tongue and allow them to dissolve. Do not swallow the tablets. The sublingual route (under the tongue) is the only effective way to take pms-BUPRENORPHINE-NALOXONE tablet.

- Take the dose once a day. If you need to take more than one tablet to achieve the dose your doctor has prescribed, you can either place all the tablets under your tongue at the same time and allow them to dissolve or separate them into two portions and place them one after the other.

- After pms-BUPRENORPHINE-NALOXONE is completely dissolved, rinse your mouth with water and swallow. Wait for at least one hour before brushing your teeth.

**Usual dose:**
Your doctor will determine the best dose for you. During your treatment, the doctor may adjust the dose, depending upon your response. The effectiveness of this treatment depends on the dose taken, and on medical, psychological and social treatment provided.

Your dose is tailored / personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

After the first dose of pms-BUPRENORPHINE-NALOXONE, you may have some opioid withdrawal symptoms such as shaking, sweating, headache, pain, stomach pain, back pain, muscle aches, diarrhea, nausea, insomnia, runny nose, and watery eyes.

**How long should you take it?**
The length of treatment will be determined by you and your doctor. After a time of successful treatment, the doctor may reduce the dose gradually to a lower maintenance dose until you eventually stop the treatment, if your condition allows it.

Do not change the treatment in any way or stop treatment without the agreement of the doctor who is treating you. Stopping treatment suddenly may cause withdrawal symptoms.

**Stopping your Medication**

If you have been taking pms-BUPRENORPHINE-NALOXONE for more than a few days, you should not stop taking it suddenly. Your doctor will monitor and guide you on how to slowly stop taking pms-BUPRENORPHINE-NALOXONE.

You should do it slowly to reduce the occurrence of withdrawal symptoms such as:

- body aches
- diarrhea
- goosebumps
- loss of appetite or nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- heart palpitations or rapid heart rate
- having trouble sleeping
- an unusual increase in sweating
- an unexplained fever
- weakness
- yawning

By reducing or stopping your pms-BUPRENORPHINE-NALOXONE treatment, your body will become less used to opioids. If you start treatment or using opioids again, your doctor will determine the best dose to restart treatment. You may overdose if you restart at the last dose you took before you slowly stopped taking pms-BUPRENORPHINE-NALOXONE.

**Overdose:**

Signs of overdose may include:
- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

If you think you, or a person you are caring for, have taken too much pms-BUPRENORPHINE-NALOXONE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If a single dose of this medication has been missed, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once.

In the case you have missed more than one dose of pms-BUPRENORPHINE-NALOXONE, contact your pharmacist or prescribing doctor as soon as possible.

**Refilling Prescriptions for pms-BUPRENORPHINE-NALOXONE:**

A new written prescription is required from your doctor each time you need more pms-BUPRENORPHINE-NALOXONE. Therefore, it is important that you contact your doctor

before your current supply runs out.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for opioid dependence treatment.

**What are possible side effects from using pms-BUPRENORPHINE-NALOXONE?**

These are not all the possible side effects you may have when taking pms-BUPRENORPHINE-NALOXONE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Headache, drowsiness, or dizziness
- Insomnia
- Nausea, vomiting, or poor appetite
- Dry mouth
- Problems with vision
- Weakness
- Sweating
- Constipation, or stomach pain
- Pain, or itching
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using pms-BUPRENORPHINE-NALOXONE.

| **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** | | | |
| Chest pain | | ✓ | |
| Feeling depressed | | ✓ | |
| **Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing | | | ✓ |
| Wheezing | | | ✓ |
| **UNCOMMON** | | | |
| Convulsion or seizure | | | ✓ |
| Dark urine | | ✓ | |
| **Hypotension** (Low blood pressure): dizziness, fainting, | | ✓ | |

| 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** | |
| light- headedness | | | |
| **Hallucination:** seeing or hearing things that are not really there | | ✓ | |
| High blood sugar symptoms such as dry mouth, increased hunger, thirst, frequent urination | | ✓ | |
| Jaundice (your skin or the white part of your eyes look yellow) | | ✓ | |
| Light coloured stools | | ✓ | |
| Low blood sugar symptoms such as feeling faint, dizzy, confused | | ✓ | |
| **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. | | ✓ | |
| **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, tell 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:**

- **Keep unused or expired pms-BUPRENORPHINE-NALOXONE in a secure place to prevent theft, misuse or accidental exposure**
- Store between 15°C to 30°C. Protect from light and moisture.
- **Keep pms-BUPRENORPHINE-NALOXONE under lock, out of sight and reach of children and pets**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes pms-BUPRENORPHINE-NALOXONE, get emergency help right away**

Do not use this product after the expiration date on the package. Check for signs of visible deterioration.

**Disposal:**
**pms-BUPRENORPHINE-NALOXONE should never be thrown into household trash, where children and pets may find it.** It should be returned to a pharmacy for proper disposal.

**If you want more information about pms-BUPRENORPHINE-NALOXONE:**

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

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