PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

 **pms-BUTORPHANOL**

(Butorphanol Tartrate Nasal Spray)

10 mg/mL
(1 mg/spray)

Analgesic

PHARMASCIENCE INC.

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THERAPEUTIC CLASSIFICATION

Analgesic

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Nasal	Nasal Spray, 10 mg/mL	Benzethonium chloride, citric acid, sodium chloride, sodium hydroxide and/or hydrochloride acid (pH adjustment) and purified water

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INDICATIONS AND CLINICAL USE

Adult
pms-BUTORPHANOL (butorphanol tartrate) is indicated for the relief of moderate to severe acute pain. The efficacy of butorphanol tartrate for periods longer than 3 days has not been established.

pms-BUTORPHANOL is not indicated as an as-needed (prn) analgesic.

Geriatrics (> 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, or cardiac function, concomitant disease or other drug therapy (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Pediatrics (< 18 years of age)
The safety and efficacy of butorphanol tartrate has not been studied in the pediatric population. Therefore, the use of pms-BUTORPHANOL is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance butorphanol tartrate or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- In 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 mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- 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).
- Women who are breast-feeding, and during pregnancy, or during labour and delivery (see Serious Warnings and Precautions, and WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, pms-BUTORPHANOL (butorphanol tartrate nasal spray) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

pms-BUTORPHANOL poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing pms-BUTORPHANOL, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). pms-BUTORPHANOL should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of pms-BUTORPHANOL. Infants exposed *in-utero* or through breast milk are at risk of

life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of pms-BUTORPHANOL or following a dose increase.

Accidental Exposure
Accidental ingestion of even one dose of pms-BUTORPHANOL, especially by children, can result in a fatal overdose of butorphanol tartrate (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

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

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

Risks From Concomitant Use with Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of pms-BUTORPHANOL and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

General

Patients should be instructed not to give pms-BUTORPHANOL (butorphanol tartrate) nasal spray to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. pms-BUTORPHANOL should be stored securely to avoid theft or misuse.

pms-BUTORPHANOL should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of
patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking **pms-BUTORPHANOL** as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of butorphanol tartrate can occur at particularly high doses. A butorphanol tartrate dose reduction or change in opioid may be required.

Abuse and Misuse

Like all opioids, **pms-BUTORPHANOL** is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, **pms-BUTORPHANOL** should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as **pms-BUTORPHANOL**, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Carcinogenesis and Mutagenesis

See TOXICOLOGY section.

Cardiovascular

Butorphanol tartrate 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, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of pms-BUTORPHANOL.

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

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of pms-BUTORPHANOL and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction.
Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Endocrine

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of 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 of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Use in Drug and Alcohol Addiction

pms-BUTORPHANOL is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to pms-BUTORPHANOL; extreme caution and awareness is warranted to mitigate the risk.

Gastrointestinal Effects

Butorphanol tartrate and other morphine-like opioids have been shown to decrease bowel motility. Butorphanol tartrate may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see CONTRAINDICATIONS).

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid

used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

pms-BUTORPHANOL is not recommended to be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the risks. If **pms-BUTORPHANOL** was used during pregnancy, special attention to NOWS is warranted.

Neurologic

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

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol)
Butorphanol tartrate should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, 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 opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see DRUG INTERACTIONS). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, 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 analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, 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-BUTORPHANOL 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 DRUG INTERACTIONS).

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

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Head Injury
The respiratory depressant effects of butorphanol tartrate, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, butorphanol tartrate may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, pms-BUTORPHANOL must be used with extreme caution and only if it is judged essential (see CONTRAINDICATIONS).

Peri-Operative Considerations

pms-BUTORPHANOL is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with pms-BUTORPHANOL for at least 24 hours before the operation and pms-BUTORPHANOL should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if pms-BUTORPHANOL is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Butorphanol tartrate and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

pms-BUTORPHANOL should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Psychomotor Impairment

pms-BUTORPHANOL 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 accordingly. Patients should also be cautioned about the combined effects of butorphanol tartrate with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Respiratory

Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. pms-BUTORPHANOL should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see CONTRAINDICATIONS).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of pms-BUTORPHANOL, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with pms-BUTORPHANOL and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of pms-BUTORPHANOL are essential. Overestimating the pms-BUTORPHANOL dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non- opioid analgesics should be considered, if feasible (see WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups, and DOSAGE AND ADMINISTRATION).

Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with pms-BUTORPHANOL, as in these patients, even usual therapeutic doses of pms-BUTORPHANOL may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of pms-BUTORPHANOL is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see CONTRAINDICATIONS).

Sexual Function/Reproduction

Reproduction studies in mice, rats and rabbits during organogenesis did not reveal any teratogenic potential of butorphanol. Pregnant rats treated subcutaneously with butorphanol at 1 mg/kg (5.9 mg/m^2) had a higher frequency of stillbirths than controls. Butorphanol administered orally at 30 mg/kg (5.1 mg/m^2) and 60 mg/kg (10.2 mg/m^2) also showed higher incidences of post-implantation loss in rabbits. Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see ADVERSE REACTIONS, Post- Marketing Experience).

Special Populations

Special Risk Groups

pms- BUTORPHANOL should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Pregnant Women

Studies in humans have not been conducted. **pms-BUTORPHANOL** crosses the placental barrier and is not recommended to be administered to pregnant women unless, in the judgment of the physician, potential benefits outweigh the risks.

There are no adequate and well-controlled studies of butorphanol tartrate in pregnant women before 37 weeks of gestation. The use of pms-BUTORPHANOL in women of childbearing potential requires that the expected benefit of the drug be weighed against the potential risk to the mother and fetus.

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events 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 WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS), and ADVERSE REACTIONS, Post-Marketing Experience).

Labour, Delivery and Nursing Women

Since opioids can cross the placental barrier and are excreted in breast milk, **pms-BUTORPHANOL** is not recommended to be used in nursing women and during labour and delivery unless, in the judgement of the physician, the potential benefits outweigh the risks. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if pms-BUTORPHANOL is used in this population.

pms-BUTORPHANOL is not recommended during labour or delivery because there is no clinical experience with its use in this setting. Butorphanol tartrate injection has been used during labour, and there have been rare reports of neonatal respiratory depression of the newborn occurring after delivery.

There is no clinical experience with the use of butorphanol tartrate nasal spray in nursing mothers. If pms-BUTORPHANOL is administered to a nursing mother, consideration should be given to the possibility that pharmacologically active drug could be available to a nursing infant. Butorphanol tartrate administered intravenously or intramuscularly is secreted in low concentrations in human milk; however, the clinical significance of this finding has not been systematically evaluated.

Pediatrics (< 18 years of age)
The safety and efficacy of butorphanol tartrate have not been studied in the pediatric population in patients under 18 years of age.

Geriatrics (> 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 titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

The mean half-life of butorphanol tartrate is increased to 6 hours in patients over the age of 65 (see ACTIONS AND CLINICAL PHARMACOLOGY). In addition to having a somewhat reduced ability to eliminate butorphanol tartrate, elderly patients may be more sensitive to its side effects, particularly dizziness (see DOSAGE AND ADMINISTRATION).

Patients with Hepatic Impairment
pms-BUTORPHANOL should be administered with caution to patients with liver disease (see ACTIONS AND CLINICAL PHARMACOLOGY: Pharmacokinetics, and DOSAGE AND ADMINISTRATION: Dosage Adjustments).

Patients with Renal Impairment
Impaired renal function necessitates alterations in dosing schedule (see ACTIONS AND CLINICAL PHARMACOLOGY: Pharmacokinetics, and DOSAGE AND ADMINISTRATION: Dosage Adjustments).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of pms-BUTORPHANOL (butorphanol tartrate) nasal spray are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class.

The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The most frequently observed adverse effects of butorphanol tartrate nasal sprays are:

Commonly Observed
Across all controlled and uncontrolled acute treatment clinical trials (799 patients exposed to butorphanol tartrate nasal spray) the most commonly observed adverse experiences (with incidence of least 10%) regardless of relationship to butorphanol tartrate nasal spray were; drowsiness (35%), somnolence (17%), dizziness (25%), and nausea and vomiting (11%). These adverse events appeared dose-related. They also occurred more frequently in patients given butorphanol tartrate nasal spray for migraine. In nearly all cases, the type and incidence of side effects were those expected of a potent opioid analgesic, and no unforeseen or unusual toxicity was reported.

Severe Adverse Reactions
During controlled and uncontrolled acute clinical trials involving 799 patients exposed to butorphanol tartrate nasal spray, the following adverse events regardless of relationship (incidence in parentheses) were rated as severe in greater than 1% of patients: drowsiness and somnolence (7.7%), dizziness (4.4%), nausea and vomiting (3.4%), and confusion (1%).

Clinical Trial Adverse Drug Reactions

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

Controlled Clinical Studies
The incidences of adverse reactions (> 3%) to butorphanol tartrate nasal spray in the following table are derived from placebo-controlled trials (N = 662) in a variety of post-operative pain models at doses of 1 or 2 mg, and from two placebo-controlled trials involving the treatment of migraine pain at doses of 2 to 3 mg.

Table 1: Summary of Adverse Events in Patients Receiving Butorphanol Tartrate Nasal Spray **or Placebo in Post Operative Pain and Migraine Trials (only adverse events reported by > 3% of patients treated with butorphanol tartrate nasal spray at the specified dose are included)**

	Migraine Pain Trials (% of Patients)				Post Operative Pain (% of Patients)			
	Butorphanol Tartrate Nasal Spray			Placebo	Butorphanol Tartrate Nasal Spray			Placebo
	1+1 mg N=32	2 mg N=33	2+1 mg N=16	N=78	1 mg N=128	1+1 mg N=70	2 mg N=149	N=156
BODY AS A WHOLE								
Asthenia	9	18	6	3				
Chills	-	6	-	3				
Headache					4	4	-	3
Pain	-	6	-	1				
Sensation of Heat	6	12	6	3	-	-	5	1
CARDIOVASCULAR SYSTEM								
Chest Pain	-	6	-	-				
Palpitation	6	-	-	-				
Syncope	-	9	-	-				
Vasodilation	6	-	6	1				
DIGESTIVE SYSTEM								
Dry Mouth	6	21	12	-				
Increased Appetite	-	6	-	-				
Nausea/Vomiting	22	61	37	4	-	-	8	1
Thirst	-	-	6	-				
NERVOUS SYSTEM								
Abnormal Feelings	6	12	6	-				
Abnormal Thinking	-	6	-	-				
Anxiety	-	6	-	-				
Confusion	9	24	6	-	-	6	-	-
Dizziness	50	85	75	10	23	6	25	1
Drowsiness	41	51	50	5	26	33	40	16
Euphoria	-	3	6	-				
Incoordination	-	6	-	-				
Nervousness	16	9	6	-				
Paresis	-	15	6	-				
Paresthesia	6	21	-	-				
Somnolence					23	36	39	12
Vertigo	9	6	-	1				
RESPIRATORY SYSTEM								
Epistaxis	-	-	6	-				
Nasal Irritation	-	6	6	1				
DERMATOLOGICAL								
Pruritus	6	12	6	-	-			
Sweating	6	30	19	-		4	-	1
SPECIAL SENSES								
Blurred Vision	12	9	12	1	-	-	-	-
Diplopia	6	-	-	-	-	-	-	-
Ear Disorder	-	6	-	-	-	-	-	-
Hearing Loss	-	-	6	-	-	-	-	-
Unpleasant Taste	12	9	6	-	-	-	-	-

Sedation
Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting
Nausea is a common side effect on initiation of therapy with opioid analgesics 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 with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

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. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

The following adverse effects occur less frequently with opioid analgesics and include those reported in butorphanol clinical trials, whether related or not to butorphanol tartrate.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Body as a Whole
Infrequent: sensation of cold, fever, edema, accidental injury, back pain.

Cardiovascular
Frequent: hypotension.
Infrequent: blood pressure elevated, hypertension, tachycardia, pallor, arrhythmia.

Dermatological
Infrequent: rash, erythema.

Gastrointestinal
Infrequent: pharyngitis, stomach pain, abdominal pain, dysphagia, flatulence.

General and CNS
Infrequent: hallucinations, feel calm, insomnia, abnormal dreams, agitation, abnormal gait, dysarthria, ataxia, tremor, derealization, intoxication, spasms, stupor, hyperesthesia, motor retardation, vivid imagination, abnormal involuntary movement, slowed movement.

Genitourinary
Infrequent: impaired urination, libido increased.

Respiratory
Infrequent: dyspnea, cough, hypoventilation, respiratory disorder, sinus congestion, nasal congestion.

Musculoskeletal
Infrequent: muscle relaxation, leg pain.

Nasal Experiences
Infrequent: nasal symptoms, nose pain.

Special Senses
Infrequent: visual disturbance, photophobia, hyperacusia, eye pain, ear pain, tinnitus, eye disorder, taste loss.

Hemic and Lymphatic
Infrequent: petechiae.

Post-Marketing Experience

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.

The following adverse events also have occurred in less than 1% of patients in short-term butorphanol trials and postmarketing experience.

Body as a Whole: Excessive drug effect associated with transient difficulty speaking and/or executing purposeful- movements.

Cardiovascular: Chest pain, hypertension, tachycardia.

Nervous System: Convulsions, drug dependence.

DRUG INTERACTIONS

Serious Drug Interactions

- Concurrent use of pms-BUTORPHANOL with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in additive central nervous system depressant effects. The dose of pms-BUTORPHANOL should be minimized and the frequency of dosing reduced when it is administered concomitantly with drugs that potentiate the action of opioids.
- It is not known if the effects of butorphanol tartrate are altered by concomitant medications that affect hepatic metabolism of drugs (erythromycin, theophylline, etc.), but physicians should be alert to the possibility that longer intervals between doses may be needed.
- Caution should be exercised in using pms-BUTORPHANOL concomitantly with MAO inhibitors, as the latter have been associated with severe and sometimes fatal adverse reactions in certain susceptible individuals when used with meperidine and other narcotic analgesics.

Overview

Coadministration of butorphanol tartrate with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see WARNINGS AND PRECAUTIONS).

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

Drug-Drug Interactions

Administration of a single 2 mg dose of butorphanol tartrate nasal spray to 18 subjects with allergic rhinitis resulted in a higher C_{max} and shorter T_{max} compared to healthy subjects, although bioavailabilities were similar. When these 18 subjects were pre-treated with the nasal vasoconstrictor, oxymetazoline, bioavailability of butorphanol was not affected, however, C_{max} was reduced and T_{max} was increased to values similar to those observed in healthy subjects.

No significant pharmacokinetic interactions between butorphanol tartrate nasal spray (1 mg) and sumatriptan (6 mg s.c.) were observed in a single dose clinical trial involving 24 healthy volunteers. However, the safety and efficacy of butorphanol tartrate nasal spray in the treatment of migraine headache pain refractory to sumatriptan has not been established.

In another study among 16 healthy male volunteers, the plasma concentrations of a 1 mg dose of butorphanol tartrate nasal spray (q.i.d. for 4 days) were not affected when cimetidine was co-administered (300 mg q.i.d. for 4 days). Conversely, the pharmacokinetics of cimetidine (300 mg q.i.d. for 4 days) were not altered when butorphanol tartrate nasal spray (1 mg q.i.d.) was co-administered for 4 days.

Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see WARNINGS AND PRECAUTIONS, General).

DOSAGE AND ADMINISTRATION

pms-BUTORPHANOL should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

For acute pain, it is recommended that pms-BUTORPHANOL be used for a maximum of 3 days at the lowest dose that provides adequate pain relief.

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. If pms-BUTORPHANOL is used for more than 3 days for the management of chronic non-cancer, non-palliative pain, it is recommended that a daily maximum of 16 sprays corresponding to 16 mg of pms-BUTORPHANOL (80 morphine milligram equivalent) not be exceeded. Each patient should be assessed for their risk prior to prescribing pms-BUTORPHANOL, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of pms-BUTORPHANOL (see DOSAGE AND ADMINISTRATION - Adjustment or Reduction of Dosage).

Dosing Considerations

pms-BUTORPHANOL (butorphanol tartrate nasal spray) should be used with caution within 12 hours pre-operatively and within the first 12 to 24 hours post-operatively (see WARNINGS AND PRECAUTIONS, Peri-operative Considerations).

pms-BUTORPHANOL is not indicated for rectal administration.

Recommended Dose and Dosage Adjustment

pms-BUTORPHANOL (butorphanol tartrate), has an onset of effect within 15 to 30 minutes, and requires individualization of dosage based on clinical response.

ADULTS

The usual recommended dose for initial nasal administration is one (1) spray in one (1) nostril (1 mg). Adherence to this dose may reduce the likelihood of drowsiness, dizziness, and nausea and vomiting. If adequate pain relief is not achieved within 60 to 90 minutes, an additional 1 mg dose may be given.

The initial dose sequence of pms-BUTORPHANOL may be repeated in 3 to 4 hours as needed. Due to limited clinical experience with higher doses, total daily doses of more than 16 mg are not recommended.

Depending on the severity of the pain, an initial dose of 2 mg (1 spray in each nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occur. In such patients, additional doses should not be given for 3 to 4 hours.

Table 2 - OPIOID ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES[1]

Drug	Equivalent Dose (mg)[2] (compared to morphine 10 mg IM)		Duration of Action (hours)
	Parenteral	Oral	
Strong Opioid Agonists:			
Morphine	10	60[3]	3-4
Oxycodone	15	30[4]	2-4
Hydromorphone	1.5	7.5	2-4
Anileridine	25	75	2-3
Levorphanol	2	4	4-8
Meperidine[6]	75	300	1-3
Oxymorphone	1.5	5 (rectal)	3-4
Methadone[5]	-	-	-
Heroin	5-8	10-15	3-4
Weak Opioid Agonists:			
Codeine	120	200	3-4
Propoxyphene	50	100	2-4
Mixed Agonist-Antagonists[7]:			
Pentazocine[6]	60	180	3-4
Nalbuphine	10	-	3-6
Butorphanol	2	-	3-4

Footnotes:
[1] References:

Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.
Foley KM. The treatment of cancer pain. N Engl J Med 1985;313(2):84-95.
Aronoff GM, Evans WO. Pharmacological management of chronic pain: A review. In: Aronoff GM, editor. Evaluation and treatment of chronic pain. 2nd ed. Baltimore (MD): Williams and Wilkins; 1992. p. 359- 68.
Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. New York: Churchill Livingstone; 1994. p. 1437-67.

[2] **Most of the data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain. As analgesic conversion factors are approximate and patient response may vary, dosing should be individualized according to relief of pain and side effects. Because of incomplete cross-tolerance, dose reductions of 25% to 50% of the equianalgesic dose may be appropriate in some patients when converting from one opioid to another, particularly at high doses. † Upward titration may be required to reach appropriate maintenance doses.**
†Levy MH. Pharmacologic treatment of cancer pain. N Engl J Med 1996;335:1124-1132.

3 **For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2:1 to 3:1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).**

4 Based on single entity oral oxycodone in acute pain.

5 Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.

6 Not recommended for the management of chronic pain.

7 Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

Geriatrics
Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. pms-BUTORPHANOL should be initiated at a low dose and slowly titrated to effect (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Use with Non-Opioid Medications
If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. **pms-BUTORPHANOL** can be safely used concomitantly with usual doses of other non-opioid analgesics.

Dose Titration
Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage
Patients with Hepatic Impairment
The elimination half-life of pms-BUTORPHANOL is prolonged in patients with impaired hepatic function (see ACTIONS AND CLINICAL PHARMACOLOGY: Pharmacokinetics). pms-BUTORPHANOL should thus be used with caution in this population. The initial dosage interval should be increased to 6 to 12 hours until the response is well characterized. Subsequent dosings should be determined by patient response rather than being scheduled at fixed intervals.

Patients with Renal Impairment
The elimination half-life of pms-BUTORPHANOL is prolonged in patients with impaired renal function (see ACTIONS AND CLINICAL PHARMACOLOGY: Pharmacokinetics). Dosage adjustments may thus be necessary. In patients with severe renal disease (i.e. creatinine clearance < 30 mL/min), the initial dosage interval should be increased to 6 to 8 hours until the response has been well characterized. Subsequent dosings of pms-BUTORPHANOL should be determined by patient response rather than being scheduled at fixed intervals.

Geriatrics
Because elderly patients may have a somewhat decreased ability to eliminate butorphanol (see ACTIONS AND CLINICAL PHARMACOLOGY: Pharmacokinetics) and may be more sensitive to butorphanol's side effects, the effects of the initial dose should be carefully assessed, and it may be appropriate to modify the frequency of subsequent dosing.

Initially a 1 mg dose of pms-BUTORPHANOL should generally be used in elderly patients, and 90 to 120 minutes should elapse before deciding whether a second 1 mg dose is needed. The repeat dose sequence should be determined by the patient's response rather than at fixed times, but will generally be no less than at 6 hour intervals (see WARNING AND PRECAUTIONS).

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including **pms-BUTORPHANOL**. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These 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.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient’s condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualised and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids 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.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

Disposal

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

pms-BUTORPHANOL should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired pms-BUTORPHANOL should be properly disposed of as soon as it is no longer needed 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.

Missed Dose

If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms
Based on its pharmacology, butorphanol tartrate overdosage could produce signs of respiratory depression, cardiovascular failure (especially in predisposed patients), or central nervous system depression. There have been no clinical reports of fatal overdosage of butorphanol as a single drug in healthy individuals, but the injectable product has been reported in a fatal overdose in combination with other drugs or alcohol.

Treatment
The specific treatment of suspected butorphanol tartrate overdosage is immediate establishment of adequate airway and ventilation, followed (if necessary) by an opioid antagonist such as intravenous naloxone. Physicians are reminded that the duration of butorphanol action exceeds the duration of action of naloxone, and repeated dosing of naloxone may be required. The patient should be carefully monitored, especially the respiratory and cardiac status, and appropriate supportive measures, such as oxygen, intravenous fluids and/or vasopressors, should be instituted if necessary.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Butorphanol acts as an agonist at kappa-opioid receptors and a mixed agonist-antagonist at mu-opioid receptors in the central nervous system to alter the perception of pain. The drug is believed to act at sites in the periventricular and periaqueductal gray matter, and at sites in the spinal cord.

In an animal model, the dose of butorphanol tartrate required to antagonize morphine analgesia by 50% was similar to that for nalorphine, less than that for pentazocine and more than that for naloxone.

The analgesic activity of 2 mg of butorphanol tartrate administered parenterally is approximately equivalent to 10 mg morphine sulfate, 80 mg meperidine hydrochloride or 40 mg pentazocine. In normal volunteers, the same doses of these drugs produced nearly equivalent respiratory depression. Butorphanol, in contrast to morphine or meperidine, produces respiratory depression in a limited dose range, reaching a plateau at approximately 4 mg. The magnitude of respiratory depression with butorphanol is not appreciably increased at a dose of 4 mg; however, the duration of respiratory depression appears to be dose-related. Respiratory rates were monitored in controlled clinical studies with therapeutic doses of butorphanol tartrate nasal spray and no untowards effects were observed. Respiratory depression noted after administration of butorphanol by any route is reversed by treatment with naloxone, a specific opioid antagonist (see OVERDOSAGE).

Butorphanol tartrate has a marked sedative effect that is dose related and this property should be considered in its clinical application (see WARNINGS AND PRECAUTIONS).

The hemodynamic changes after the intravenous administration of butorphanol are similar to those produced by pentazocine. These include increased pulmonary artery pressure, pulmonary wedge pressure, left ventricular end diastolic pressure, systemic arterial pressure, and pulmonary vascular resistance. Although smaller than those associated with pentazocine, these changes are nevertheless in a direction that increases the work of the heart, especially in the pulmonary circuit.

Butorphanol, like other mixed agonist-antagonists with a high affinity for the kappa receptor, produced unpleasant psychotomimetic effects in some individuals.

Pharmacokinetics

The pharmacokinetics (including absorption times and peak blood levels) of a nasal spray dose and an intramuscular dose of butorphanol tartrate are similar. In addition, after an initial absorption phase, the pharmacokinetics of a nasal spray dose are also similar to those of an intravenous dose.

Butorphanol tartrate is rapidly absorbed without significant biotransformation following nasal administration. In both young and elderly normal volunteers, peak blood levels occur around one-half hour following nasal administration. Peak plasma concentrations after a 1 mg dose vary from a mean of 0.9 to 1.04 ng/mL (see Table 2). Elderly subjects may have a somewhat decreased ability to eliminate butorphanol, with an apparent elimination half-life of 6.6 hours as opposed to

4.7 hours for younger subjects. The mean absolute bioavailability may be somewhat less for elderly women (48%) than for elderly men or younger subjects (75% and 69% respectively).

Table 3: Mean Pharmacokinetic Parameters Of Butorphanol Tartrate Nasal Spray In Young And Elderly Subjects[a]

Parameter	Young	Elderly
T_{max}[b] (hr)	0.62 (0.50 - 2.00)[e]	0.75 (0.25 - 3.00)
C_{max}[c] (ng/mL)	1.04 (0.35 - 1.97)	0.90 (1.10 - 2.68)
AUC(inf)[d] (hr • ng/mL)	4.93 (2.16 - 7.27)	5.24 (0.30 - 10.34)
Half - life (hr)	4.7 (2.89 - 8.79)	6.6 (3.75 - 9.17)
Absolute Bioavailability (%)	69 (44 - 113)	62 (3 - 121)
Volume of Distribution [f] (L)	487 (305 - 901)	552 (305 - 737)
Clearance[f] (L/hr)	98 (70 - 154)	82 (52 - 143)

a) Young subjects (n=24) are from 20 to 40 years old (mean M/F, 25/30 years) and elderly subjects (n=24) are from 65 to 83 years old (mean M/F, 71 years).
b) Time to peak plasma concentration, median values.
c) Peak plasma concentration normalized to 1 mg dose.
d) Area under the plasma concentration time curve after a 1 mg dose.
e) (range of observed values).
f) Derived from i.v. data

The mean plasma half-life of butorphanol is 5.1 hours after a 2 mg intranasal administration.

Serum protein binding is independent of concentration over the range achieved in clinical practice (up to 7 ng/mL) with a bound fraction of approximately 80%. Butorphanol crosses the blood brain and placental barriers and is found in human milk (see WARNINGS AND PRECAUTIONS).

The volumes of distribution of butorphanol varies from 305 to 901 litres and total body clearance from 52 to 154 liters/hour.

Intranasal butorphanol pharmacokinetic studies determined that steady-state plasma levels of butorphanol were dose proportional (in doses up to 4 mg every 6 hours). Steady-state is achieved within 2 days, and plasma concentrations are approximately 1.8 times those following a single dose.

Butorphanol is extensively metabolized in the liver and is eliminated as oxidized and conjugated metabolites. Metabolism is qualitatively and quantitatively similar with nasal, intravenous, or intramuscular administration. Less than 5% of an intravenous dose is recovered in the urine as unchanged drug. Because of extensive first-pass metabolism, the bioavailability of oral butorphanol is less than 10%.

Hydroxybutorphanol is the main urinary metabolite of butorphanol (49% of dose); small amounts of norbutorphanol (< 5%) are also excreted in urine. The analgesic activity of these two metabolites has not been determined in humans.

In Patients with Renal Insufficiency

Eighteen female volunteers (age 30 to 65 years) with normal or varying degrees of renal impairment were given single 1 mg intranasal doses of butorphanol. As shown below, the elimination half-life of butorphanol was prolonged, and the AUC increased, in patients with reduced creatinine clearance (CrCl). No effect, however was observed on C_{max} or T_{max}.

	CrCl (mL/min)	$t_{1/2}$ (h)	AUC (h•ng/mL)
Normal	> 70	5.75	4.32 (1.63)*
Moderately Impaired	30 - 60	8.55	6.49 (l.32)
Severely Impaired	< 30	10.48	7.41 (2.64)

* Standard deviation

In Patients with Hepatic Disease

The pharmacokinetics and absolute bioavailability of a 1 mg dose of transnasal butorphanol was studied in 12 (8M, 4F) subjects with hepatic impairment, and 12 normal subjects matched for sex, age and weight. Compared to normal subjects, patients with hepatic impairment had on average a 3-fold increase in $t_{1/2}$ and a 2- to 3-fold increase in AUC. Absolute bioavailability was 99% in the subjects with hepatic impairment compared to 73% in controls. C_{max}, and T_{max}, however remained unaltered regardless of the liver conditions.

Pharmacodynamics

Following intranasal administration of butorphanol tartrate nasal spray, onset of analgesia is within 15 to 30 minutes, and peak analgesic activity generally occurs within 1 to 2 hours. The duration of analgesia varies depending on the pain model but is generally 3 to 6 hours with intranasal doses of 1 to 2 mg.

Central Nervous System

Butorphanol tartrate produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO2 tension and to electrical stimulation.

Butorphanol tartrate depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Butorphanol tartrate causes 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 butorphanol tartrate overdose.

Gastrointestinal Tract and Other Smooth Muscle

Butorphanol tartrate causes 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.

Cardiovascular System
Butorphanol tartrate 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.

Endocrine System
Opioids may influence the hypothalamic-pituitary-adrenal 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.

Special Populations and Conditions

Pediatrics
Individuals under 18 years of age should not take pms-BUTORPHANOL nasal spray.

STORAGE AND STABILITY

pms-BUTORPHANOL should be stored at room temperature (15°C to 30°C).

SPECIAL HANDLING INSTRUCTIONS

pms-BUTORPHANOL is an open delivery system that has a risk of accidental exposure to health care workers. In the priming process, a certain amount of butorphanol may be aerosolized; therefore, the pump sprayer should be aimed away from the patient or animals.

Significant absorption from accidental dermal exposure is unlikely, and the contents of a spilled system should be washed from the skin by rinsing with cool water.

The best way to dispose of the unit safely is to unscrew the cap, rinse the bottle and spray assembly under the water faucet, then dispose of the parts in a waste can where children cannot get to them easily.

DOSAGE FORMS, COMPOSITION AND PACKAGING

pms-BUTORPHANOL is an aqueous solution of butorphanol tartrate for administration as a metered spray to nasal mucosa.

pms-BUTORPHANOL (butorphanol tartrate) is supplied in 2.5 mL bottles containing 10 mg/mL butorphanol tartrate, with a metered-dose spray pump with protective clip and dust cover, and a patient instruction leaflet. After priming, each metered spray delivers 1.0 mg of butorphanol tartrate. The 2.5 mL bottle will deliver on average 14 to 15 metered doses, if no repriming is necessary.

Composition: Each bottle of pms-BUTORPHANOL contains a 10 mg/mL solution of butorphanol tartate with sodium chloride, citric acid, and 0.2 mg/mL benzethonium chloride as a preservative, in purified water with sodium hydroxide and/or hydrochloric acid added to adjust the pH to 5.0.

PART II: SCIENTIFIC INFORMATION

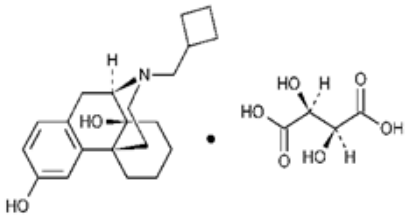
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Butorphanol tartrate

Chemical Name: (-)-17- (cyclobutylmethyl) morphinan-3, 14-diol D-(-)-tartrate (1:1)salt

Structural Formula:



Molecular Formula: $C_{21}H_{29}NO_2 \bullet C_4H_6O_6$

Molecular Weight: 477.56 g/mol

Description: White, odourless crystalline powder.

Solubility: Sparingly soluble in water, slightly soluble in methanol, practically insoluble in ethanol, chloroform, ether, ethyl acetate and hexane; soluble in diluted acids.

pKa: 8.34

Melting Range: Melting point 217° to 219°C with decomposition.

Partition Coefficient: The n-octanol/aqueous buffer partition coefficient of butorphanol is 180:1 at pH 7.5.

CLINICAL TRIALS

Migraine Headache Pain

The analgesic efficacy of two 1 mg doses one hour apart of butorphanol in migraine headache pain was compared with a single dose of 10 mg intramuscular methadone or placebo (32 patients per treatment group). Significant onset of analgesia occurred within 15 minutes for both butorphanol tartrate nasal spray and intramuscular methadone. Peak analgesic effect occurred at 2 hours for butorphanol and 1.5 hours for methadone. The median duration of pain relief was 6 hours with butorphanol and 4 hours with methadone as judged by the time when approximately half of the patients remedicated.

In the two other trials in patients with migraine headache pain, a 2 mg initial dose of butorphanol tartrate nasal spray followed by an additional 1 mg dose 1 hour later (76 patients) was compared with either 75 mg intramuscular meperidine (24 patients) or placebo (72 patients). Onset peak activity and duration were similar with both active treatments; however, the incidence of adverse experiences (nausea, vomiting, dizziness) was higher in these two trials with the 2 mg initial dose of butorphanol tartrate nasal spray than in the trial with the 1 mg initial dose.

Postoperative Analgesia

The analgesic efficacy of butorphanol tartrate nasal spray was investigated in placebo-controlled studies in postoperative surgical pain (abdominal, orthopedic, gynecologic) and in postoperative caesarian section pain. Patients had moderate to severe pain at baseline.

In the general surgery study, a single 1 or 2 mg dose of butorphanol tartrate nasal spray (33 to 36 patients per treatment group) was compared to a single dose of 37.5 or 75 mg intramuscular meperidine. In this blinded study, the effects of the lower doses of each drug could be distinguished from those of the higher doses. Analgesia provided by the 1 and 2 mg doses of butorphanol was equivalent to that of 37.5 and 75 mg meperidine respectively. The duration of pain relief was 2 to 3 hours with 1 mg butorphanol tartrate nasal spray and 3 to 4 hours with 2 mg butorphanol tartrate nasal spray, as judged by the time when approximately half of the patients required a repeat dose.

In the caesarian section study, a single dose of 2 mg butorphanol tartrate nasal spray (37 patients) or two 1 mg doses butorphanol tartrate nasal spray given 1 hour apart (35 patients), were compared to a single dose of 2 mg intravenous butorphanol (37 patients) or placebo (37 patients). Significant pain relief began within 5 minutes for intravenous butorphanol, 15 minutes for 2 mg butorphanol tartrate nasal spray, and 30 minutes for the two 1 mg doses of butorphanol tartrate nasal spray. Peak analgesic effects were similar for the three butorphanol treatments. The duration of pain relief, as judged by this time when approximately half of the patients required a repeat dose, was 2 to 3 hours for 2 mg i.v. butorphanol and 4 to 5 hours for 2 mg butorphanol tartrate nasal spray administered either as a single dose or two 1 mg doses given 1 hour apart.

DETAILED PHARMACOLOGY

Animal Pharmacology

Butorphanol produced analgesia in the phenylquinone writhing test in mice and rats (respective ED_{50} values, 0.05 mg/kg and 0.04 mg/kg, s.c.). A 0.5 mg dose in 200 mcL of saline produced peak analgesic effect when administered intranasally in the rat tail flick test. Antagonism of morphine analgesia was demonstrated in the rat tail flick test at 0.43 mg/kg, s.c. Depressed locomotor activity and impaired coordination were produced in rodents in doses beginning at approximately 54 mg/kg.

Behavioural depression occurred in monkeys in doses of 1 to 5 mg/kg, s.c. and while the high dose represented a plateau in effect the duration was prolonged up to 5 hours at this dose.

Direct physical dependence has been demonstrated in mice in low doses and precipitation of withdrawal in morphine-dependent mice was produced in high doses (9 to 80 mg/kg, s.c.). In addition, butorphanol produced antitussive action in guinea pigs and some anticonvulsant activity in mice. The agonist actions of butorphanol (analgesia, respiratory depression and antitussive effects) can be reversed by naloxone.

In conscious dogs, butorphanol (0.03 to 1.0 mg/kg, i.v.) produced little effect on cardiovascular or respiratory functions. In anesthetized dogs, doses of 3 mg/kg, i.v. produced decreased blood pressure, heart rate and cardiac output. A dose of 5 mg/kg, i.v. produced convulsions in dogs.

Human Pharmacology

Butorphanol produced miosis in dogs and humans but this effect plateaued without a well-defined dose response such as is produced by morphine.

In humans following a 1 mg intravenous and a 2 mg intramuscular administration of tritium labelled butorphanol tartrate, a mean of 50% of the radioactivity was excreted in the urine after 24 hours and 72% after 96 hours; about 11% of the intravenous and 15% of the intramuscular dose was recovered in the feces after 104 hours.

Apparent volumes of distribution of butorphanol and its major metabolite are small, minimizing the liability for tissue accumulation on prolonged drug administration.

The dispositions of butorphanol and hydroxybutorphanol are as follows:

	I.M.	I.V.
Butorphanol		
Renal clearance rate	4.7 L/hr	8.4 L/hr
4 to 8 hour total plasma concentration half time	4.9 hrs	3.9 hrs
Peak plasma concentration	2.02 mcg/L	1.80 mcg/L
Mean 0 to 8 hour area under the curve	10.8 mcg/hr/L	3.4 mcg/hr/L
Hydroxybutorphanol		
Rate of metabolism of butorphanol to hydroxybutorphanol	0.68 ± 0.02 mcg/L/hr	0.68 ± 0.02 mcg/L/hr
Overall elimination half time	1.06 hrs	0.34 hrs
Renal clearance rate	15.5 L/hr	11.2 L/hr
Mean 0 to 8 hour area under the curve	5.9 mcg/hr/L	2.0 mcg/hr/L

TOXICOLOGY

Acute Toxicity

Species / Strain	Sex (No. Per group)	Route	Doses (mg/kg)	LD_{50} (mg/kg)
Mouse / Swiss-Webster	Male (10)	Oral	319, 402, 506, 638	395
Mouse / Swiss-Webster	Female (10 or 20)	Oral	319, 402, 506, 568, 638	527
Mouse / Carworth Farms	Male (10)	I.V.	31.6, 39.8, 44.7, 50.1	40.1 (36.0 - 43.6)
Mouse / Carworth Farms	Female (10)	I.V.	39.8, 44.7, 63.1, 79.4	56.7 (42.2 - 85.6)
Mouse / Carworth Farms	Male (10)	S.C.	251, 282, 316, 355	299 (257 - 347)
Mouse / Carworth Farms	Female (10)	S.C.	398, 447, 501	432 (326 - 482)
Rat / Long Evans	Male (10)	Oral	568, 638, 675, 715, 802	756
Rat / Long Evans	Female (10)	Oral	451, 506, 568, 600, 675	570
Dog / Beagle	Male (2) Female (2)	I.V.	5, 10, 15, 20	10 - 15
Dog / Beagle	Male (2) Female (2)	I.M	15, 20, 25, 30	23.4 (17.2 - 29.3)
Monkey / Rhesus	Male (2) Female (2)	Oral	50	>50

Signs of toxicity were generally ataxia, muscle tremors, nervousness, decreased activity and convulsions. The acute single dose toxicologic studies revealed a safe therapeutic ratio of butorphanol tartrate in animals compared to the usual maximum single dose in man of 0.04 mg butorphanol tartrate/kg/day intravenously and 0.2 mg/kg/day intranasal.

Subacute Toxicity

SPECIES/STRAIN (Number Used)	ROUTE	DURATION	DOSAGE	TREATMENT RELATED FINDINGS
Rat / Sprague Dawley (10 males and 10 females per dosage level)	Intranasal	2 weeks	0, 0.4 and 0.8 mg/day	Decreased mean absolute and relative ovary weights for the female 0.8 mg/day group. The dosage level of 0.4 mg/day is considered to be a no-effect level.
Rat / Sprague Dawley (10 males and 10 females per dosage level)	Intranasal	4 weeks	0, 2, and 4 mg/day	Hyperactivity and incidences of alopecia in all treated groups. Decreased body weight gain in both male treated groups. A minimal decrease in serum albumin levels in females at 2 and 4 mg/day and males at 4 mg/day. A slight increase in lactic dehydrogenase in males at 4 mg/day.
Dog / Beagle (3 males and 3 females per dosage level)	Intranasal	2 weeks	0, 2, and 4 mg/day	Mean body weight losses at both doses after one week of dosing. Decreased food consumption in the female 4 mg/day group after one week of dosing.
Dog / Beagle (3 males and 3 females per dosage level)	Intranasal	4 weeks	0, 8, and 16 mg/kg	Observations of hypoactivity, ataxia, tremors, salivation, altered gait, emesis, or diarrhea at all doses. Mean body weight loss and decreased food consumption in all groups after one week of dosing.
Monkey / Rhesus (1 male and 1 female per dosage level)	Oral	4 weeks	5 (for 8 days) increased to 10, 40, and 80 mg/kg/day	Male (day 29) and female (day 3) at 80 mg/kg/day found dead. Subdued behaviour and episodes of collapsing at 40 and 80 mg/kg/day. Slight body weight losses and decreased food intake at 40 and 80 mg/kg/day. Elevated alanine and aspartate transaminase and leucine aminopeptidase levels in one monkey at 40 mg/kg/day, but no microscopic hepatic changes at any dose. The dosage of 5-10 mg/kg/day was established as a no-effect level.

Chronic Toxicity

Multiple dose studies of 0.1, 0.5 and 1.0 mg/kg (butorphanol base) for 13 weeks revealed an incidence of pericholangitis, and mild bile duct hyperplasia, associated with increases in serum transaminase and serum alkaline phosphatase occurring in 2 of the 10 dogs at the high dose. A high incidence of similar spontaneous lesions in this colony of dogs has been previously reported.

Rhesus Monkey studies conducted intravenously for 2 weeks at doses of 0.15, 0.75 and 1.5 mg/kg (butorphanol base) and intramuscularly at daily doses of 0.5 and 1.0 mg/kg (butorphanol base) for 6 months revealed no drug related pericholangitis, bile duct hyperplasia or other organ toxicity.

In a subcutaneous study in rats at daily doses of 0.4, 2.0 and 4.0 mg/kg (butorphanol base) for 6 months, animal exhibited a decreased weight gain in the high dose females and mild decrease in white blood cell counts in the high dose males. All rats exhibited increased activity, excitement and sporadic self-mutilation (chewing of tails). No histopathologic evidence of pericholangitis, bile duct hyperplasia or other organ toxicity was observed in the rats.

Muscle, eye and venous irritation studies in rabbits, prolonged intramuscular injections in rats and in vitro hemolytic potential study failed to disclose any safety liabilities with butorphanol tartrate.

Reproduction Studies

The results of the fertility and general reproductive performance studies revealed that the subcutaneous administration of butorphanol tartrate at 2.5 or 0.5 mg/kg/day (in terms of butorphanol base) to male rats for 75 days prior to mating and to female rats from Day 14 prior to mating to Day 21 post partum produced no adverse response to spermatogenesis or oogenesis, estrous cycle, mating behaviour, conception rate, gestation, parturition, and viability of the newborns. The survival rate of the newborns between Days 4 and 21 post partum, however, was found to be significantly lower in both treated groups (99%), apparently due to drug-induced species-specific (as compared to other species used for toxicologic studies) nervousness exhibited by the dams resulting in decreased care for the newborns.

Parenteral administration of the compound to pregnant female mice and rats subcutaneously at 1.0, 0.5 or 0.1 mg/kg/day (in terms of butorphanol base) and to pregnant female rabbits by the intramuscular route at 1.0 or 0.1 mg/kg/day (in terms of butorphanol base) during organogenesis in the teratology studies did not produce any evidence of teratogenic effects in the offspring of these species.

The subcutaneous treatment of female rats with butorphanol during the last third of pregnancy and for 21 days post partum at 1.0 or 0.1 mg/kg/day (in terms of butorphanol base) in the Peri- and Postnatal Study had no discernible effect of duration of pregnancy, late fetal development, labour and delivery, lactation, nursing instinct, neonatal viability, and growth of the newborns.

Tumorigenicity in Rats

Rats were administered butorphanol tartrate in the diet at levels of approximately 1.0 and 2.0 mg/kg/day for 78 weeks and observed without drug treatment for an additional 26 weeks. Two control groups were included, one which received no drug and one which received pentazocine (40 mg/kg/day). Although no drug-related increase in tumour incidence was reported, a firm conclusion regarding the carcinogenicity of butorphanol in this species is not possible, since the study did not meet full requirements for a bioassay.

REFERENCES

1. Abboud TK. et al. Transnasal butorphanol: A new method for pain relief in post-cesarean section pain. Acta Anaesthesio Scand 1991; 35: 14-18.

2. Beaver WT. Measurement of analgesic efficacy in man. Adv in Pain Res Ther 1983; 5: 411-434.

3. Bloomfield SS. et al. Analgesic sensitivity of two postpartum pain models. Pain 1986; 27: 171-179.

4. Carter R. et al. A double-blind clinical evaluation of butorphanol and pentazocine in the alleviation of pain following gynecological therapy. Curr Ther Res 1978; 23(1): 48-54.

5. Del Pizzo A. Butorphanol, a new intravenous analgesic: Double-blind comparison with morphine sulfate in postoperative patients with moderate to severe pain. Curr Ther Res 1976; 20(3): 221-232.

6. Del Pizzo A. Double-blind evaluation of butorphanol and meperidine given intramuscularly before anesthesia. Curr Ther Res 1976; 20(6): 763-767.

7. Dobkin AB. et al. Butorphanol: A double-blind evaluation in postoperative patients with moderate to severe pain. Can Anaesth Soc J 1975; 21(6): 600-610.

8. Dobkin AB. et al. Butorphanol and pentazocine in patients with severe postoperative pain. Clin Pharm Ther 1975; 18(5) Part 1: 547-553.

9. Dobkin AB. et al. Butorphanol tartrate: 1. Safety and efficacy in multidose control of postoperative pain. Can Anaesth Soc J 1976; 23: 596-600, 601-608. Gilbert MS. et al. Butorphanol: A double-blind comparison with pentazocine in postoperative patients with moderate to severe pain. J Int Med Res 1976: 255-264.

10. Gilbert MS. et al. Intramuscular butorphanol and meperidine in postoperative pain. Clin Pharm Ther 1976; 20(3): 359-364.

11. Kallos T., Caruso F. Respiratory effects of butorphanol. Clin Pharm Ther Abstract 1977; 21: 107.

12. Kliman A. et al. Clinical experience with intramuscular butorphanol for the treatment of variety of chronic pain syndromes. Curr Ther Res 1977; 22(l): 105-115.

13. Lasagna L. Benefit risk ratio of agonist-antagonist analgesics. Drug and Alcohol Dependence 1987; 20: 385-393.

14. Lawhorn CD. et al. Epidural morphine with butorphanol for postoperative analgesia after cesarean delivery. Anest Analg 1991; 72: 53-57.

15. Nagashima H. et al. Respiratory and circulatory effects of intravenous butorphanol and morphine. Clin Pharm Ther; 19(6): 738-745.

16. Pachter IJ. and Evens RP. Butorphanol. Drug and Alcohol Dependence 1985; 14: 325-338.

17. Pittman KA et al. Human perinatal distribution of butorphanol. Am J Obstet Gynecol 1980; 138: 797-800.

18. Rosow CE. The clinical usefulness of agonist-antagonist analgesics in acute pain. Drug and Alcohol Dependence 1987; 20: 329-337.

19. Schug SA. et al. Adverse effects of systemic opioid analgesics. Drug Safety 1992; 2(3): 200-213.

20. Steg NL. Use of intramuscular butorphanol for the treatment of postoperative orthopedic pain in adolescents: A pilot study. Clin Ther 1988; 10(4): 406-413.

21. CPS Monograph. Stadol NS® (Butorphanol Tartrate) - Analgesic. IN: Welbanks L, Bisson R, Bergeron D, et al., eds. Compendium of Pharmaceuticals and Specialties. Canadian Pharmacists Association, Ottawa, 2000; pp. 1489-1491.

22. Product Monograph of BUTORPHANOL Nasal Spray by AA Pharma Inc. (Control #212498) dated May 28, 2018.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

pms-BUTORPHANOL
(Butorphanol Tartrate Nasal Spray)
10 mg/mL

Read this carefully before you start taking **pms-BUTORPHANOL** 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-BUTORPHANOL**.

Serious Warnings and Precautions

- **Even if you take pms-BUTORPHANOL as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **You may get life-threatening breathing problems while taking pms-BUTORPHANOL. This is less likely to happen if you take it as prescribed by your doctor. 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-BUTORPHANOL. They could die from taking it. If a person has not been prescribed pms-BUTORPHANOL, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took pms-BUTORPHANOL while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever**

  Seek immediate medical help for your baby.
- **Taking pms-BUTORPHANOL with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

What is pms-BUTORPHANOL used for?

pms-BUTORPHANOL is a pain medication containing butorphanol tartrate (an opioid analgesic) used to control moderate to severe pain. It is intended to treat acute (short-term) not chronic (long-term) pain.

How does pms-BUTORPHANOL work?

pms-BUTORPHANOL contains butorphanol tartrate which is a pain medication belonging to the class of drugs known as opioids which includes codeine, fentanyl, morphine and oxycodone. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in pms-BUTORPHANOL?

Medicinal ingredient: butorphanol tartrate

Non-medicinal ingredients: Sodium Chloride, Citric Acid, 0.2 mg/mL Benzethonium Chloride as preservative, Purified Water, with Sodium Hydroxide and/or Hydrochloric Acid to adjust the pH.

pms-BUTORPHANOL comes in the following dosage forms:
Nasal spray, 10 mg/mL

Do not use pms-BUTORPHANOL if:

- your doctor did not prescribe it for you
- you are allergic to butorphanol tartrate, or any of the other ingredients in pms-**BUTORPHANOL** nasal spray (see **What are the ingredients in pms-BUTORPHANOL?**)
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you have a brain tumor
- you suffer from alcoholism
- 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 are going to have, or recently had, a planned surgery
- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-BUTORPHANOL. 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 severe kidney, liver or lung disease
- have a heart disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your adrenal or prostate gland
- have, or had in the past, hallucinations or other severe mental problems
- suffer from migraines
- are planning to become pregnant.

Other warnings you should know about:

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour and delivery:

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

If you are pregnant and are taking pms-BUTORPHANOL, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking pms-BUTORPHANOL. This may help avoid serious harm to your unborn baby.

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

- drowsiness
- dizziness or
- light headedness

This can usually occur after you take your first dose and when your dose is increased.

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

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

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off pms-BUTORPHANOL.

Serotonin Syndrome: pms-BUTORPHANOL can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take pms-BUTORPHANOL with certain anti-depressants or migraine medications.

Serotonin Syndrome 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/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.

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

The following may interact with pms-BUTORPHANOL:

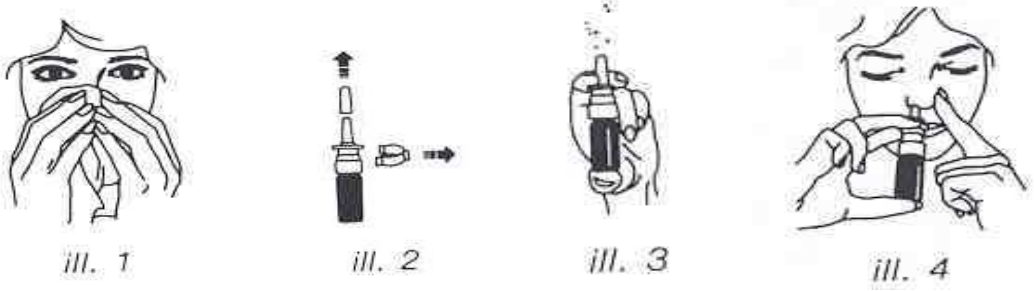
- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking **pms-BUTORPHANOL**. It can lead to:
  - drowsiness
  - unusually slow or weak breathing
  - serious side effects or
  - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by pms-BUTORPHANOL
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take **pms-BUTORPHANOL** with MAO inhibitors (MAOi) or if you have taken MAOi's 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 of vomiting)
- drugs used to treat muscle spasms and back pain
- some heart medication (such as beta blockers)

- drugs used to treat migraines (e.g. triptans)
- St. John's Wort
- warfarin (such as coumadin) and other anticoagulants (used for prevention or treatment of blood clots)
- anti-retroviral drugs (used to treat viral infections)
- anti-fungal drugs (used to treat fungal infections)
- antibiotic drugs (used to treat bacterial infections)
- grapefruit juice

How to take pms-BUTORPHANOL:

Take the medication as directed by your physician. For proper use of the nasal spray bottle, read the following instructions carefully.

Instructions:



1) Blow your nose (*ill. 1*).
2) Pull the clear cover off pump unit. Remove protective clip (*ill. 2*).
3) Prior to initial use, pump sprayer unit FIRMLY and QUICKLY until a fine spray appears (*ill. 3*).
4) Insert the spray tip approximately 1 cm into **one nostril**, close the other nostril with your forefinger and pump the spray unit once firmly and quickly (*ill.4*).
5) Your doctor will tell you whether a two-spray dose is needed. If needed, administer a second spray in the other nostril.

USUAL DOSE IS ONE SPRAY: Spray ONLY ONCE into ONE NOSTRIL ONLY. DO NOT spray into both nostrils unless directed by your doctor. DO NOT repeat sooner than directed by your doctor.

If not used for 48 hours or longer, the unit must be primed with one or two strokes.

Note: Each priming reduces the number of effective doses per bottle.

pms-BUTORPHANOL should not be used by anyone other than the person for whom it was prescribed. To prevent this, and to reduce the chance of children taking the drug, it is important to dispose of any excess pms-BUTORPHANOL as soon as it is no longer needed.

The best way to safely dispose of the unit is to unscrew the cap, rinse the bottle and spray assembly under the water faucet, and dispose of the parts in a waste can where children cannot easily get to them.

Usual Adult Starting Dose:

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.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take pms-BUTORPHANOL for up to 3 days as it is not known if it is effective beyond this time period. If you need to take

pms-BUTORPHANOL for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need **pms-BUTORPHANOL**. Be sure to use **pms-BUTORPHANOL** only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking **pms-BUTORPHANOL**, tell your doctor immediately.

Stopping your Medication

If you have been taking **pms-BUTORPHANOL** for more than a few days you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking pms-BUTORPHANOL. You should do it slowly to avoid uncomfortable symptoms such as having:

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

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking pms-BUTORPHANOL.

Refilling your Prescription for pms-BUTORPHANOL:

A new written prescription is required from your doctor each time you need more **pms-BUTORPHANOL**. 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 your pain management.

Overdose:

If you think you have taken too much **pms-BUTORPHANOL**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

Missed Dose:

If you miss one dose, 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. If you miss several doses in a row, talk to your doctor before restarting your medication.

What are possible side effects from using pms-BUTORPHANOL?

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

Side effects may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Light headedness
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

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

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	
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.			√
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			√
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea.			√
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		√	
Fast, Slow or Irregular Heartbeat: heart palpitations.		√	
Low Blood Pressure: dizziness, fainting,	√		

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.			
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea.			√

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

Reporting Side Effects

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

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

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

Storage:

- **Keep unused or expired pms-BUTORPHANOL in a secure place to prevent theft, misuse or accidental exposure.**
- Store at room temperature 15°C to 30°C.
- Store spray unit in the child resistant container.
- **Keep pms-BUTORPHANOL 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-BUTORPHANOL, get emergency help right away.**

Disposal:

pms-BUTORPHANOL 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-BUTORPHANOL:

- 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); the manufacturer's website www.pharmascience.com or by contacting Pharmascience Inc. at 1-888-550-6060

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