PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

BUTORPHANOL Nasal Spray

Butorphanol Tartrate Nasal Spray

Solution, 10 mg/mL (1 mg per spray), Nasal

USP

Analgesic

AA PHARMA INC.
1165 Creditstone Road Unit #1,
Vaughan, Ontario
L4K 4N7
www.aapharma.ca

Date of Initial Authorization:
MAR 24, 2015

Date of Revision:
JAN 26, 2023

Submission Control Number: 266559

RECENT MAJOR LABEL CHANGES

3 Serious Warnings and Precautions Box, Cytochrome P450 3A4 Interaction	12/2022
4 Dosage and Administration, 4.1 Dosing Considerations	12/2022
7 Warnings and Precautions, General	12/2022
7 Warnings and Precautions, Cardiovascular	12/2022
7 Warnings and Precautions, Dependence/Tolerance	12/2022
7 Warnings and Precautions, Gastrointestinal	12/2022
7 Warnings and Precautions, Neurologic	12/2022
7 Warnings and Precautions, Respiratory	12/2022
7 Warnings and Precautions, 7.1.1 Pregnant women	12/2022
7 Warnings and Precautions, 7.1.2 Breast-feeding	05/2022
7 Warnings and Precautions, 7.1.4 Geriatrics	12/2022

TABLE OF CONTENTS

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

RECENT MAJOR LABEL CHANGES 2

TABLE OF CONTENTS 2

PART I: HEALTH PROFESSIONAL INFORMATION 4

1 INDICATIONS 4

1.1 Pediatrics 4

1.2 Geriatrics 4

2 CONTRAINDICATIONS 4

3 SERIOUS WARNINGS AND PRECAUTIONS BOX 5

4 DOSAGE AND ADMINISTRATION 6

4.1 Dosing Considerations 6

4.2 Recommended Dose and Dosage Adjustment 7

4.4 Administration 10

4.5 Missed Dose 10

5 OVERDOSAGE 10

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 11

7 WARNINGS AND PRECAUTIONS 12
7.1 Special Populations 21
7.1.1 Pregnant Women 21
7.1.2 Breast-feeding 22
7.1.3 Pediatrics 23
7.1.4 Geriatrics 23
8 ADVERSE REACTIONS 23
8.1 Adverse Reaction Overview 23
8.2 Clinical Trial Adverse Reactions 24
8.3 Less Common Clinical Trial Adverse Reactions 27
8.5 Post-Market Adverse Reactions 28
9 DRUG INTERACTIONS 29
9.1 Serious Drug Interactions 29
9.3 Drug-Behavioural Interactions 29
9.4 Drug-Drug Interactions 30
9.5 Drug-Food Interactions 32
9.6 Drug-Herb Interactions 32
9.7 Drug-Laboratory Test Interactions 32
10 CLINICAL PHARMACOLOGY 32
10.1 Mechanism of Action 32
10.2 Pharmacodynamics 32
10.3 Pharmacokinetics 34
11 STORAGE, STABILITY AND DISPOSAL 37
12 SPECIAL HANDLING INSTRUCTIONS 38
PART II: SCIENTIFIC INFORMATION 39
13 PHARMACEUTICAL INFORMATION 39
14 CLINICAL TRIALS 40
14.1 Clinical Trials by Indication 40
15 MICROBIOLOGY 41
16 NON-CLINICAL TOXICOLOGY 41
PATIENT MEDICATION INFORMATION 45

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Adults

BUTORPHANOL Nasal Spray (butorphanol tartrate) is indicated for:

- the relief of moderate to severe acute pain.

The efficacy of BUTORPHANOL Nasal Spray for periods longer than 3 days has not been established.

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

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage; 7.1.4 Geriatrics and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics.

2 CONTRAINDICATIONS

BUTORPHANOL Nasal Spray is contraindicated in:

- Patients who are hypersensitive to the active substance butorphanol or other opioid analgesics or to the preservative benzethonium chloride, or to any ingredient in the formulation (e.g., anaphylaxis), including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- 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 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7.1.1 Pregnant Women and 7.1.2 Breast-feeding.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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, BUTORPHANOL Nasal Spray (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 4.1 Dosing Considerations.
- **Addiction, Abuse, and Misuse**
  BUTORPHANOL Nasal Spray 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 BUTORPHANOL Nasal Spray, and all patients should be monitored regularly for the development of these behaviors or conditions. See 7 WARNINGS AND PRECAUTIONS, Addiction, Abuse and Misuse. BUTORPHANOL Nasal Spray 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 BUTORPHANOL Nasal Spray. 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 BUTORPHANOL Nasal Spray or following a dose increase. See 5 OVERDOSAGE and 7 WARNINGS AND PRECAUTIONS, Respiratory.
- **Accidental Exposure**
  Accidental ingestion of even one dose of BUTORPHANOL Nasal Spray, especially by children, can result in a fatal overdose of butorphanol tartrate. See 11 STORAGE, STABILITY AND DISPOSAL, for instructions on proper disposal.
- **Neonatal Opioid Withdrawal Syndrome**
  BUTORPHANOL Nasal Spray is contraindicated in women who are breast-feeding, and during pregnancy, or during labour and delivery (see 2 CONTRAINDICATIONS). Prolonged maternal use of BUTORPHANOL Nasal Spray during pregnancy can result in neonatal

opioid withdrawal syndrome, which may be life-threatening. See 7.1.1 Pregnant Women.

- **Cytochrome P450 3A4 Interaction**
  The concomitant use of BUTORPHANOL Nasal Spray with all cytochrome P450 3A4 inhibitors may result in an increase in butorphanol plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in butorphanol plasma concentration. Monitor patients receiving BUTORPHANOL Nasal Spray and any CYP3A4 inhibitor or inducer. See 7 WARNINGS AND PRECAUTIONS, General, Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers and 9.4 Drug-Drug Interactions, Cytochrome P450 (CYP 450) Interactions.
- **Interaction with Alcohol**
  The co-ingestion of alcohol with BUTORPHANOL Nasal Spray should be avoided as it may result in dangerous additive effects, causing serious injury or death. See 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and 9.4 Drug-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 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and 9.4 Drug-Drug Interactions.
  - Reserve concomitant prescribing of BUTORPHANOL Nasal Spray 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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse. See 7 WARNINGS AND PRECAUTIONS, Addiction, Abuse and Misuse.

Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with BUTORPHANOL Nasal Spray and adjust the dosage accordingly. See 7 WARNINGS AND PRECAUTIONS, Respiratory, Respiratory Depression.

For acute pain, it is recommended that BUTORPHANOL Nasal Spray 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 BUTORPHANOL Nasal Spray 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 BUTORPHANOL Nasal Spray (80 morphine milligram equivalent) not be exceeded. Each patient should be assessed for their risk prior to prescribing BUTORPHANOL Nasal Spray, 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 BUTORPHANOL Nasal Spray. See 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage.

BUTORPHANOL Nasal Spray (butorphanol tartrate nasal spray) should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively. See 7 WARNINGS AND PRECAUTIONS, Peri-Operative Considerations.

Geriatrics (> 65 years of age): 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. BUTORPHANOL Nasal Spray should be initiated at a low dose and slowly titrated to effect. See 7.1.4 Geriatrics and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics.

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. BUTORPHANOL Nasal Spray 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.

4.2 Recommended Dose and Dosage Adjustment

BUTORPHANOL Nasal Spray (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 BUTORPHANOL Nasal Spray 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 1 - 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 2-3:1 (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.

Adjustment or Reduction of Dosage:

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including BUTORPHANOL Nasal Spray. 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 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance. 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.

Patients with Hepatic Impairment: The elimination half-life of BUTORPHANOL Nasal Spray is prolonged in patients with impaired hepatic function. See 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency. BUTORPHANOL Nasal Spray should thus be used with caution in this population. The initial dosage interval should be increased to 6 to12 hours until the response is well characterized. Subsequent dosing's should be determined by patient response rather than being scheduled at fixed intervals.

Patients with Renal Impairment: The elimination half-life of BUTORPHANOL Nasal Spray is prolonged in patients with impaired renal function. See 10.3 Pharmacokinetics, Special Populations and Conditions, Renal insufficiency. 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 BUTORPHANOL Nasal Spray should be determined by patient response rather than being scheduled at fixed intervals.

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use.

Geriatrics (> 65 years of age): Because elderly patients may have a somewhat decreased ability to eliminate butorphanol, (see 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics) 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 BUTORPHANOL Nasal Spray 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 7.1.4 Geriatrics.

4.4 Administration

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

BUTORPHANOL Nasal Spray is not indicated for rectal administration.

4.5 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.

5 OVERDOSAGE

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, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema,

bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death; also, toxic leukoencephalopathy and delayed post-hypoxic leukoencephalopathy. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations. 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.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Nasal	Solution, 10 mg/mL of butorphanol tartrate	Benzethonium chloride, citric acid, hydrochloric acid, purified water, sodium chloride and sodium hydroxide.

Composition

Each bottle of BUTORPHANOL Nasal Spray contains a 10 mg/mL solution of butorphanol tartrate with sodium chloride, citric acid, and 0.2 mg/mL benzethonium chloride as a preservative, in purified water with hydrochloric acid or sodium hydroxide added to adjust the pH to 4.8 to 5.2.

Packaging

BUTORPHANOL Nasal Spray (butorphanol tartrate) Nasal Spray 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. The 2.5 mL bottle will deliver on average 14 to 15 metered doses, if no repriming is necessary.

7 WARNINGS AND PRECAUTIONS

General

Patients should be instructed not to give BUTORPHANOL Nasal Spray (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. BUTORPHANOL Nasal Spray should be stored securely to avoid theft or misuse.

BUTORPHANOL Nasal Spray 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 BUTORPHANOL Nasal Spray as it may increase the chance of experiencing serious adverse events, including death.

Addiction, Abuse and Misuse: Like all opioids, BUTORPHANOL Nasal Spray is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, BUTORPHANOL Nasal Spray should be prescribed and handled with caution.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed BUTORPHANOL Nasal Spray. Addiction can occur at recommended dosages and if the drug is misused or abused.

Patients with a history of alcohol and illicit/prescription drug abuse or addiction to drugs or alcohol or other mental disorders including, but not limited to, major depression and anxiety, may be at higher risk of becoming addicted to BUTORPHANOL Nasal Spray; extreme caution and awareness is warranted to mitigate the risk.

- 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 are sought by people with substance use disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing BUTORPHANOL Nasal Spray. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug.

Special Risk Groups: Butorphanol tartrate should be administered with caution to patients with a history of alcohol and drug abuse or other mental disorders including but not limited to major depression and anxiety, 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.

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers: Concomitant use of BUTORPHANOL Nasal Spray with a 3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of butorphanol and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression (see

7 WARNINGS AND PRECAUTIONS, Respiratory, Respiratory Depression), particularly when an inhibitor is added after a stable dose of BUTORPHANOL Nasal Spray is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in BUTORPHANOL Nasal Spray-treated patients may increase butorphanol plasma concentrations and prolong opioid adverse reactions. When using BUTORPHANOL Nasal Spray with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in BUTORPHANOL Nasal Spray-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of BUTORPHANOL Nasal Spray until stable drug effects are achieved. See 9.4 Drug-Drug Interactions, Cytochrome P450 (CYP 450) Interactions.

Concomitant use of BUTORPHANOL Nasal Spray with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could decrease butorphanol plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to butorphanol. When using BUTORPHANOL Nasal Spray with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur. See 9.4 Drug-Drug Interactions, Cytochrome P450 (CYP 450) Interactions.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity and 16 NON-CLINICAL TOXICOLOGY, Genotoxicity.

Cardiovascular

Because butorphanol may increase the work of the heart, especially the pulmonary circuit, the use of BUTORPHANOL Nasal Spray in patients with acute myocardial infarction, ventricular dysfunction, or coronary insufficiency should be limited to those situations where the benefits clearly outweigh the risk.

Severe hypertension has been reported rarely during BUTORPHANOL Nasal Spray therapy. In such cases, BUTORPHANOL Nasal Spray should be discontinued and the hypertension treated with antihypertensive drugs.

Hypotension associated with syncope during the first hour of dosing with BUTORPHANOL Nasal Spray has been reported rarely, particularly in patients with past history of similar reactions to opioid analgesics. Therefore, patients should be advised to avoid activities with potential risks.

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 BUTORPHANOL Nasal Spray.

The use of BUTORPHANOL Nasal Spray 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, as well as physical dependence may develop upon repeated administration of opioids, 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.

Use in Drug and Alcohol Addiction: BUTORPHANOL Nasal Spray 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.

Withdrawal Symptoms: 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 8.2 Clinical Trial Adverse Reactions and 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage.

Additionally, the use of BUTORPHANOL Nasal Spray, a mixed agonist/antagonist opioid analgesic, in patients who are receiving a full opioid agonist analgesic may reduce the analgesic effect and/or precipitate withdrawal symptoms. Avoid concomitant use of BUTORPHANOL Nasal Spray with a full opioid agonist analgesic.

Neonatal Opioid Withdrawal Syndrome (NOWS): Prolonged maternal use of opioid 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. Use of BUTORPHANOL Nasal Spray is contraindicated in pregnant women (See section 2 CONTRAINDICATIONS and 7.1.1 Pregnant Women).

Driving and Operating Machinery

Psychomotor Impairment: BUTORPHANOL Nasal Spray 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.

Endocrine and Metabolism

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.

Gastrointestinal

BUTORPHANOL Nasal Spray is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus.

Butorphanol in BUTORPHANOL Nasal Spray may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

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 2 CONTRAINDICATIONS.

Hepatic/Biliary/Pancreatic

Patients with Hepatic Impairment: Butorphanol tartrate nasal spray should be administered with caution to patients with liver disease. See 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency and 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage.

Neurologic

Serotonin Syndrome: BUTORPHANOL Nasal Spray could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Serotonin toxicity is characterized by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

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

Treatment with the serotoninergic drug should be discontinued if such events occur and supportive symptomatic treatment should be initiated. BUTORPHANOL Nasal Spray is contraindicated in combination with MAO inhibitors (see 2 CONTRAINDICATIONS), should not be used with 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 9.4 Drug-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, gabapentinoids, baclofen, 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 9.4 Drug-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 BUTORPHANOL Nasal Spray is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs. See 9.4 Drug-Drug Interactions.

BUTORPHANOL Nasal Spray should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death. See 2 CONTRAINDICATIONS, 8.2 Clinical Trial Adverse Reactions, Sedation and 9.3 Drug-Behavioural Interactions.

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

Increased Risk of Seizures in Patients with Seizure Disorders: The butorphanol in BUTORPHANOL Nasal Spray may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures occurring in other clinical settings associated with seizures. Therefore, BUTORPHANOL Nasal Spray should not be used in these patients (see 2 CONTRAINDICATIONS).

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: 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. In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), BUTORPHANOL Nasal Spray may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Also, butorphanol tartrate may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury, impaired consciousness or coma. In such patients, butorphanol tartrate must be used with extreme caution and only if it is judged essential. See 2 CONTRAINDICATIONS**.**

Opioid induced hyperalgesia: Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. Clinically, OIH may be associated with high opioid doses, long term opioid treatment, and intra-operative opioid use. OIH may manifest as an unexplained increase in pain, more diffuse pain than pre-existing, or as pain from ordinary (i.e. non-painful) stimuli (allodynia) in the absence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible. It is reasonable to consider opioid rotation, or the use of a non-opioid strategy for pain control. There is currently no well-established treatment for OIH.

Peri-Operative Considerations

BUTORPHANOL Nasal Spray 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 BUTORPHANOL Nasal Spray for at least 24 hours before the operation and BUTORPHANOL Nasal Spray should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if BUTORPHANOL Nasal Spray 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 professionals 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.

BUTORPHANOL Nasal Spray 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.

Renal

Patients with Renal Impairment: Impaired renal function necessitates alterations in dosing schedule. See 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage and 10.3 Pharmacokinetics, Special Populations and Conditions, Renal insufficiency.

Reproductive Health: Female and Male Potential

- **Fertility**

  Long-term use of opioids may be associated with infertility. See 8.5 Post-Market Adverse Reactions.

- **Function**

  Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido or erectile dysfunction. See 8.5 Post-Market Adverse Reactions.

- **Teratogenic Risk**

  See 2 CONTRAINDICATIONS and 7.1.1 Pregnant Women.

  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. See 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology.

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. See 5 OVERDOSAGE. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can

exacerbate the sedating effects of opioids. Butorphanol tartrate should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia. See 2 CONTRAINDICATIONS.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of BUTORPHANOL Nasal Spray, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with BUTORPHANOL Nasal Spray and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients. See 7 WARNINGS AND PRECAUTIONS, Respiratory, Elderly, Cachetic, or Debilitated Patients. To reduce the risk of respiratory depression, proper dosing and titration of BUTORPHANOL Nasal Spray are essential. Overestimating the BUTORPHANOL Nasal Spray 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 7 WARNINGS AND PRECAUTIONS, General, Special Risk Groups; 4.1 Dosing Considerations, Geriatrics and 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage.

Accidental exposure to even one dose of BUTORPHANOL Nasal Spray, especially by children, can result in respiratory depression and death due to an overdose of butorphanol. Health Canada has not authorized an indication in pediatric patients.

Educate patients and caregivers on how to recognize respiratory depression and getting emergency medical help right away in the event of a known or suspected overdose.

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 pre existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with BUTORPHANOL Nasal Spray, as in these patients, even usual therapeutic doses of BUTORPHANOL Nasal Spray 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 BUTORPHANOL Nasal Spray is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus. See 2 CONTRAINDICATIONS.

Sleep Apnea: Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance and 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage).

Elderly, Cachetic, or Debilitated Patients: 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.

Monitor such patients closely, particularly when initiating and titrating BUTORPHANOL Nasal Spray and when BUTORPHANOL Nasal Spray is given concomitantly with other drugs that depress respiration. In these patients, the use of non-opioid analgesics should be considered, if feasible. See 7 WARNINGS AND PRECAUTIONS, General, Special Risk Groups; 4.1 Dosing Considerations, Geriatrics and 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage.

Patient Counselling Information

A patient information sheet should be provided to patients when BUTORPHANOL Nasal Spray is dispensed to them.

Patients receiving BUTORPHANOL Nasal Spray should be given the following instructions by the physician:

1. Patients should be informed that accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal consequences. BUTORPHANOL Nasal Spray should be kept under lock and out of sight and out of reach of children.
2. Patients should be advised that BUTORPHANOL Nasal Spray, contains butorphanol tartrate, an opioid pain medicine.
3. Patients should be advised that BUTORPHANOL Nasal Spray should only be taken as directed. The dose of BUTORPHANOL Nasal Spray should not be adjusted without consulting with a physician.
4. Patients should be advised to report episodes of pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
5. Patients should not combine BUTORPHANOL Nasal Spray with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.
6. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with BUTORPHANOL Nasal Spray.
7. Patients should be advised that if they have been receiving treatment with BUTORPHANOL Nasal Spray and cessation of therapy is indicated, it may be appropriate to taper the BUTORPHANOL Nasal Spray dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
8. Patients should be advised of the most common adverse reactions that may occur while taking BUTORPHANOL Nasal Spray: constipation, dizziness, nausea, sedation, sweating and vomiting. If symptoms worsen, seek immediate medical attention.
9. Patients should be advised that BUTORPHANOL Nasal Spray may cause drowsiness, dizziness or light-headedness, and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on BUTORPHANOL Nasal Spray or patients whose dose has been

adjusted should be advised not to drive a car or operate machinery unless they are tolerant to the effects of BUTORPHANOL Nasal Spray.

10. Patients should be advised that BUTORPHANOL Nasal Spray is a potential drug of abuse. They should protect it from theft or misuse.
11. Patients should be advised that BUTORPHANOL Nasal Spray should never be given to anyone other than the individual for whom it was prescribed.
12. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with BUTORPHANOL Nasal Spray. Women who are breast-feeding or pregnant should not use BUTORPHANOL Nasal Spray.
13. Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting BUTORPHANOL Nasal Spray or when the dosage is increased, and that it can occur even at recommended dosages.
    Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of getting emergency medical help right away in the event of a known or suspected overdose.
14. Patients should be advised that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare professional if they are taking, or plan to take serotonergic medications.
15. Patients should be advised that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms.
16. Patients should be advised that anaphylaxis has been reported with ingredients contained in BUTORPHANOL Nasal Spray. Advise patients how to recognize such a reaction and when to seek medical attention.
17. Patients should be informed that BUTORPHANOL Nasal Spray could cause seizures if they are at risk for seizure or have epilepsy. Patients should be advised not to take BUTORPHANOL Nasal Spray if they have seizure disorders. Patients should be advised to stop taking BUTORPHANOL Nasal Spray if they have a seizure while taking BUTORPHANOL Nasal Spray and seek medical help immediately.
18. Advise patients to dispose of BUTORPHANOL Nasal Spray by unscrewing the cap, rinsing the bottle, and placing the parts in a waste container.

7.1 Special Populations

7.1.1 Pregnant Women

BUTORPHANOL Nasal Spray crosses the placental barrier and is contraindicated during pregnancy, or during labour and delivery. See 2 CONTRAINDICATIONS.

There are no adequate and well-controlled studies of butorphanol in pregnant women before 37 weeks of gestation. The use of butorphanol tartrate 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.

Labour or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. BUTORPHANOL Nasal Spray is contraindicated for use in pregnant women or during labour or delivery, when other analgesic techniques are more appropriate. Opioid analgesics, including BUTORPHANOL Nasal Spray, can prolong labour through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labour. Monitor neonates exposed to opioid analgesics during labour for signs of excess sedation and respiratory depression.

Neonatal Opioid Withdrawal Syndrome (NOWS)

BUTORPHANOL Nasal Spray is contraindicated in pregnant women during pregnancy, or during labour and delivery (see 2 CONTRAINDICATIONS).

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome (NOWS), unlike opioid withdrawal syndrome in adults, may be life-threatening. See 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance and 8.5 Post-Market Adverse Reactions.

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. Observe new-borns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

7.1.2 Breast-feeding

Since opioids can cross the placental barrier and are excreted in breast milk, BUTORPHANOL Nasal Spray is contraindicated in women who are breast-feeding and during labour and delivery (see 2 CONTRAINDICATIONS). 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 BUTORPHANOL Nasal Spray is used in this population.

There is no clinical experience with the use of butorphanol tartrate nasal spray in nursing mothers. 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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Elderly patients (aged 65 years or older) may have increased sensitivity to BUTORPHANOL Nasal Spray.

The mean half-life of butorphanol tartrate is increased to 6 hours in patients over the age of 65. See 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics. In addition to having a somewhat reduced ability to eliminate butorphanol, elderly patients may be more sensitive to its side effects, particularly dizziness. See 4.1 Dosing Considerations, Geriatrics.

In clinical studies of BUTORPHANOL Nasal Spray, elderly patients had an increased frequency of headache, dizziness, drowsiness, vertigo, constipation, nausea and/or vomiting, and nasal congestion compared with younger patients. There are insufficient efficacy data for patients ≥65 years to determine whether they respond differently from younger patients.

Initially a 1 mg dose of BUTORPHANOL Nasal Spray should be generally used in geriatric patients and 90 to 120 minutes should elapse before administering a second 1 mg dose, if needed.

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 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics.

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse effects of BUTORPHANOL Nasal Spray (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 Nasal Spray 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%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 3 - 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
Cardiac disorders								
Palpitation	6	--	--	--				
Ear and labyrinth disorders								
Ear Disorder	--	6	--	--		--	--	--
Hearing Loss	--	--	6	--	--	--	--	---
Eye disorders								
Blurred Vision	12	9	12	1	--	--	--	--
Diplopia	6	--	--	--	--	--	--	--
Gastrointestinal disorders								
Dry Mouth	6	21	12	--				
Nausea/Vomiting	22	61	37	4				
Unpleasant Taste	12	9	6	--	--	--	--	--
General disorders and administration site conditions								
Pain	--	6	--	1				
Sensation of Heat	6	12	6	3	--	--	5	1
Chest Pain	--	6	--	--	--	--		
Thirst	--	-	6				8	1
Asthenia	9	18	6	3				
Chills	--	6	--	3				
Metabolism and Nutrition								
Increased Appetite	--	6	--	--				

	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
Nervous System disorders								
Abnormal Feelings	6	12	6	--				
Dizziness	50	85	75	10	23	6	25	1
Drowsiness	41	51	50	5	26	33	40	16
Headache					4	4	--	3
Incoordination		6	--	--				
Paresis	--	15	6	--				
Paresthesia	6	21	--	--				
Somnolence					23	36	39	12
Vertigo	9	6	--	1				
Syncope	--	9	--	--				
Psychiatric disorders								
Abnormal Thinking	--	6	--	--				
Anxiety	--	6	--	--				
Confusion	9	24	6	--	--	6	--	--
Euphoria	--	3	6	--				
Nervousness	16	9	6	--				
Respiratory, thoracic and mediastinal disorders								
Epistaxis	--	--	6	--				
Nasal Irritation	--	6	6	1				
Skin and subcutaneous tissue disorders								
Pruritus	6	12	6	--				
Sweating	6	30	19	--	--	4	--	1
Vascular disorders								
Vasodilation	6	--	6	1				

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.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse effects occur less frequently (<1%) with opioid analgesics and include those reported in BUTORPHANOL Nasal Spray clinical trials, whether related or not to butorphanol tartrate.

Blood and lymphatic system disorders: Infrequent: petechiae.

Cardiac disorders: Infrequent: tachycardia, arrythmia.

Ear and labyrinth disorders: Infrequent: hyperacusia, ear pain, tinnitus.

Eye disorders: Infrequent: visual disturbance, photophobia, eye pain, eye disorder.

Gastrointestinal disorders: Infrequent: pharyngitis, stomach pain, abdominal pain, dysphagia, flatulence, taste loss.

General disorders and administration site conditions: Infrequent: sensation of cold, fever, edema, abnormal gait.

Injury, poisoning and procedural complications: Infrequent: accidental injury, intoxication.

Investigations: Infrequent: blood pressure elevated**.**

Musculoskeletal and connective tissue disorders: Infrequent: muscle relaxation, leg pain, back pain, spasms.

Nervous system disorders: Infrequent: dysarthria, ataxia, tremor, stupor, hyperesthesia, motor retardation, vivid imagination, abnormal involuntary movement, slowed movement.

Psychiatric disorders: Infrequent: hallucinations, feel calm, insomnia, derealization, abnormal dreams, agitation, libido increased.

Renal and urinary disorders: Infrequent: impaired urination.

Respiratory, thoracic and mediastinal disorders: Infrequent: dyspnea, cough, hypoventilation, respiratory disorder, sinus congestion, nasal congestion, nasal symptoms, nose pain.

Skin and subcutaneous tissue disorders: Infrequent: rash, erythema.

Vascular disorders: Frequent: hypotension.

Infrequent: hypertension, pallor.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post approval use of BUTORPHANOL Nasal Spray. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in butorphanol tartrate nasal spray.

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 post marketing experience.

Cardiac disorders: Tachycardia.

General disorders and administration site conditions: Chest pain.

Nervous System disorders: Convulsions, excessive drug effect associated with transient difficulty speaking and/or executing purposeful movements.

Psychiatric disorders: Drug dependence.

Vascular disorders: Hypertension.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concurrent use of BUTORPHANOL Nasal Spray with central nervous system depressants (e.g., alcohol, barbiturates, tranquillizers, and antihistamines) may result in additive central nervous system depressant effects, including an increased risk of respiratory depression.
- It is not known if the effects of BUTORPHANOL Nasal Spray 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.
- BUTORPHANOL Nasal Spray is contraindicated 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 (see 2 CONTRAINDICATIONS).
- The concomitant use of BUTORPHANOL Nasal Spray with a cytochrome P450 3A4 inhibitor may result in an increase in butorphanol plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in butorphanol plasma concentration (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Cytochrome P450 3A4 Interactions and 7 WARNINGS AND PRECAUTIONS, Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers).

9.3 Drug-Behavioural Interactions

BUTORPHANOL Nasal Spray should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects (See 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance).

9.4 Drug-Drug Interactions

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, gabapentin, pregabalin, baclofen, and alcohol) and beta-blockers, increases the risk of hypotension, respiratory depression, profound sedation, coma, and death.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation. See 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and 7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery, Psychomotor Impairment. BUTORPHANOL Nasal Spray should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Interaction with Serotonergic Agents: BUTORPHANOL Nasal Spray may increase the risk of serotonin syndrome, a potentially life-threatening condition when co-administered with:

- monoamine oxidase (MAO) inhibitors. BUTORPHANOL Nasal Spray is contraindicated in patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy) (see 2 CONTRAINDICATIONS),
- serotonin-precursors (such as L-tryptophan, oxitriptan). BUTORPHANOL Nasal Spray should not be used with serotonin-precursors
- other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, mirtazapine, trazodone, tramadol). BUTORPHANOL Nasal Spray should be used with caution in combination with other serotonergic drugs
- Selective Serotonin Re-Uptake Inhibitor or a Serotonin Norepinephrine Re-Uptake Inhibitor
- 5-HT_3 receptor antagonists
- certain muscle relaxants (i.e., cyclobenzaprine, metaxalone)

(See 7 WARNINGS AND PRECAUTIONS, Neurologic)

If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue butorphanol tartrate nasal spray if serotonin syndrome is suspected.

Cytochrome P450 (CYP 450) Interactions: It is not known if the effects of BUTORPHANOL Nasal Spray are altered by concomitant medications that affect hepatic metabolism of drugs (CYP 450 inhibitors or inducers) (e.g., erythromycin, theophylline, etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.

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

Table 4 – Other Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Cimetidine	CT	↔ Cimetidine	In a 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 coadministered (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 coadministered for 4 days.
Oxymetazoline	CT	↑ C_{max}, ↓T_{max} and ↔ bioavailability of butorphanol	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.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Sumatriptan	CT	↔sumatriptan	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. However, it should be noted that both products are capable of producing transient increases in blood pressure. Use with Caution due to increased risk of serotonin syndrome.

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

BUTORPHANOL Nasal Spray should be used with caution in combination with St. John's Wort due to the risk of serotonergic syndrome.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 grey matter, and at sites in the spinal cord.

10.2 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 CO_2 tension and to electrical stimulation. The agonist actions of butorphanol, including on respiratory depression, can be reversed by 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 5 OVERDOSAGE.

Butorphanol tartrate has a marked sedative effect that is dose related and this property should be considered in its clinical application. See 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and 7 WARNINGS AND PRECAUTIONS, Neurologic.

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

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.

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

Abuse potential of butorphanol tartrate has been observed in animals. 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.).

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.

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.

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.

10.3 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.

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:

Table 5:

	I.M.	I.V.
BUTORPHANOL Renal Clearance Rate	4.7 L/hr	8.4 L/hr
4-8 Hour Total Plasma Concentration Half-Time	4.9 hrs	3.9 hrs
Peak Plasma Concentration	2.02 mcg/L	1.80 mcg/L
Mean 0-8 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	11.21/hr
Mean 0-8 Hour Area Under the Curve	5.9 mcg/hr/L	2.0 mcg/hr/L

Absorption

Butorphanol tartrate is rapidly absorbed without significant biotransformation following nasal administration.

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

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.

Distribution:

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%.

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

Butorphanol crosses the blood-brain barrier.

Metabolism:

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.

Elimination

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.

Special Populations and Conditions

- **Pediatrics (<18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.
- **Geriatrics:** 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 6). 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 6 - 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 IV data.

- **Pregnancy and Breast-feeding:** Butorphanol crosses the placental barrier and is found in human milk. See 7.1.1 Pregnant Women and 7.1.2 Breast-feeding.
- **Hepatic Insufficiency:** The pharmacokinetics and absolute bioavailability of a 1 mg dose of transnasal butorphanol tartrate 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 $t_{½}$ 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.
- **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}.

  Table 7:

	CrCl (mL/min)	$t_{½}$ (h)	AUC (h•ng/mL)
Normal	>70	5.75	4.32 (1.63)*
Moderately Impaired	30 - 60	8.55	6.49 (1.32)
Severely Impaired	<30	10.48	7.41 (2.64)

*Standard Deviation

11 STORAGE, STABILITY AND DISPOSAL

BUTORPHANOL Nasal Spray should be stored at room temperature 15°C to 30°C.

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

BUTORPHANOL Nasal Spray should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired BUTORPHANOL Nasal Spray 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.

12 SPECIAL HANDLING INSTRUCTIONS

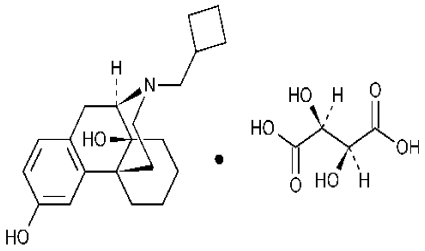
BUTORPHANOL Nasal Spray is an open delivery system that has a risk of accidental exposure to health care workers. In the priming process, a certain amount of butorphanol may be aerosolized; therefore, the pump sprayer should be aimed away from the patient or animals.

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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Butorphanol tartrate
Chemical name:	1) Morphinan-3,14-diol, 17-(cyclobutylmethyl)-, (-), [S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt); 2) (-)-17-(Cyclobutylmethyl) morphinan-3,14-diol D-(-)-tartrate (1:1) (salt).
Molecular formula and molecular mass:	$C_{21}H_{29}NO_{24}•C_4H_6O_6$ and 477.56 g/mol.
Structural formula:	

Physicochemical properties:

Description:	White, odourless crystalline powder. Its solutions are slightly acidic.
Solubility:	Sparingly soluble in water, slightly soluble in methanol; insoluble in alcohol, chloroform, ethyl ether, ethyl acetate and hexane; soluble in dilute acids.
pK:	8.34
Partition Coefficient:	The n-octanol/aqueous buffer partition coefficient of butorphanol is 180:1 at pH 7.5
Melting Range:	Between 217°C to 219°C, with decomposition.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Relief of moderate to severe acute pain

Migraine Headache Pain

The analgesic efficacy of two 1 mg doses one hour apart of butorphanol tartrate nasal spray 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 tartrate nasal spray and 1.5 hours for methadone. The median duration of pain relief was 6 hours with butorphanol tartrate nasal spray 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 of 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 of 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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

Table 8: Acute single dose toxicity studies

Species/Strain	Sex/No. 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/Female 2 M, 2 F per group	I.V.	5,10,15,20	10-15
Dog Beagle	Male/Female 2 M, 2 F per group	I.M.	15,20,25,30	23.4 (17.2-29.3)
Monkey Rhesus	2 Males 2 Females	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

Table 9: Subacute dose toxicity studies

Species/Strain (Number used)	Route	Duration	Dosage	Treatment Related Findings
RAT Sprague Dawley (10 M, 10 F per dosage level)	Intra-nasal	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 M, 10 F per dosage level)	Intra-nasal	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 M, 3 F per dosage level)	Intra-nasal	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 M, 3 F per dosage level)	Intra-nasal	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 M, 1 F 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 amino-peptidase 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.

Repeat dose 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.

Carcinogenicity: 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.

Genotoxicity: Butorphanol was not genotoxic in the in vitro bacterial reverse mutation assay (Ames) or in an in vitro unscheduled DNA synthesis and repair assay conducted in cultured human fibroblast cells.

Reproductive and Developmental Toxicology: 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

©BUTORPHANOL Nasal Spray

Butorphanol Tartrate Nasal Spray

Read this carefully before you start taking **BUTORPHANOL Nasal Spray** 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 **BUTORPHANOL Nasal Spray**.

Serious Warnings and Precautions

- Even if you take BUTORPHANOL Nasal Spray as prescribed you are at a risk for opioid addiction, abuse, and misuse. This can lead to overdose and death. To understand your risk of opioid addition, abuse, and misuse, you should speak to your healthcare professional.
- Life-threatening breathing problems can happen while taking BUTORPHANOL Nasal Spray, especially if not taken as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.
- Never give anyone your BUTORPHANOL Nasal Spray. They could die from taking it. If a person has not been prescribed BUTORPHANOL Nasal Spray, taking even one dose can cause a fatal overdose. This is especially true for children.
- If you took BUTORPHANOL Nasal Spray 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 BUTORPHANOL Nasal Spray with medicines that can affect your blood levels may cause unwanted and serious side effects. Life-threatening breathing problems may be caused if you:
  - take a medicine that increases the blood levels of BUTORPHANOL Nasal Spray, or
  - when you stop taking a medicine that decreases the blood levels of BUTORPHANOL Nasal Spray.

  In addition, you may experience withdrawal effects if you:

- take a medicine that decreases the blood levels of BUTORPHANOL Nasal Spray, or
- when you stop taking a medicine that increases the blood levels of BUTORPHANOL Nasal Spray.

Therefore, you must tell your healthcare professional if you are taking any of these medicines, and when you stop taking them. If you are unsure about the medicines you take, ask your healthcare professional. Your healthcare professional will regularly monitor your health and adjust your dose accordingly.

- Taking BUTORPHANOL Nasal Spray 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 BUTORPHANOL Nasal Spray used for?

BUTORPHANOL Nasal Spray is used in adults to manage moderate to severe short-term (acute) pain. It is NOT used "as needed" to treat pain that you only have once in a while.

How does BUTORPHANOL Nasal Spray work?

BUTORPHANOL Nasal Spray is a painkiller belonging to the class of drugs known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in BUTORPHANOL Nasal Spray?

Medicinal ingredient: butorphanol tartrate.

Non-medicinal ingredients: benzethonium chloride, citric acid, hydrochloric acid, purified water, sodium chloride, and sodium hydroxide.

BUTORPHANOL Nasal Spray comes in the following dosage forms:

Solution, 10 mg/mL of butorphanol tartrate.

Do not use BUTORPHANOL Nasal Spray if:

- your healthcare professional did not prescribe it for you.
- you are allergic to butorphanol tartrate, other opioids, benzethonium chloride (a preservative), or any of the other ingredients in BUTORPHANOL Nasal Spray.
- you have mild pain that can be controlled by the occasional use of painkillers including those available without a prescription.
- you have severe asthma, trouble breathing, or other breathing problems.
- you have any heart problems.
- you have bowel blockage or narrowing of the stomach or intestines.

- you have a condition where the bowel does not work properly (ileus) or you have severe pain in your abdomen.
- you have increased pressure in your skull or have a head injury.
- you have or have a history with epilepsy.
- you suffer from alcoholism or alcohol withdrawal.
- 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 a surgery or operation, or have had a surgery in the last 24 hours.
- you are pregnant, or you are in labour or delivery.
- you are breastfeeding or planning to breastfeed.
- you have severe central nervous system (CNS) depression (nervous system slows down).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BUTORPHANOL Nasal Spray. 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 or liver problems.
- have been told you are at risk of having heart problems or seizures.
- have low blood pressure.
- have or have had problems with your mood (such as depression or anxiety), hallucinations, or other mental health problems.
- suffer from chronic or severe constipation.
- have pancreas or gallbladder problems.
- have problems with your thyroid, adrenal, or prostate gland.
- suffer from migraines.
- have a sleep disorder which causes pauses in breathing or shallow breathing while sleeping (sleep apnea).
- are planning to become pregnant.
- are planning on drinking alcohol. Drinking alcohol while taking BUTORPHANOL Nasal Spray may cause dangerous side effects, including death. Do not drink alcohol while taking BUTORPHANOL Nasal Spray.
- have a condition that causes weakness or frailty.
- have difficulty urinating.
- have circulatory problems (e.g., body does not get enough oxygen and nutrients to function properly due to a lack of blood flow).
- are elder or over 65 years of age.

Other warnings you should know about:

Taking BUTORPHANOL Nasal Spray can cause the following serious side effects:

- **Disorder of the adrenal gland:** You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:
    - nausea, vomiting;
    - feeling tired, weak or dizzy;
    - decreased appetite.

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

- **Serotonin toxicity (also known as serotonin syndrome):** BUTORPHANOL Nasal Spray can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take BUTORPHANOL Nasal Spray with certain anti-depressants or migraine medications.

  Serotonin toxicity symptoms include:

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

- **Sleep Apnea:** Opioids can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your healthcare professional if you have a history of sleep apnea or if anyone notices that you stop breathing from time to time while sleeping.

See the **Serious side effects and what to do about them table** below for more information on these and other serious side effects.

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

Pregnancy, nursing, labour and delivery: Do not use BUTORPHANOL Nasal Spray while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. BUTORPHANOL Nasal Spray can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking BUTORPHANOL Nasal Spray, 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 healthcare professional will monitor and guide you on how to slowly stop taking BUTORPHANOL Nasal Spray. 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 BUTORPHANOL Nasal Spray. BUTORPHANOL Nasal Spray can cause:

- drowsiness,
- dizziness, or
- light headedness.

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

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.

Worsened pain: Taking opioids for pain can sometimes have the unintended effect of making your pain feel worse (opioid-induced hyperalgesia) even though your opioid dose has been unchanged or increased. This can also include feeling pain in new places in your body, or feeling pain from something that would not normally hurt, for example, feeling pain from clothing touching your skin. Tell your healthcare professional if you notice a change like this in your pain while you are taking BUTORPHANOL Nasal Spray.

Testing and check-ups: Your healthcare professional will regularly monitor your health. This includes monitoring signs of:

- misuse and abuse;
- sleep apnea (a sleep disorder which causes pauses in breathing or shallow breathing while sleeping);
- respiratory depression and sedation (e.g., slow, shallow, or weak breathing).

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

Serious Drug Interactions

Serious drug interactions with BUTORPHANOL Nasal Spray include:

- central nervous system (CNS) depressants used to slow down the nervous system. These can include:
  - alcohol. This includes prescription and non-prescription medications that contain alcohol. Do not drink alcohol while taking BUTORPHANOL Nasal Spray. It can lead to drowsiness, unusually slow or weak breathing, serious side effects, or a fatal overdose;
  - other opioids used to relieve pain (e.g., tramadol);
  - medicines used to treat anxiety (anxiolytics) or help with sleep (tranquilizers, sedatives or hypnotics). These include benzodiazepines and barbiturates;
  - muscle relaxants, medicines used to treat muscle spasms and back pain (e.g., cyclobenzaprine, baclofen, and metaxalone);
  - antiemetics, medicines used to prevent nausea or vomiting;
  - antihistamines, medicines used to treat allergies;

- antipsychotics (also called neuroleptics), including phenothiazines. These are medicines used to treat mental health disorders;
- general anesthetics, medicines used during surgery;
- certain types of antidepressants;
- beta-blockers, medicines used to lower blood pressure;
- pregabalin, a medicine used to treat nerve pain;
- gabapentin, a medicine used to prevent and control seizures in the treatment of epilepsy.

- medicines that can affect drug metabolism in the liver. This can include:
  - antiretrovirals, medicines used to treat viral infections (e.g., ritonavir);
  - antifungals, medicines used to treat fungal infections (e.g., ketoconazole);
  - antibiotics, medicines used to treat bacterial infections (e.g., erythromycin and rifampin);
  - antiepileptics, medicines used to treat seizures (e.g., carbamazepine and phenytoin);
  - theophylline, a medicine used to treat asthma and other lung diseases.
- monoamine oxidase inhibitors (MAOIs), medicines used to treat depression. **Do not** take BUTORPHANOL Nasal Spray with MAOIs or if you have taken MAOI's in the last 14 days.

The following may interact with BUTORPHANOL Nasal Spray:

- medicines that act on a brain chemical called serotonin. This includes:
  - antidepressants, medicines used to treat depression (e.g., Selective Serotonin Re-Uptake Inhibitors (SSRIs), Serotonin Norepinephrine Re-Uptake Inhibitors (SNRIs), tricyclic antidepressants, mirtazapine, and trazodone);
  - lithium, a medicine used to treat bipolar disorder;
  - triptans, medicines used to treat migraines (e.g., sumatriptan);
  - medicines known as 5-HT_3 receptor antagonists, used to prevent nausea and vomiting caused by chemotherapy, radiation therapy, and postoperatively;
  - St. John's Wort, a herbal medicine used for depression and mood disorders.
- anticoagulants, medicines used to prevent or treat blood clots (e.g., warfarin such as coumadin).
- cimetidine, a medicine used to treat ulcers.
- oxymetazoline, a medicine used to treat nasal congestion.
- grapefruit juice.

If you are unsure, ask your healthcare professional.

How to take BUTORPHANOL Nasal Spray:

- Take the BUTORPHANOL Nasal Spray exactly as directed by your healthcare professional. BUTORPHANOL Nasal Spray is sprayed into your nose and must not be taken any other way. DO NOT repeat your dose sooner than directed by your healthcare professional. Check with your healthcare professional if you are unsure.

- BUTORPHANOL Nasal Spray should not be used by anyone other than the person for whom it was prescribed.

For proper use of the nasal spray bottle, read the following instructions carefully.

Instructions for use:

1) Blow your nose. (Fig. 1)
2) Pull the clear cover off pump unit. Remove protective clip. (Fig. 2)
3) Prior to initial use, prime the unit by pumping sprayer **firmly** and **quickly** until a fine spray appears (up to 4-5 strokes). While priming the unit, direct the pump sprayer away from yourself, others, or animals. (Fig. 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. (Fig. 4)
5) Your healthcare professional will tell you whether a two spray dose is needed. If needed, administer a second spray in the other nostril.

Fig. 1

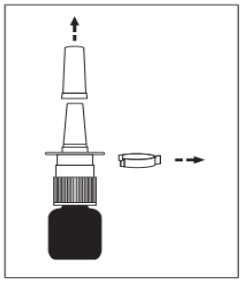


Fig. 2

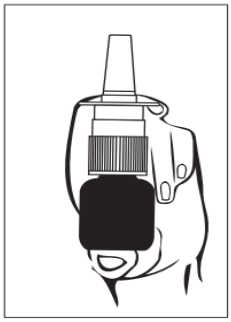


Fig. 3

Fig. 4

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.

Usual dose:

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

If you are prescribed ONE SPRAY, only spray once into ONE NOSTRIL ONLY. DO NOT spray into both nostrils unless directed by your healthcare professional. DO NOT repeat sooner than directed by your healthcare professional.

Your healthcare professional will prescribe the lowest dose that works to control your pain. It is recommended that you only take BUTORPHANOL Nasal Spray for up to 3 days as it is not known if it is effective beyond this time period. If you need to take BUTORPHANOL Nasal Spray for longer, your healthcare professional 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 healthcare professional to determine if you still need BUTORPHANOL Nasal Spray. Be sure to use BUTORPHANOL Nasal Spray only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking BUTORPHANOL Nasal Spray, tell your healthcare professional immediately.

Stopping your Medication: If you have been taking BUTORPHANOL Nasal Spray for more than a few days you should not stop taking it all of a sudden. Your healthcare professional will monitor and guide you on how to slowly stop taking BUTORPHANOL Nasal Spray. 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 BUTORPHANOL Nasal Spray.

Refilling your Prescription for BUTORPHANOL Nasal Spray: A new written prescription is required from your healthcare professional each time you need more BUTORPHANOL Nasal Spray. Therefore, it is important that you contact your healthcare professional before your current supply runs out.

Only obtain prescriptions for this medicine from the healthcare professional in charge of your treatment. Do not seek prescriptions from other healthcare professionals unless you switch to another healthcare professional for your pain management.

Overdose:

Signs of overdose may include:

- unusually slow or weak breathing,
- dizziness,
- confusion,
- toxic leukoencephalopathy (a brain disorder affecting the brain's white matter),
- extreme drowsiness.

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

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 healthcare professional before restarting your medication.

What are possible side effects from using BUTORPHANOL Nasal Spray?

These are not all the possible side effects you may have when taking BUTORPHANOL Nasal Spray. If you experience any side effects not listed here, tell 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. Talk with your healthcare professional about ways to prevent constipation when you start using BUTORPHANOL Nasal Spray;
- low sex drive, impotence (erectile dysfunction), or infertility;
- sore throat;
- taste loss;
- feeling cold;
- fever.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Bowel blockage (impaction): abdominal pain, severe constipation, or nausea.			√
Fast, slow or irregular heartbeat: heart palpitations.		√	
Gastrointestinal disorders: severe constipation, nausea	√		
Paresis (muscle weakness caused by nerve damage or disease): memory problems, language problems, mental status changes, mood changes, delusions, hallucinations, or irritability.		√	
UNCOMMON			
Drug dependence: feeling of craving, feeling you need more drug to achieve the same effect, taking higher dose of the drug that is recommended		√	
Ear and labyrinth disorders: unusual tolerance to ordinary environmental sounds (hyperacusia), ear pain, or tinnitus.	√		
Edema: swelling caused by excess fluid trapped in your body's tissues	√		

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**	
Eye disorders: visual disturbance, photophobia, eye pain, or eye problems.	√		
Gastrointestinal disorders: abdominal pain, passing gas (flatulence)	√		
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness, fainting, chest pain, chest pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse, or heart palpitations.		√	
Hypotension (low blood pressure): dizziness, fainting, or light-headedness.	√		
Neurological disorders: walking abnormality (abnormal gait), speech disorder caused by muscle weakness (dysarthria), increase in the sensitivity of any of your senses, such as sight, sound, touch, and smell (hyperesthesia), transient difficulty speaking (aphasia), or executing purposeful movements (apraxia).			√
Psychiatric problems: vivid imagination, or abnormal dreams.			√
Renal and urinary disorders: impaired urination.	√		
Respiratory depression: slow, shallow, or weak breathing.			√
Seizures (fit): uncontrollable shaking with or without loss of consciousness.			√
RARE			

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	
Allergic reaction: itchy, red, painful, and irritated or swollen skin (rash), outbreak of pale red bumps or welts on the skin that appear suddenly (hives), swelling of the face, lips, tongue or throat, difficulty swallowing (dysphagia), or difficulty breathing (dyspnea).			√
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, dizziness, floppy muscles/low muscle tone (hypotonia), or cold and clammy skin.			√
Serotonin toxicity (also known as serotonin syndrome): a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (>38°C), or rigid muscles.			√
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, or sweating.		√	
UNKNOWN FREQUENCY			
Androgen deficiency: decreased interest in sexual activity (low libido), inability in a man to achieve an erection or orgasm (impotence), inability to get and keep an erection firm enough for sex (erectile		√	

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	
dysfunction), absence of menstruation (amenorrhea), or not being able to get pregnant (conceive) after one year (or longer) of unprotected sex (infertility).			
Disorder of the adrenal gland: nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure.			√
Sleep apnea: stop breathing for short periods during your normal nightly sleep.		√	

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

Reporting Side Effects

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

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

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

Storage:

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

Disposal: To prevent accidental ingestion, and to reduce the chance of children taking the medication, it is important to dispose of any excess BUTORPHANOL Nasal Spray as soon as it is no longer needed. 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 BUTORPHANOL Nasal Spray:

- 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 (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc., 1165 Creditstone Road Unit #1, Vaughan, Ontario, L4K 4N7.

Last Revised: JAN 26, 2023