PRODUCT MONOGRAPH

BUTORPHANOL

Nasal Spray, 10 mg/mL

(Butorphanol Tartrate Nasal Solution USP)

Analgesic

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THERAPEUTIC CLASSIFICATION

Analgesic

ACTIONS AND CLINICAL PHARMACOLOGY

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.

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

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

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

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

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

PHARMACOKINETICS

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

Butorphanol tartrate is rapidly absorbed without significant biotransformation following nasal administration. In both young and elderly normal volunteers, peak blood levels occur around one-half hour following nasal administration. Peak plasma concentrations after a 1 mg dose vary from a mean of 0.9 to 1.04 ng/mL (see Table 1). 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 1
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] (hrAng/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.

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

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

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

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

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

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

In Patients with Renal Insufficiency

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

	CrCl (mL/min)	$t_{½}$ (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

In Patients with Hepatic Disease

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.

PHARMACODYNAMICS

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

CLINICAL STUDIES

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.

INDICATIONS AND CLINICAL USE

BUTORPHANOL (butorphanol tartrate) Nasal Spray 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.

CONTRAINDICATIONS

BUTORPHANOL (butorphanol tartrate) Nasal Spray is contraindicated in patients hypersensitive to butorphanol tartrate or to any component of the preparation.

WARNINGS

PATIENTS DEPENDENT ON NARCOTICS

Because of the opioid antagonist properties of butorphanol tartrate, patients who are physically dependent on narcotics should not be given butorphanol tartrate as they may experience withdrawal symptoms. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol tartrate nasal spray therapy.

Butorphanol tartrate nasal spray has precipitated opioid withdrawal symptoms in patients taking opioid analgesics chronically. Adverse experiences include those of the central nervous system (anxiety, agitation, mood changes, hallucinations, and dysphoria) more frequently than typical somatic opioid withdrawal symptoms. Because of the difficulty in assessing opioid tolerance in patients who have recently received repeated doses of narcotic analgesic medication, caution should be used in the administration of butorphanol tartrate nasal spray to such patients.

PRECAUTIONS

GENERAL

Hypotension associated with syncope during the first hour of dosing with butorphanol tartrate 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.

The sedative property should be considered in the clinical use of butorphanol tartrate nasal spray. In addition, patients receiving recommended therapeutic doses may experience severe dizziness, nausea, vomiting and confusion. Infrequently, hallucinations have also occurred at 2 mg. The patient should be advised accordingly (see ADVERSE REACTIONS).

Limited clinical experience appears to suggest that patients with migraine headache may be more susceptible to certain adverse reactions associated with butorphanol tartrate nasal spray (see ADVERSE REACTIONS).

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE

As with other opioids, butorphanol used in patients with head injury may be associated with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, miosis, and alterations in mental state that would obscure the interpretation of the clinical course of head injuries. In such patients, butorphanol should be used only if the benefits of use outweigh the risks.

RESPIRATORY DEPRESSION

As a class, the mixed agonist-antagonist opioid drugs are less likely than morphine to produce significant respiratory depression. Nevertheless, drugs of this class may produce respiratory depression in susceptible individuals, especially patients receiving other CNS active agents or suffering from CNS diseases or respiratory impairment.

HEPATIC DISEASE

Butorphanol tartrate nasal spray should be administered with caution to patients with liver disease (see ACTIONS AND CLINICAL PHARMACOLOGY: Pharmacokinetics, and DOSAGE AND ADMINISTRATION: Dosage Adjustments).

RENAL DISEASE

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

CARDIOVASCULAR EFFECTS

Because butorphanol tartrate nasal spray increases the work of the heart, especially the pulmonary circuit, the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those patients for whom the benefits clearly outweigh the risk.

Severe hypertension has been reported rarely during parenteral administration of butorphanol. Because of the similarity in pharmacokinetics (See ACTIONS AND CLINICAL PHARMACOLOGY), this adverse event could potentially occur during use of butorphanol tartrate nasal spray. In such cases, butorphanol should be discontinued and the hypertension treated with antihypertensive drugs. In patients who are not opioid dependent, naloxone has also been reported to be effective.

USE IN ANESTHESIA

Butorphanol tartrate nasal spray has not been evaluated for use in anesthesia.

OCCUPATIONAL HAZARDS

Use in Ambulatory Patients

Drowsiness and dizziness related to the use of butorphanol tartrate nasal spray may impair mental and/or physical abilities required for the performance of potentially hazardous tasks (e.g., driving, operating machinery, etc.). Patients should be told to use caution in such activities until their individual response to butorphanol has been well characterized.

USE IN PREGNANCY

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.

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.

USE IN LABOUR AND DELIVERY

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

NURSING MOTHERS

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

USE IN CHILDREN

Safety and efficacy of butorphanol tartrate nasal spray in patients under 18 years of age have not been established.

USE IN THE ELDERLY

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

DEPENDENCE LIABILITY

Although, as a class, the mixed agonist-antagonist opioid analgesics have a much lower abuse potential than morphine, all such drugs have been reported to be abused.

Among 161 patients who used butorphanol tartrate nasal spray for 2 months or longer, during a controlled clinical trial, there were 5 reports suggestive of possible abuse, including 3 reports of clinically significant overuse. Post-treatment symptoms such as anxiety, agitation, and diarrhea were observed in 6 patients. Symptoms suggestive of opioid withdrawal occurred in 2 patients who stopped the drug abruptly after using 16 mg a day or more for longer than 3 months.

Neither withdrawal nor symptoms suggestive of withdrawal occurred when the drug was used for less than a week or when the dose was tapered if use exceeded 1 - 2 weeks. Special care should be exercised in administering butorphanol to emotionally unstable patients and to those with a history of drug abuse.

DRUG INTERACTIONS

Concurrent use of butorphanol tartrate with central nervous system depressants (e.g., alcohol, barbiturates, tranquillizers, and antihistamines) may result in additive central nervous system depressant effects. The dose of butorphanol tartrate nasal spray should be minimized and the frequency of dosing reduced when it is administered concomitantly with drugs that potentiate the action of opioids.

It is not known if the effects of butorphanol are altered by concomitant medications that affect hepatic metabolism of drugs (erythromycin, theophylline, etc.), but physicians should be alert to the possibility that longer intervals between doses may be needed.

Caution should be exercised in using butorphanol concomitantly with MAO inhibitors, as the latter have been associated with severe and sometimes fatal adverse reactions in certain susceptible individuals when used with meperidine and other narcotic analgesics.

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

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

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

ADVERSE REACTIONS

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%).

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 - 3 mg.

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

	Migraine Pain Trials (% of Patients)				Post Operative Pain (% of Patients)			
	Butorphanol tartrate nasal spray			Placebo	Butorphanol tartrate nasal spray			Placebo
	1+1 mg N=32	2 mg N=33	2+1 mg N=16	N=78	1 mg N=128	1+1 mg N=70	2 mg N=149	N=156
Body As A Whole								
Asthenia	9	18	6	3				
Chills	--	6	--	3				
Headache					4	4	--	3
Pain	--	6	--	1				
Sensation of Heat	6	12	6	3	--	--	5	1
Cardiovascular								
Chest Pain	--	6	--	--				
Palpitation	6	--	--	--				
Syncope	--	9	--	--				
Vasodilation	6	–	6	1				
Digestive								
Dry Mouth	6	21	12	--				
Increased Appetite	--	6	--	--				
Nausea/Vomiting	22	61	37	4				
Thirst	--	--	6	--	--	--	8	1
Nervous System								
Abnormal Feelings	6	12	6	--				
Abnormal Thinking	--	6	--	--				
Anxiety	--	6	--	--				
Confusion	9	24	6	--	--	6	--	--
Dizziness	50	85	75	10	23	6	25	1
Drowsiness	41	51	50	5	26	33	40	16
Euphoria	--	3	6	--				
Incoordination	--	6	--	--				
Nervousness	16	9	6	--				
Paresis	--	15	6	--				
Paresthesia	6	21	--	--				
Somnolence					23	36	39	12
Vertigo	9	6	--	1				
Respiratory								
Epistaxis	--	--	6	--				
Nasal Irritation	--	6	6	1				
Dermatological								
Pruritus	6	12	6	--				
Sweating	6	30	19	--	--	4	--	1
Special Senses								
Blurred Vision	12	9	12	1	--	--	--	--
Diplopia	6	--	--	--	--	--	--	--
Ear Disorder	--	6	--	--	--	--	--	--
Hearing Loss	--	--	6	--	--	--	--	--
Unpleasant Taste	12	9	6	--	--	--	--	--

Other adverse reactions (≤3%) that were reported with butorphanol tartrate nasal spray in all acute (controlled and non-controlled) clinical trials (N=799) are listed below.

These adverse events, regardless of relationship to butorphanol tartrate nasal spray, are listed in order of decreasing frequency according to the following definitions: Frequent events were reported on one or more occasions by at least 1/100 individuals; Infrequent events by 1/100 to 1/1000 individuals. (All events **except those already listed in the previous table are included)**.

Body as a Whole

Infrequent: sensation of cold, fever, edema, accidental injury, back pain.

Gastrointestinal

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

Cardiovascular

Frequent: hypotension.

Infrequent: blood pressure elevated, hypertension, tachycardia, pallor, arrythmia.

Musculoskeletal

Infrequent: muscle relaxation, leg pain.

Nervous System

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

Respiratory

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

Dermatological

Infrequent: rash, erythema.

Genitourinary

Infrequent: impaired urination, libido increased.

Nasal Experiences

Infrequent: nasal symptoms, nose pain.

Special Senses

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

Hemic and Lymphatic

Infrequent: petechiae.

POSTMARKETING EXPERIENCE

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

Body as a Whole

Excessive drug effect associated with transient difficulty speaking and/or executing purposeful movements.

Cardiovascular

Chest pain, hypertension, tachycardia.

Nervous System

Convulsions, drug dependence.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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.

DOSAGE AND ADMINISTRATION

BUTORPHANOL (butorphanol tartrate) Nasal Spray has an onset of effect within 15 - 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 - 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 - 4 hours.

DOSAGE ADJUSTMENTS

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

Patients with Renal Impairment: The elimination half-life of BUTORPHANOL Nasal Spray is prolonged in patients with impaired renal function (see ACTIONS AND CLINICAL PHARMACOLOGY: Pharmacokinetics). Dosage adjustments may thus be necessary. In

patients with severe renal disease (i.e., creatinine clearance <30 mL/min), the initial dosage interval should be increased to 6 - 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.

Elderly Patients

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

Initially a 1 mg dose of BUTORPHANOL Nasal Spray should generally be used in elderly patients, and 90 - 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 PRECAUTIONS).

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

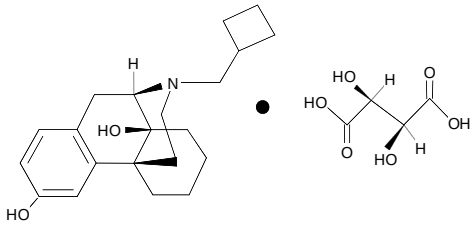
Proper Name: Butorphanol tartrate

Chemical Name(s):

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).

Structural Formula:



Molecular Formula: $C_{21}H_{29}NO_2AC_4H_6O_6$

Molecular Weight: 477.56

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 - 219°C, with decomposition.

COMPOSITION

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

STABILITY AND STORAGE RECOMMENDATIONS

BUTORPHANOL Nasal Spray should be stored at room temperature 15-30°C (59-86°F).

SPECIAL 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.

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

AVAILABILITY OF DOSAGE FORMS

BUTORPHANOL (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 - 15 metered doses, if no repriming is necessary.

INFORMATION FOR THE PHARMACIST

INSTRUCTION FOR ASSEMBLY OF NASAL SPRAY UNIT

Assemble BUTORPHANOL (butorphanol tartrate) Nasal Spray prior to dispensing to the patient, according to the following instructions.

1) Open the container and remove the spray pump and solution bottle.

2) Assemble BUTORPHANOL Nasal Spray by first unscrewing the white cap from the solution bottle and screwing the pump unit tightly onto the bottle. Make sure the clear cover is on the pump unit.

3) Return BUTORPHANOL Nasal Spray bottle to the container for dispensing to the patient. Patients should be instructed in the proper use of BUTORPHANOL Nasal Spray.

INFORMATION FOR THE PATIENT

Please read this information carefully before you start to take your medicine, even if you have taken this drug before. Do not throw away this leaflet until you have finished your medicine as you may need to read it again. For further information or advice, please ask your doctor or pharmacist.

What is BUTORPHANOL?

- BUTORPHANOL (butorphanol tartrate) Nasal Spray belongs to the family of medicines called analgesics.
- BUTORPHANOL Nasal Spray has been prescribed to you by your doctor to relieve your symptoms of pain.

IMPORTANT POINTS: You Must Tell Your Doctor *Before* Taking BUTORPHANOL:

- all your medical conditions, including a history of drug dependency, head injuries, central nervous system diseases, respiratory impairment, liver disease, kidney disease, heart or blood pressure disorders.
- any medications (prescription or non-prescription) which you are taking, especially central nervous system depressants, such as alcohol, barbiturates, tranquillizers, and antihistamines; medications that affect the ability of the liver to metabolize drugs, such as erythromycin and theophylline, or monoamine oxidase antidepressants, such as phenelzine, trancyclopromine or moclobemide.
- if you are pregnant or thinking about becoming pregnant, or if you are breast feeding.
- your habits concerning alcohol consumption.

How to Use BUTORPHANOL Nasal Spray

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

Instructions:

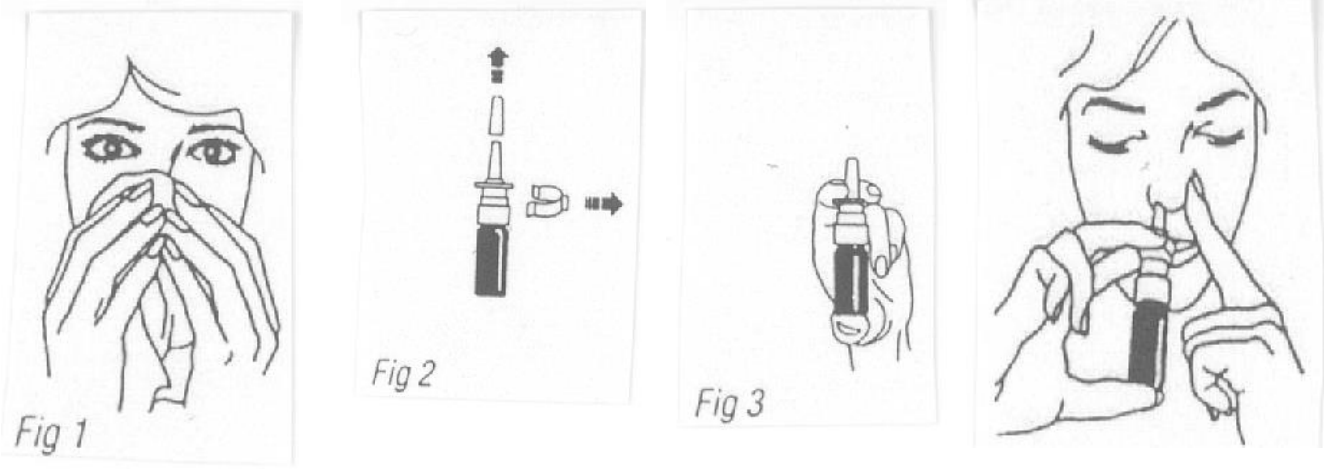
1) Blow your nose. (Fig.1)

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). (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)

Fig. 1 **Fig. 2** **Fig. 3** **Fig. 4**



5) Your doctor will tell you whether a two spray dose is needed. If needed, administer a second spray in the other nostril.

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

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

Note: Each priming reduces the number of effective doses per bottle.
BUTORPHANOL should not be used by anyone other than the person for whom it was prescribed. To prevent this, and to reduce the chance of children taking the drug, it is important to dispose of any excess BUTORPHANOL Nasal Spray as soon as it is no longer needed.

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

When Not to Use BUTORPHANOL

- Do not use BUTORPHANOL if you are allergic to it or to any of the components of its formulation (see list of components at the end of this section). Stop taking the drug and contact your doctor immediately if you experience an allergic reaction or any severe or unusual side effects.

Precautions When Taking BUTORPHANOL

- You may experience some side effects such as drowsiness, dizziness, somnolence and nausea. Consult your doctor if you experience these or other side effects.
- Refrain from potentially hazardous tasks, such as driving a car or operating dangerous machines until you are sure that this medication does not affect your mental alertness or physical coordination.
- Avoid alcoholic drinks and other central nervous system depressants such as barbiturates, tranquillizers and antihistamines while taking BUTORPHANOL.

What to Do in Case of Overdose

- Contact your doctor or the nearest hospital emergency department.

How to Store BUTORPHANOL Nasal Spray

- Store at room temperature 15-30°C (59-86°F).
- Store spray unit in the child resistant container.
- Keep out of reach of children.

What Does BUTORPHANOL Nasal Spray Contain?

- BUTORPHANOL Nasal Spray is available as an aqueous solution containing 10 mg/mL of butorphanol tartrate as the active ingredient. Non-medicinal ingredients include sodium chloride, citric acid, 0.2 mg/mL benzethonium chloride as a preservative, purified water with hydrochloric acid or sodium hydroxide added to adjust the pH.

REMINDER: This medicine has been prescribed only for you. Do not give it to anybody else. If you have any further questions, please ask your doctor or pharmacist.

BUTORPHANOL Nasal Spray is a drug that must be used carefully and appropriately to relieve your pain. Use BUTORPHANOL Nasal Spray only as directed. If you feel that you are using BUTORPHANOL Nasal Spray more often than prescribed, consult your doctor immediately.

PHARMACOLOGY

ANIMAL PHARMACOLOGY

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

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

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

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

HUMAN PHARMACOLOGY

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

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

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

The dispositions of butorphanol and hydroxybutorphanol are as follows:

	I.M.	**I.V.**
BUTORPHANOL Renal Clearance Rate	4.7 L/hr	8.4 L/hr
4-8 Hour Total Plasma Concentration Half-Time	4.9 hrs	3.9 hrs
Peak Plasma Concentration	2.02 µg/L	1.80 µg/L
Mean 0-8 Hour Area Under the Curve	10.8 µg/hr/L	3.4 µg/hr/L
HYDROXYBUTORPHANOL Rate of Metabolism of Butorphanol to Hydroxybutorphanol	0.68±0.02 µg/L/hr	0.68±0.02 µg/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 µg/hr/L	2.0 µg/hr/L

TOXICOLOGY

ACUTE TOXICITY

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

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.

CHRONIC TOXICITY

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

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

In a subcutaneous study in rats at daily doses of 0.4, 2.0 and 4.0 mg/kg (butorphanol base) for 6 months, animal exhibited a decreased weight gain in the high dose females and mild decrease

in white blood cell counts in the high dose males. All rats exhibited increased activity, excitement, and sporadic self-mutilation (chewing of tails). No histopathologic evidence of pericholangitis, bile duct hyperplasia or other organ toxicity was observed in the rats.

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

REPRODUCTION STUDIES

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

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

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

TUMORIGENICITY IN RATS

Rats were administered butorphanol tartrate in the diet at levels of approximately 1.0 and 2.0 mg/kg/ day for 78 weeks and observed without drug treatment for an additional 26 weeks. Two control groups were included, one which received no drug and one which received pentazocine (40 mg/kg/day). Although no drug-related increase in tumour incidence was reported, a firm

conclusion regarding the carcinogenicity of butorphanol in this species is not possible, since the study did not meet full requirements for a bioassay.

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