

SUBLIMAZE- fentanyl citrate injection, solution
Taylor Pharmaceuticals

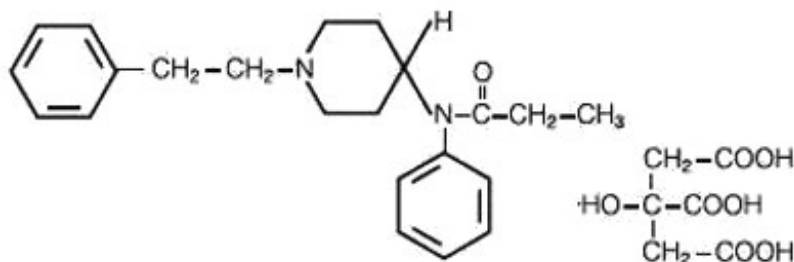
SUBLIMAZE® Injection CII

CII

Rx only

DESCRIPTION

SUBLIMAZE (fentanyl citrate) Injection is a potent narcotic analgesic. Each milliliter of solution contains fentanyl citrate equivalent to 50 mcg of fentanyl base, adjusted to pH 4.0 to 7.5 with sodium hydroxide. SUBLIMAZE is chemically identified as N-(1-phenethyl-4-piperidyl) propionanilide citrate (1:1) with a molecular weight of 528.60. The empirical formula is $C_{22}H_{28}N_2O \cdot C_6H_8O_7$. The structural formula of SUBLIMAZE is:



SUBLIMAZE is a sterile, non-pyrogenic, preservative free aqueous solution for intravenous or intramuscular injection.

CLINICAL PHARMACOLOGY

SUBLIMAZE (fentanyl citrate) is a narcotic analgesic. A dose of 100 mcg (0.1 mg) (2.0 ml) is approximately equivalent in analgesic activity to 10 mg of morphine or 75 mg of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. SUBLIMAZE appears to have less emetic activity than either morphine or meperidine. Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with SUBLIMAZE. Recent assays in man show no clinically significant histamine release in dosages up to 50 mcg/kg (0.05 mg/kg) (1 ml/kg). SUBLIMAZE preserves cardiac stability, and blunts stress-related hormonal changes at higher doses.

The pharmacokinetics of SUBLIMAZE can be described as a three-compartment model, with a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal elimination half-life of 219 minutes. The volume of distribution for SUBLIMAZE is 4 L/kg.

SUBLIMAZE plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. It accumulates in skeletal muscle and fat, and is released slowly into the blood. SUBLIMAZE, which is primarily transformed in the liver, demonstrates a high first pass clearance and releases approximately

75% of an intravenous dose in urine, mostly as metabolites with less than 10% representing the unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites.

The onset of action of SUBLIMAZE is almost immediate when the drug is given intravenously; however, the maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is 30 to 60 minutes after a single intravenous dose of up to 100 mcg (0.1 mg) (2.0 ml). Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is one to two hours. As with longer acting narcotic analgesics, the duration of the respiratory depressant effect of SUBLIMAZE may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to CO₂ stimulation following administration of SUBLIMAZE to man.

1. DIMINISHED SENSITIVITY TO CO₂ STIMULATION MAY PERSIST LONGER THAN DEPRESSION OF RESPIRATORY RATE. (Altered sensitivity to CO₂ stimulation has been demonstrated for up to four hours following a single dose of 600 mcg (0.6 mg) (12 ml) SUBLIMAZE to healthy volunteers.) SUBLIMAZE frequently slows the respiratory rate, duration and degree of respiratory depression being dose related.
2. The peak respiratory depressant effect of a single intravenous dose of SUBLIMAZE is noted 5 to 15 minutes following injection. See also WARNINGS and PRECAUTIONS concerning respiratory depression.

INDICATIONS AND USAGE

SUBLIMAZE (fentanyl citrate) is indicated:

- for analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
- for use as a narcotic analgesic supplement in general or regional anesthesia.
- for administration with a neuroleptic as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.
- for use as an anesthetic agent with oxygen in selected high risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures.

CONTRAINDICATIONS

SUBLIMAZE (fentanyl citrate) is contraindicated in patients with known intolerance to the drug or other opioid agonists.

WARNINGS

SUBLIMAZE (fentanyl citrate) SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS ANESTHETICS AND MANAGEMENT OF THE RESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.

See also discussion of narcotic antagonists in PRECAUTIONS and OVERDOSAGE.

If SUBLIMAZE is administered with a tranquilizer, the user should become familiar with the special properties of each drug, particularly the widely differing duration of action. In addition, when such a combination is used, fluids and other countermeasures to manage hypotension should be available.

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE may persist longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It

is recommended that narcotics, when required, should be used in reduced doses initially, as low as ¼ to ½ those usually recommended.

SUBLIMAZE may cause muscle rigidity, particularly involving the muscles of respiration. This rigidity has been reported to occur or recur infrequently in the extended postoperative period usually following high dose administration. In addition, skeletal muscle movements of various groups in the extremities, neck and external eye have been reported during induction of anesthesia with fentanyl; these reported movements have, on rare occasions, been strong enough to pose patient management problems. This effect is related to the dose and speed of injection and its incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUBLIMAZE; 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of eyelash reflex when SUBLIMAZE is used in anesthetic doses titrated by slow intravenous infusion; or, 3) simultaneous administration of SUBLIMAZE and a full paralyzing dose of a neuromuscular blocking agent when SUBLIMAZE is used in rapidly administered anesthetic dosages. The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status.

Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of SUBLIMAZE. Where moderate or high doses are used (above 10 mcg/kg), there must be adequate facilities for postoperative observation, and ventilation if necessary, of patients who have received SUBLIMAZE. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

SUBLIMAZE may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia and bronchoconstriction.

Severe and unpredictable potentiation by MAO inhibitors has been reported for other narcotic analgesics. Although this has not been reported for fentanyl, there are insufficient data to establish that this does not occur with fentanyl. Therefore, when fentanyl is administered to patients who have received MAO inhibitors within 14 days, appropriate monitoring and ready availability of vasodilators and beta-blockers for the treatment of hypertension is indicated.

Head Injuries and Increased Intracranial Pressure

SUBLIMAZE should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, SUBLIMAZE may obscure the clinical course of patients with head injury.

PRECAUTIONS

General

The initial dose of SUBLIMAZE (fentanyl citrate) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses.

Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of SUBLIMAZE.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see CLINICAL PHARMACOLOGY) SUBLIMAZE can also alter respiration. Therefore, when SUBLIMAZE is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

When a tranquilizer is used with SUBLIMAZE, pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high

dose or anesthetic dosages of SUBLIMAZE are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

When SUBLIMAZE is used with a tranquilizer, hypotension can occur. If it occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and repositioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease blood pressure in patients treated with a neuroleptic that blocks alpha adrenergic activity.

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of SUBLIMAZE combined with a neuroleptic. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

When SUBLIMAZE is used with a neuroleptic and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

Many neuroleptic agents have been associated with QT prolongation, torsades de pointes, and cardiac arrest. Neuroleptic agents should be administered with extreme caution in the presence of risk factors for development of prolonged QT syndrome and torsades de pointes, such as: 1) clinically significant bradycardia (less than 50 bpm), 2) any clinically significant cardiac disease, including baseline prolonged QT interval, 3) treatment with Class I and Class III antiarrhythmics, 4) treatment with monoamine oxidase inhibitors (MAOI's), 5) concomitant treatment with other drug products known to prolong the QT interval and 6) electrolyte imbalance, in particular hypokalemia and hypomagnesemia, or concomitant treatment with drugs (e.g. diuretics) that may cause electrolyte imbalance.

ECG monitoring is indicated when a neuroleptic agent is used in conjunction with SUBLIMAZE as an anesthetic premedication, for the induction of anesthesia, or as an adjunct in the maintenance of general or regional anesthesia.

Vital signs should be monitored routinely.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUBLIMAZE may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO₂ stimulation which may persist into or recur in the postoperative period. Respiratory depression secondary to chest wall rigidity has been reported in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO₂. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Impaired Respiration

SUBLIMAZE should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function

SUBLIMAZE should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

Cardiovascular Effects

SUBLIMAZE may produce bradycardia, which may be treated with atropine. SUBLIMAZE should be used with caution in patients with cardiac bradyarrhythmias.

Drug Interactions

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics and general anesthetics) will have additive or potentiating effects with SUBLIMAZE. When patients have received such drugs, the dose of SUBLIMAZE required will be less than usual. Following the administration of SUBLIMAZE, the dose of other CNS depressant drugs should be reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies have been conducted with SUBLIMAZE. Reproduction studies in rats revealed a significant decrease in the pregnancy rate of all experimental groups. This decrease was most pronounced in the high dosed group (1.25 mg/kg — 12.5X human dose) in which one of twenty animals became pregnant.

Pregnancy

Category C

SUBLIMAZE has been shown to impair fertility and to have an embryocidal effect in rats when given in doses 0.3 times the upper human dose for a period of 12 days. No evidence of teratogenic effects have been observed after administration of SUBLIMAZE to rats. There are no adequate and well-controlled studies in pregnant women. SUBLIMAZE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

There are insufficient data to support the use of SUBLIMAZE in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUBLIMAZE is administered to a nursing woman.

Pediatric Use

The safety and efficacy of SUBLIMAZE in children under two years of age have not been established.

Rare cases of unexplained clinically significant methemoglobinemia have been reported in premature neonates undergoing emergency anesthesia and surgery which included the combined use of fentanyl, pancuronium and atropine. A direct cause and effect relationship between the combined use of these drugs and the reported cases of methemoglobinemia has not been established.

ADVERSE REACTIONS

As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl citrate) are respiratory depression, apnea, rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypertension, hypotension, dizziness, blurred vision, nausea, emesis, diaphoresis, pruritus, urticaria, laryngospasm and anaphylaxis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a tranquilizer is used with SUBLIMAZE, the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of neuroleptics with SUBLIMAZE.

Cases of cardiac dysrhythmias, cardiac arrest, and death have been reported following the use of SUBLIMAZE with a neuroleptic agent.

DRUG ABUSE AND DEPENDENCE

SUBLIMAZE (fentanyl citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE

Manifestations

The manifestations of SUBLIMAZE (fentanyl citrate) overdose are an extension of its pharmacologic actions (see CLINICAL PHARMACOLOGY) as with other opioid analgesics. The intravenous LD₅₀ of SUBLIMAZE is 3 mg/kg in rats, 1 mg/kg in cats, 14 mg/kg in dogs and 0.03 mg/kg in monkeys.

Treatment

In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdose of SUBLIMAZE may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

DOSAGE AND ADMINISTRATION

50 mcg = 0.05 mg = 1 ml

Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used and the surgical procedure involved. Dosage should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

- I. Premedication — Premedication (to be appropriately modified in the elderly, debilitated and those who have received other depressant drugs) — 50 to 100 mcg (0.05 to 0.1 mg) (1 to 2 ml) may be administered intramuscularly 30 to 60 minutes prior to surgery.
- II. Adjunct to General Anesthesia — See Dosage Range Chart
- III. Adjunct to Regional Anesthesia - 50 to 100 mcg (0.05 to 0.1 mg) (1 to 2 ml) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is

required.

- IV. Postoperatively (recovery room) - 50 to 100 mcg (0.05 to 0.1 mg) (1 to 2 ml) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usage in Children: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 2 to 3 mcg/kg is recommended.

DOSAGE RANGE CHART

TOTAL DOSAGE		
<p>Low Dose — 2 mcg/kg (0.002 mg/kg) (0.04 ml/kg) SUBLIMAZE. SUBLIMAZE in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, SUBLIMAZE may also provide some pain relief in the immediate postoperative period.</p>	<p>Moderate Dose — 2 to 20 mcg/kg (0.002 to 0.02 mg/kg) (0.04 to 0.4 ml/kg) SUBLIMAZE. Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary and careful observation of ventilation postoperatively is essential.</p>	<p>High Dose — 20 to 50 mcg/kg (0.02 to 0.05 mg/kg) (0.4 to 1 ml/kg) SUBLIMAZE. During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20 to 50 mcg/kg (0.02 to 0.05 mg) (0.4 to 1 ml) of SUBLIMAZE with nitrous oxide/oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH and prolactin. When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression. The main objective of this technique would be to produce "stress free" anesthesia.</p>

DOSAGE RANGE CHART

MAINTENANCE DOSAGE		
<p>Low Dose — 2 mcg/kg (0.002 mg/kg) (0.04 ml/kg) SUBLIMAZE. Additional dosages of SUBLIMAZE are infrequently needed in these minor</p>	<p>Moderate Dose — 2 to 20 mcg/kg (0.002 to 0.02 mg/kg) (0.04 to 0.4 ml/kg) SUBLIMAZE. 25 to 100 mcg (0.025 to 0.1 mg) (0.5 to 2.0 ml) may be administered intravenously or intramuscularly when movement and/or changes in vital signs</p>	<p>High Dose — 20 to 50 mcg/kg (0.02 to 0.05 mcg/kg) (0.4 to 1.0 ml/kg) SUBLIMAZE. Maintenance dosage (ranging from 25 mcg (0.025 mg) (0.5 ml) to one half the initial loading dose) will be dictated by the changes in vital signs which indicate stress and lightening of analgesia. However,</p>

procedures.	and/or changes in vital signs indicate surgical stress or lightening of analgesia.	the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.
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As a General Anesthetic

When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg/kg (0.05 to 0.1 mg/kg) (1 to 2 ml/kg) may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg/kg (0.15 mg/kg) (3 ml/kg) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

See WARNINGS and PRECAUTIONS for use of SUBLIMAZE (fentanyl citrate) with other CNS depressants, and in patients with altered response.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

SUBLIMAZE (fentanyl citrate) Injection is available as:

NDC 11098-030-02	50 mcg/ml of fentanyl base,	2 ml ampoules in packages of 10
NDC 11098-030-05	50 mcg/ml of fentanyl base,	5 ml ampoules in packages of 10
NDC 11098-030-10	50 mcg/ml of fentanyl base,	10 ml ampoules in packages of 5
NDC-11098-030-20	50 mcg/ml of fentanyl base,	20 ml ampoules in packages of 5

STORAGE

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]. PROTECT FROM LIGHT.

TAYLOR PHARMACEUTICALS AN AKORN COMPANY

Decatur, IL 62522

AFCA0N Rev. 08/05

SUBLIMAZE			
fentanyl citrate injection, solution			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:11098-030
Route of Administration	INTRAVENOUS, INTRAMUSCULAR	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
fentanyl citrate (UNII: MUN5LYG46H) (fentanyl - UNII:UF599785JZ)		50 ug in 1 mL

Inactive Ingredients

Ingredient Name	Strength
sodium hydroxide (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:11098-030-02	10 in 1 PACKAGE		
1		2 mL in 1 AMPULE		
2	NDC:11098-030-05	10 in 1 PACKAGE		
2		5 mL in 1 AMPULE		
3	NDC:11098-030-10	5 in 1 PACKAGE		
3		10 mL in 1 AMPULE		
4	NDC:11098-030-20	5 in 1 PACKAGE		
4		20 mL in 1 AMPULE		

Labeler - Taylor Pharmaceuticals

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Taylor Pharmaceuticals