

PRODUCT MONOGRAPH

^NSUFENTANIL CITRATE INJECTION USP

Sufentanil Citrate Injection

50 mcg/mL

USP

Opioid Analgesic

Sandoz Canada Inc.
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Boucherville, QC, Canada
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^NSUFENTANIL CITRATE INJECTION USP

Sufentanil Citrate Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous or epidural injection	Injection/ 50 mcg/mL	sufentanil citrate equivalent to 50 mcg of sufentanil base, sodium chloride, citric acid and/or sodium hydroxide, water for injection.

INDICATIONS AND CLINICAL USE

Sufentanil Citrate Injection USP (sufentanil) is indicated for intravenous administration:

- As a primary anesthetic agent for the induction and maintenance of balanced general anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, for whom myocardial or cerebral oxygen imbalance would be particularly detrimental or for whom extended postoperative ventilation is anticipated.
- As an analgesic adjunct at doses up to 8 mcg/kg in the maintenance of balanced general anesthesia for major surgical procedures.

Sufentanil Citrate Injection USP is indicated for epidural administration:

- For the postoperative management of pain following general surgery, thoracic or orthopedic procedures and cesarean section.
- As an analgesic adjunct to epidural bupivacaine during labour and vaginal delivery.

Geriatrics (>65 years of age): Dose reduction should be considered, as the elderly are more susceptible to the effects of anesthetic agents.

Pediatrics (<18 years of age): The safety and efficacy in children, particularly in children younger than 2 years of age, has been documented only in a limited number of cases. For use in children younger than 12 years of age undergoing cardiovascular surgery, see specific instructions in DOSAGE AND ADMINISTRATION, Intravenous Use, Use in Children.

CONTRAINDICATIONS

- Patients who are hypersensitive to sufentanil or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING in the Product Monograph.
- Patients with known hypersensitivity to fentanyl or to other morphinomimetics.
- Intravenous use in labour or before clamping of the cord during cesarean section is not recommended due to the possibility of respiratory depression in the newborn infant. This is in contrast to the epidural use in labour, during which sufentanil in doses up to 30 mcg does not influence the condition of the mother or the newborn.
- As with other opiates administered epidurally, sufentanil should not be given to patients exhibiting the following:
 - severe hemorrhage or shock;
 - septicemia;
 - local infection at the site of proposed puncture;
 - disturbances in blood morphology and/or anticoagulant therapy or other concomitant drug therapy or medical conditions which could contraindicate the technique of epidural administration.

WARNINGS AND PRECAUTIONS

General

Sufentanil should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids and, when administered epidurally, by persons specifically trained in the techniques and patient management associated with epidural administration.

Complete resuscitation equipment and opioid antagonist should be readily available whenever sufentanil is used.

Vital signs should be monitored continuously in all patients receiving sufentanil.

Skeletal Muscle Rigidity: Intravenous administration or inadvertent intravascular injection during epidural administration of sufentanil may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence of muscular rigidity associated with intravenous sufentanil citrate can be reduced by:

- Administration of up to ¼ of the full paralyzing dose of a nondepolarising neuromuscular blocking agent just prior to administration of sufentanil at dosages of up to 8 mcg/kg.
- Incremental administration in divided doses of a full paralyzing dose of a neuromuscular blocking agent following loss of the eyelash reflex during induction with thiopental when sufentanil has been used in doses up to 8 mcg/kg in major surgical procedures.
- Simultaneous administration of sufentanil and a full paralyzing dose of a neuromuscular blocking agent when sufentanil is used in anesthetic doses (above 8 mcg/kg).

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 sufentanil. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression. Dosages above 1 mcg/kg sufentanil/hour of surgery frequently produce respiratory depression. In a clinical study involving 616 patients, 69 of the 86 patients (80%) who required naloxone in the immediate postoperative period had received a sufentanil dosage in excess of 1 mcg/kg/hour.

Nonepileptic myoclonic movements can occur.

Elderly and Debilitated Patients: The initial dose of sufentanil should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Cardiovascular

The cardiovascular effects of opioids may result in drug interactions with other drugs frequently used during anesthesia. The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status.

High doses of pancuronium may produce increases in heart rate during sufentanil oxygen anesthesia. Bradycardia and possibly asystole can occur if the patient has received an insufficient amount of anticholinergic or when sufentanil is combined with nonvagolytic muscle relaxants. Bradycardia can be treated with atropine.

Opioid analgesics may induce hypotension, especially in hypovolemic patients. Nitrous oxide may produce cardiovascular depression when given with high doses of sufentanil (see ACTION AND CLINICAL PHARMACOLOGY). Appropriate measures to maintain a stable arterial pressure should be taken.

Endocrine and Metabolism

Hypothyroidism and Alcoholism: Careful titration of dosage may be required in patients with conditions such as uncontrolled hypothyroidism or alcoholism (see DRUG INTERACTIONS). In such cases, prolonged postoperative monitoring is required.

Gastrointestinal

Smooth Muscle Spasm: Opioid analgesics stimulate the tonic contraction of the smooth muscle in the gastrointestinal system. The following conditions are associated with use of opioid analgesics, including constipation, delay of gastric emptying, postoperative ileus, and increase in intrabiliary pressure.

Nausea and Vomiting: Opioid analgesics activate the chemoreceptor trigger zone. This effect is increased by head movement. Nausea and vomiting may occur in a portion of patients.

Hepatic/Renal

In patients with liver or kidney dysfunction, sufentanil should be administered with caution due to the importance of these organs in the metabolism and excretion of sufentanil.

Neurologic and Neurosurgic

Head Injuries: Sufentanil may obscure the clinical course of patients with head injuries.

In patients with compromised intracerebral compliance, the use of rapid bolus injections should be avoided; in such patients the transient decrease in mean arterial pressure has occasionally been accompanied by a short-lasting reduction of the cerebral perfusion pressure.

Pupil Constriction: Opioid analgesics cause constriction of the pupils. There is little tolerance to this central effect. This effect is present even at high doses and repeated use.

Perioperative Considerations

Driving and Operating Machinery: Patients should be advised to allow sufficient time to elapse before operating a car or heavy machinery.

Respiratory

Respiratory Depression: Opioid analgesics depress respiration. In particular, sufentanil should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance.

During anesthesia, impaired respiration can be managed by assisted or controlled respiration. 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. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to patient discharge from the recovery area.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by sufentanil may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained.

Patients should be closely monitored for at least 2 hours following each administration of an epidural injection of sufentanil as respiratory depression may occur.

Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of sufentanil. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression. Dosages above 1 mcg/kg sufentanil/hour of surgery frequently produce respiratory depression. In a clinical study involving 616 patients, 69 of the 86 patients (80%) who required naloxone in the immediate postoperative period had received a sufentanil dosage in excess of 1 mcg/kg/hour.

Tolerance and Dependence

Repeated use of opioid analgesics result in tolerance or even dependence and, therefore, has the potential for being abused.

Patients on chronic opioid therapy or with a history of narcotic abuse may require increased amounts of sufentanil.

Urinary

Urinary Retention

Opioid analgesics can also cause tonic contraction of the urinary smooth muscle, leading to urinary retention. This effect is more likely to occur after epidural analgesia.

Special Populations

Pregnant Women: Sufentanil has been shown to have an embryocidal effect in rats and rabbits when given at doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of sufentanil in rats or rabbits. Since the safety of sufentanil in pregnant women has not been established, this drug should be used in pregnancy only if the expected benefits are considered to outweigh any potential risks.

Labour and Delivery: Although the use of epidurally administered sufentanil is indicated for labour and delivery (see INDICATIONS AND CLINICAL USE and DOSAGE AND ADMINISTRATION), caution should be exercised in the presence of fetal distress. The use of intravenous sufentanil in labour and delivery is not recommended (see CONTRAINDICATIONS).

Nursing Women: It is not known whether this drug is excreted in human milk. Because fentanyl analogues are excreted in human milk, caution should be exercised when sufentanil is administered to a nursing woman.

Pediatrics (<12 years of age): The safety and efficacy of intravenous sufentanil in children, particularly under 2 years of age, has been documented only in a limited number of cases. Likewise, documented use of epidural sufentanil in pediatric cases is limited.

For use in children younger than 12 years of age undergoing cardiovascular surgery, see specific instructions in DOSAGE AND ADMINISTRATION, Intravenous Use, Use in Children.

Geriatrics: The initial dose of sufentanil should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Intravenous Use: The most frequent adverse reactions in 320 patients administered sufentanil intravenously were:

- hypotension (7%);
- hypertension (3%);

- chest wall rigidity (3%);
- bradycardia (3%).

Other adverse reactions that may occur (reported incidence of less than 1%) are:

- cardiovascular: tachycardia, arrhythmia;
- gastrointestinal: nausea, vomiting;
- respiratory: apnea, postoperative respiratory depression, bronchospasm;
- dermatological: itching;
- central nervous system: chills;
- miscellaneous: intraoperative muscle movement.

Allergic reactions and asystole have been reported; but since several drugs were coadministered during anesthesia, it is uncertain whether there is a causal relationship to the drug.

Epidural Use: The frequency of adverse experiences associated with the use of epidural sufentanil was evaluated in 1478 postoperative patients and 14,467 parturients. The most frequently reported adverse experiences were somnolence or sedation, pruritus, nausea, vomiting and urinary retention.

During clinical trials, slow respiratory rate (<10 breaths/min) and apneic periods were noted in 3.5% and 2.5% of postoperative patients, respectively. These episodes developed early after drug administration and were resolved within 1 hour. Concomitant use of epinephrine may reduce the incidence and severity of respiratory depression. No respiratory depressive episodes were observed in patients receiving epidural sufentanil during labour and delivery.

Other observed adverse experiences include:

- cardiovascular: hypotension (2%);
- central nervous system: motor block (18%, labour patients only), dizziness (2%), euphoria (2%);
- urinary system disorders: urinary incontinence (1%);
- miscellaneous: fever (1%), shivering (2%), pain at injection site (1%), miosis (1%).

Adverse experiences that occurred in less than 1% of patients are: bradycardia, hypopnea, rash, headache, and confusion.

Post-Market Adverse Drug Reactions

Post-marketing reports describe patients with symptoms suggestive of, or diagnostic of, serotonin syndrome following the concomitant use of fentanyl with a serotonergic drug, such as Selective Serotonin Reuptake Inhibitor or a Serotonin Norepinephrine Reuptake Inhibitor (see DRUG INTERACTIONS).

Post-marketing adverse reports include: laryngospasm, dizziness, myoclonic movements, respiratory depression and cough.

DRUG INTERACTIONS

Overview

As sufentanil is used for intravenous anesthesia and epidural analgesia during childbirth, drug interactions with medications used in general anaesthesia and obstetrics are likely.

Drug-Drug Interactions

Cytochrome P450 3A4 (CYP 3A4) Enzyme Inhibitors: Sufentanil is metabolised mainly via the human cytochrome CYP 3A4 enzyme. However, no *in vivo* inhibition by erythromycin (a known cytochrome CYP 3A4 enzyme inhibitor) has been observed. Although clinical data are lacking, other drugs such as ketoconazole, itraconazole, and ritonavir, are also known to be clinically important inhibitors of cytochrome CYP 3A4. As such they may inhibit the metabolism of sufentanil. This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such drugs requires special patient care and observation; in particular, it may be necessary to lower the dose of sufentanil.

Interaction with other Central Nervous System Depressants: An additive effect with sufentanil may be exhibited in patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants (e.g. alcohol). In such cases of combined treatment, the dose of sufentanil and/or these agents should be reduced.

MAO Inhibitors: It is usually recommended to discontinue monoamine oxidase (MAO) inhibitors 2 weeks prior to any surgical or anesthetic procedure.

Interactions with Beta-Blockers: As with all opioids, a decrease in heart rate and/or blood pressure may be seen when sufentanil is administered to patients who are on beta-blocker medication.

Serotonergic Drugs

Coadministration of fentanyl with a serotonergic agent, such as a Selective Serotonin Reuptake Inhibitor or a Serotonin Norepinephrine Reuptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life threatening condition (see also ADVERSE REACTIONS).

Drug-Food Interactions

Grapefruit juice is known to produce clinically relevant inhibition of CYP 3A4. It may inhibit the metabolism of sufentanil.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Sufentanil can only be administered by qualified professionals working in adequate facilities. Complete equipment for artificial respiration, resuscitation, and opioid antagonism must be readily available whenever sufentanil is used (see WARNINGS AND PRECAUTIONS).

Vital signs should be monitored routinely in all patients receiving sufentanil.

Dosing Considerations

The dosage of sufentanil should be individualised in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see WARNINGS AND PRECAUTIONS).

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of particular muscle relaxants and the degree of skeletal muscle relaxation required (see ACTION AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS).

Recommended Dose and Dosage Adjustment

Intravenous Use: See dosage range chart for the use of sufentanil citrate by intravenous injection:

- in doses of up to 8 mcg/kg as an analgesic adjunct to general anesthesia;
- in doses ≥ 8 mcg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

Usage in Children: For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 mcg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of 25-50 mcg are recommended for maintenance based on response to initial dose and as determined by changes in vital signs indicating surgical stress or depth of anesthesia. Since experience with the use of sufentanil, particularly in the young age group, is limited, anesthetists should be guided by progressive experience with the use of the drug in children.

Epidural Use: Proper placement of the needle or catheter in the epidural space should be verified prior to sufentanil citrate to preclude inadvertent intravascular or intrathecal administration. If analgesia is inadequate, the placement and integrity of the catheter should be verified prior to the administration of any additional epidural medication.

Postoperative Management of Pain: An initial dose of 30-60 mcg sufentanil in 10 mL normal saline may be expected to provide adequate pain relief for up to 4-6 hours. Additional boluses of up to 25 mcg sufentanil may be administered at not less than one-hour intervals if there is evidence of lightening of analgesia.

Analgesic Adjunct during Labour and Delivery: The recommended initial dose for sufentanil, administered with 0.125%-0.25% bupivacaine, is 10 mcg in 10 mL normal saline. If required, two subsequent injections of the combination may be given; supplemental doses should be separated by intervals of at least one hour. It is recommended that the total sufentanil dose administered not exceed 30 mcg.

Adult Dosage Range Chart – Intravenous Use

Administration with Nitrous Oxide/Oxygen				
Indication	Approximate Duration of Anesthesia	Initial Dose	Maintenance Increments (included in total dosage)	Total Dosage (A cumulative dosage in the range of 0.5-1 mcg/kg is recommended)
As an adjunct to major surgery	At least one hour	A minimum of 0.5 mcg/kg is necessary to control or abolish cardiovascular response to laryngoscopy and intubation. The initial dosage should represent at least 75% of the total dosage administered during the procedure.	10-25 mcg as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental doses should be individualized and adjusted to the remaining operative time anticipated.	0.5-2 mcg/kg administered as an analgesic adjunct with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.
As an adjunct to more complicated major surgery	At least two hours		25-50 mcg as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated.	2-8 mcg/kg administered as an analgesia adjunct with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, sufentanil citrate has been shown to attenuate sympathetic reflex activity in response to surgical stimuli, maintain cardiovascular stability and provide relatively rapid recovery.
Administration with 100% Oxygen				
Indication	Initial Dose	Maintenance Increments (included in total dosage)	Total Dosage	
As primary anesthetic agent	The initial dose should be individualized with due consideration given to patient status, concomitant medications and anticipated level of surgical stimulation. See total dosage guidelines.	25-50 mcg as determined by changes in vital signs that indicate stress or lightening of anesthesia.	8-30 mcg/kg (anesthetic doses) administered with 100% oxygen and a muscle relaxant. Sufentanil citrate has been found to produce sleep at dosages ≥ 8 mcg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 mcg/kg, catecholamine release is attenuated. High doses are indicated in patients undergoing surgical procedures such as cardiovascular surgery and neurosurgery in the sitting position, in whom myocardial or cerebral oxygen imbalance would be detrimental. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	

NOTE: The suggested intravenous administration rate for sufentanil citrate is 250-300 mcg/minutes.

OVERDOSAGE

Symptoms: Overdosage would be manifested by an extension of the pharmacological actions of sufentanil (see ACTIONS AND CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression, which varies from bradypnoea to apnoea.

Treatment: Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with sufentanil may be longer than the duration of action of the opioid antagonist; additional doses of the latter may therefore be required.

Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

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

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Sufentanil is an opioid analgesic. The analgesic potency of sufentanil is approximately 5 to 7 times that of fentanyl. Dosage requirements for equianalgesic effect will be 1/5 to 1/7 those of fentanyl on a mcg/kg basis.

Intravenous Use: At intravenous doses of up to 8 mcg/kg, sufentanil provides profound analgesia; at doses ≥ 8 mcg/kg, sufentanil produces a deep level of anesthesia. Sufentanil produces a dose related attenuation of catecholamine release, particularly norepinephrine.

At intravenous dosages of ≥ 8 mcg/kg, sufentanil citrate produces hypnosis and anesthesia without the use of additional anesthetic induction agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 mcg/kg attenuate the sympathetic response to surgical stress and maintain cardiovascular stability. The sympathetic response is blocked at doses of sufentanil of 25 to 30 mcg/kg, with dependable cardiovascular stability, infrequent bradycardia and preservation of myocardial oxygen balance.

Pancuronium may produce a dose-dependent elevation in heart rate and blood pressure during sufentanil oxygen anesthesia that is not suppressed by the minimal effects of high doses of sufentanil on cardiac function, heart rate or blood pressure. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide together with sufentanil. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent should

maintain stable lower heart rate and blood pressure.

In patients administered high doses of sufentanil, dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane or isoflurane.

Bradycardia is seen infrequently in patients administered sufentanil citrate-oxygen anesthesia. The use of nitrous oxide with high doses of sufentanil may decrease mean arterial pressure, heart rate and cardiac output.

In one study of patients undergoing craniotomy, sufentanil at 20 mcg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation. During carotid endarterectomy, sufentanil produced EEG patterns and reductions in cerebral blood flow and oxygen utilisation comparable to those of fentanyl.

The intraoperative use of sufentanil at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. Requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of sufentanil as compared to patients given inhalation agents.

Decreased respiratory drive and increased airway resistance occur with increased doses of sufentanil. The duration and degree of respiratory depression are dose related when sufentanil is used at subanesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnoea may be produced.

Epidural Use: Epidural sufentanil produces spinal analgesia of rapid onset, within 5 to 10 minutes and moderate duration, generally 4 to 6 hours. The onset and duration of analgesia appear to be dose related.

During labour and vaginal delivery, the addition of 10 to 30 mcg sufentanil to bupivacaine (0.125% to 0.25%) provided analgesia of better quality and longer duration versus bupivacaine (0.25%) alone. Apgar scores and neurobehavioural scores of neonates were not affected by the epidural administration of sufentanil to women in labour.

Pharmacokinetics

Assays of histamine in patients administered sufentanil citrate have shown no elevation in plasma histamine levels and no indication of histamine release.

Intravenous Use: Intravenous sufentanil citrate has an immediate onset of action, with a distribution of 0.72 minute, redistribution of 13.7 minutes and an elimination half-life of 148 minutes. It is rapidly and extensively metabolised into a large number of inactive metabolites that are excreted with the urine and feces. The liver and small intestine are the major sites of biotransformation; oxidative O- and N-dealkylation are the primary metabolic pathways. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of sufentanil is approximately 92.5%

The pharmacokinetics of intravenous sufentanil can be described as a three-compartment model, with relatively limited accumulation and rapid elimination from tissue storage sites, allowing for relatively more rapid recovery than with fentanyl.

Epidural Use: Peak plasma concentrations following single epidural doses of sufentanil are reached within 10 minutes and are 4 to 6 times lower than those after intravenous administration. Systemic absorption within the first 3 hours after epidural administration is approximately 1/3 to 1/2 that of an intravenous bolus. Vascular uptake of sufentanil after high thoracic (T3-T4) administration is 3 to 4 times lower than after mid thoracic to lumbar epidural injection. Coadministration of epinephrine reduces systemic availability of sufentanil, especially in the first hours after injection. Time to peak plasma concentrations and maximum plasma concentrations increase with repeated epidural doses of sufentanil.

Mean sufentanil concentrations in CSF exceeded 2 ng/mL within a few minutes after an epidural injection of 75 mcg; peak concentrations in the CSF occurred within 5 to 90 minutes. Thereafter, the decay of sufentanil concentrations in the CSF was biphasic with an average sufentanil terminal half-life of 165 minutes compared to 355 minutes in plasma.

Placental transfer of sufentanil was investigated in women undergoing cesarean section. Within 30 to 55 minutes of epidural doses of 22 to 38 mcg sufentanil, maternal plasma concentrations varied from 0.02 to 0.16 ng/mL; neonatal concentrations were generally below 0.02 ng/mL with measurable levels up to 0.9 ng/mL found in only a few neonates. Fetal plasma concentrations rapidly equilibrate with maternal concentrations. Individual umbilical vein to maternal plasma concentration ratios averaged 0.4. Plasma protein binding of sufentanil, related to the α_1 acid glycoprotein level, was 90.7% in mothers and 79.3% in neonates.

STORAGE AND STABILITY

Store between 15 and 30°C. Protect from light. Discard unused portion.

SPECIAL HANDLING INSTRUCTIONS

Dilution of Sufentanil Citrate Injection USP: Sufentanil Citrate Injection USP 10-60 mcg may be diluted in 10 mL of 0.9% Sodium Chloride Injection, stored at room temperature between 15 and 30°C and used within 24 hours.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitation, discoloration and leakage prior to administration whenever solution and container permit. Solution showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Sufentanil Citrate Injection USP is available in 1 mL ampoules, boxes of 10. **For single use.**

Sufentanil Citrate Injection USP is also available in 5 mL **single use** vials, boxes of 10.

Sufentanil Citrate Injection USP is a preservative free, sterile aqueous solution. Each mL contains sufentanil citrate equivalent to 50 mcg of sufentanil base, sodium chloride for isotonicity, citric acid and/or sodium hydroxide to adjust pH and water for injection.

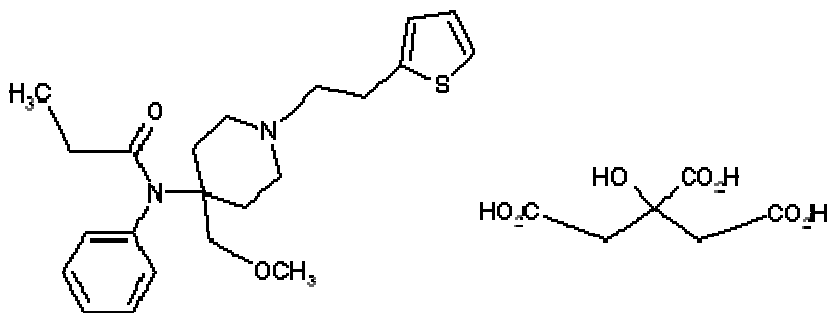
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Sufentanil citrate
Chemical name:	Propanamide, N-[4-(methoxymethyl)-1-[2-(thienyl)-ethyl]-4-piperidinyl]-N-phenyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)
Molecular formula and molecular mass:	$C_{22}H_{30}N_2O_2S \cdot C_6H_8O_7$; 578.74 g/mol

Structural Formula:



Physicochemical Properties:	pH (Solution of 0.005%): 3.5-6.0 Sufentanil citrate is a white or almost white powder with a melting point of 140°C (with decomposition) and a pK _a of 8.01. It is soluble in water; sparingly soluble in ethanol, acetone and chloroform; freely soluble in methanol.
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DETAILED PHARMACOLOGY

Analgesic Activity: The narcotic analgesic effect of intravenous sufentanil has been studied in mice, rats and dogs. In mice, sufentanil had in the hot plate test an ED₅₀ of 0.0028 mg/kg, compared to an ED₅₀ of 0.026 mg/kg for fentanyl and 6.45 mg/kg for morphine. In rats, the ED₅₀ on the tail withdrawal test is 0.00071 mg/kg. Sufentanil was found to be 4,520 times more potent than morphine and 16 times more potent than fentanyl. In dogs, the minimal effective analgesic dose, defined as the dose needed to intubate an awake, unpremedicated dog without producing heart rate or blood pressure changes, was 0.00025 mg/kg for sufentanil, 0.012 mg/kg for fentanyl, 0.15 mg/kg for morphine and 0.45 mg/kg for meperidine. Sufentanil was 1.875 times more potent than meperidine, 625 times more potent than morphine and 5 times more potent than fentanyl.

The analgesic effect of epidural sufentanil has been studied in a variety of species. In rats, the ED₅₀ on the tail withdrawal test was 0.26 and 0.59 mcg/rat for significant and surgical analgesia, respectively. Sufentanil was >30 times more active than morphine after epidural administration. In guinea pigs, the epidural morphine:fentanyl:sufentanil potency ratio was 1:30:20 for threshold electric current that evoked a vocalization response. An epidural dose of 2.5 mcg sufentanil suppressed the noxiously evoked activity of wide-dynamic-range neurons for more than 2 hours in cats.

In rats, the analgesic potency of epidural sufentanil was comparable to intravenous and intrathecal but 3 times more potent than subcutaneous sufentanil. The order of onset of analgesia was intrathecal > epidural > subcutaneous sufentanil. For the dissociation from central behavioural effects, especially blockade of the pinna reflex, the epidural route produced a greater selectivity than the other routes.

After repeated epidural sufentanil administration to rats and dogs, tolerance was observed to develop to the analgesic and behavioural effects of sufentanil.

Cardiovascular and Respiratory Effects: Sufentanil was administered to awake, unsedated, nonventilated dogs in increasing dosages from 0.16-10 mcg/kg. Sufentanil produced dose-related decreases in heart rate up to 5 mcg/kg. No further decrease was seen at 10 mcg/kg. Diastolic aortic blood pressure decreased significantly after the injection of 0.32 mcg/kg and respiratory rate decreased after 25 mcg/kg. Arterial pO₂ decreased following 5 and 10 mcg/kg and arterial pCO₂ increased from 0.16 mcg/kg reflecting respiratory depressant activity.

Starting at 2.5 mcg/kg, atrioventricular dissociations and ventricular extrasystoles were observed in several dogs. Doses of 1.2 mcg/kg and higher induced metabolic acidosis. Salivation and convulsions were observed after 5 and 10 mcg/kg. The effects of sufentanil on peripheral circulation were studied in mongrel dogs. Sufentanil produced a slight decrease in skeletal muscle surface pH, and a decrease in mixed venous arterial pH, whereas morphine produced a prompt and highly significant decrease in muscle pH and a 20% decrease in calculated blood volume. No adverse effects were noted for sufentanil or morphine following propranolol-induced beta-blockade. In propranolol-sufentanil treated dogs, peripheral perfusion was adequate, with only a minor decrease in muscle pH and mixed venous pH, similar to that noted in animals treated with sufentanil alone. In comparison, propranolol-morphine treated animals showed severe impairment of peripheral perfusion.

At analgesic doses in rats, epidural sufentanil produces no detectable effects on respiration. Epidural sufentanil was associated with early respiratory depression at 4 times the analgesic dose. In contrast, late respiratory depression was measured up to 7 hours after injection with morphine. The effects of epidural sufentanil and morphine on respiration were further evaluated in rats by whole body plethysmography, measuring tidal volume and frequency of breathing in rats exposed to 8% CO₂. The dose at which compounds reduce the minute volume of respiration by 25% (ID₂₅) was compared with the dose for significant analgesia (ED₅₀ for a TWR latency >6.0 sec). A 133-fold difference between ID₂₅ and ED₅₀ was observed for morphine; whereas for sufentanil the difference was 12.

Cardiovascular Effects of High-Dose Sufentanil: The early (30 minutes) hemodynamic effects of high doses of intravenous sufentanil 0.01 mg/kg have been investigated in mongrel dogs ventilated with 50% N₂O/50% O₂.

Results are summarised below:

Sufentanil	Morphine
Moderate, insignificant decrease in mean arterial pressure (MAP).	During the first 5 min MAP fell to below 50% of the control value.
30% decrease in cardiac index (CI) due to more than 50% decrease in heart rate (HR) – partly compensated for by increased stroke volume index (SVI).	CI was reduced to 50% of control due to significant decreases in HR and SVI; calculated SVR I was unchanged. Within 30 minutes, some of the above changes returned to control levels.
Central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) increased immediately (returned to control with time).	CVP and PCWP decreased (returned to control with time).
Peak left ventricular dP/dt decreased 20-50% (both groups).	
Rate-pressure product (RPP) decreased to less than 50% of control values (both groups).	
Mixed venous oxygen tension (PvO ₂), O ₂ transport and consumption significantly decreased.	PvO ₂ , O ₂ transport and consumption immediately decreased but gradually returned toward control values.

The authors concluded that apart from initial, transient changes, sufentanil provided stable cardiovascular dynamics. Morphine was characterised by changes in several hemodynamic parameters.

Cardiovascular Effects of High-Dose Sufentanil in Propranolol-Treated Dogs: The immediate cardiovascular effects of sufentanil 0.01 mg/kg and morphine 4 mg/kg in dogs pretreated with 2 mg/kg propranolol were compared. Their study was based upon the recommended use of high-dose analgesic anesthesia for high-risk patients, many of whom were being treated with beta-blockers. Sudden withdrawal of beta-blockers prior to surgery can result in tachyarrhythmias or myocardial infarction. In addition, high-risk patients may have preexisting disorders (angina, arrhythmia, hypertension) that preclude the use of analgesic anesthesia agents that may produce adverse cardiovascular effects.

Summary of Results

Sufentanil	Morphine
40% decrease in CI (both drugs)	
MAP, CVP, MPAP- no significant change PCWP increased 50%	MAP decreased 65% MPAP, 14% decrease and PCWP, 33% decrease
HR decreased 30%	No further decrease in HR apart from 16% decrease resulting from propranolol
SVRI increased by 51%	SVRI decreased by 32%
PVRI – no change	PVRI significantly increased
RVSWI – no effect	RVSWI – no effect
LVSWI – minor decrease of 20%	LVSWI – 80% decrease
O ₂ transport index and RPP declined significantly (both drugs)	
O ₂ consumption reduced 20%	O ₂ consumption unchanged

The authors concluded that sufentanil was associated with cardiovascular stability in the presence of total beta-blockade induced by propranolol.

Massive doses (up to 0.16 mg/kg) of sufentanil in mongrel dogs administered after severe asphyxia had no significant delay in the classical effects of asphyxia. Large doses of sufentanil (up to 40 mcg/kg/min) had little effect on cardiovascular dynamics in atropinized dogs. Small decreases in heart rate, blood pressure and cardiac output were observed in nonatropinized dogs irrespective of infusion rate.

Effect on Cerebral Blood Flow (CBF) and Oxygen Consumption (CMRO₂): The effect of 5, 10, 20, 40, 80 and 160 mcg/kg of sufentanil on CBF and CMRO₂, was investigated in male Wistar-rats anesthetised with halothane and ventilated with 70% N₂O/30% O₂; MAP, PaCO₂ and temperature were similar in all groups, but CBF decreased in the sufentanil groups compared to a control group ventilated with 70% N₂O/30% O₂. Reduction in CMRO₂ of up to 36% occurred in groups receiving 20 mcg/kg.

Marked depression in EEG tracing with low frequency, high amplitude and burst suppression occurred in the sufentanil groups. Short periods of epileptoid patterns and spikes were seen in the 80 and 160 mcg/kg groups.

EEG Effects: The effects of morphine, fentanyl, sufentanil and alfentanil on the EEG were investigated in Beagle dogs. All compounds increased the amplitude of the EEG, decreased the frequency of the EEG and produced spindle-like bursts of biphasic waves. Frontal cortex changes in the total power were the shortest (18 minutes) after 0.004 mg/kg fentanyl. Sufentanil produced the shortest effects in the amygdala (18 minutes); longer lasting effects (60 minutes) occurred in the frontal cortex and hippocampus.

In rabbits, equipotent doses of sufentanil (0.01 mg) induced a deeper narcotic effect (burst suppression) than fentanyl (0.1 mg). Otherwise, conventional EEG and amplitude frequency spectra were reported to be equal for both drugs.

Drug Interaction Studies: Mongrel dogs received a loading dose of sufentanil (0.01 mg/kg) followed by an intravenous injection of succinylcholine (1 mg/kg). Animals were ventilated with 50% N₂O/50% O₂, and analgesia was maintained with a slow intravenous infusion of 0.00025 mg/kg sufentanil. Ten minutes later, an intravenous test dose of 1 mg/kg succinylcholine was given, followed 45 minutes later by an intravenous dose of 0.1 mg/kg pancuronium bromide, and another 45 minutes later by an intravenous dose of 0.16 mg/kg propranolol. Sufentanil in combination with succinylcholine seemed to induce some slight positive inotropic effects. A pronounced stimulating effect on cardiac and hemodynamic parameters was seen with the addition of pancuronium bromide, possibly due to its sympathomimetic action. Propranolol caused a significant increase in pulmonary artery pressure, left ventricular end-diastolic pressure and pulmonary vascular resistance. There was a decrease in cardiac output and left ventricular stroke work.

Miscellaneous Studies: In dogs and rats, the narcotic effects of sufentanil were reversed by nalorphine. In dogs, the ED₅₀ values for the antagonism of apomorphine-induced emesis were 0.00028 mg/kg for sufentanil, 0.0012 mg/kg for fentanyl and 0.68 mg/kg for morphine. Plasma levels of histamine were unaffected by intravenous administration of sufentanil (0.15 mg/kg) in dogs. *In vitro*, sufentanil (500 mg/mL) failed to induce hemolysis in human blood.

Metabolism and Pharmacokinetics: The pharmacokinetics of sufentanil was determined using a sensitive radioimmunoassay. In rats receiving tritiated sufentanil, the excretion of radioactivity was very rapid and complete. After 24 hours, 86.8% of the administered radioactivity had been excreted; 10.6% was excreted in the second day of dosing. Excretion was predominantly in the feces (61.6%) and in the urine (37.8%). Sufentanil was rapidly metabolised to a large number of metabolites, with oxidative *N*-dealkylation at the piperidine nitrogen being the major pathway. In dogs, 60% of the dose was excreted in the urine and 40% in the feces. Biliary excretion was shown to be an important elimination pathway, as suggested by the large fraction of metabolites excreted in the feces. In rats, 93.1% of sufentanil was bound to plasma protein, compared to 92.8% in dogs and 92.5% in man.

Placental transfer of sufentanil was determined in Wistar rats. Placental concentrations were 25% higher than those in maternal blood. The ratio of maternal to umbilical blood levels averaged 1.2. Placental concentrations were 2-2.5 times higher than fetal radioactivity levels. Total radioactivity recovered from placenta, uteri, fetal membranes and fetuses represented 0.1-0.4% of maternal dose over the course of the 120 minute test period.

Plasma levels and tissue distribution of ³H-sufentanil were determined in Wistar rats. Radioactivity gradually became undetectable in plasma following an initial rapid distribution phase lasting up to approximately 2 hours. The terminal elimination had a half-life of 8 hours. Plasma levels of unchanged sufentanil declined triexponentially with t_{1/2}=1.6 minutes, t_{1/2}=10.6 minutes and t_{1/2}=63 minutes. Total plasma clearance averaged 69.1 mL/min/kg. Peak radioactivity levels reported were in the lung, adrenals, kidney and liver. Twenty-nine to fifty-two percent of the dose was recovered in the small intestine 1-2 hours after injection. A peak level of 36% was found in the large intestine at 8 hours. Sixty-five percent of unchanged drug was measured in the brain at 8 hours.

TOXICOLOGY

Sufentanil has been administered by the intravenous or epidural routes either acutely or subacutely to mice, rats, guinea pigs and dogs. The chronic toxicity of subcutaneous sufentanil was evaluated in the rat.

Acute Toxicity		
Animals	No. Animals/Dose	LD ₅₀ (mg/kg) 14 Days
Albino mice	10 M	16.8 (10.6-26.6)
	10 F	18.0 (13.7-23.5)
Wistar rats	10 M	12.5 (7.87-19.7)
	10 F	9.34 (5.88-14.8)
Guinea pigs	10 M	11.8 (7.87-17.7)
	10 F	13.0 (8.17-20.6)
Dogs	4 M	10.1 (3.82-26.9)
	4 F	19.5 (9.14-41.8)

Signs of Toxicity: convulsions, exophthalmos, excitation, palpebral ptosis, loss of righting reflex, tremors, dyspnea and cyanosis (high dose in mice), diuresis and diarrhea (in rats), cyanosis and hypothermia (in guinea pigs), sedation or prostration (in dogs).

The acute LD₅₀ (14 days after administration) in Wistar rats after epidural sufentanil administration was >320 mcg/rat (>1.28 mg/kg). No pathological changes in the brain and spinal cord were noted.

Subacute Toxicity

Four-Week Intravenous Toxicity Study in Wistar Rats: Rats (10 M, 10 F/group) received sufentanil intravenously once a day, 6 days a week, during 4 weeks at 0, 0.31, 1.25 and 5 mg/kg doses. The findings were: increased mortality in sufentanil-treated groups, loss of righting reflex, muscle rigidity and exophthalmos, lower food consumption and body weight gain in all dosed animals; decrease in BUN and SGOT in females at all doses; increase in specific gravity of urine in mid-dosed but not high-dosed males; decrease in creatinine in urine in low-dosed females only; increase in urine pH in high-dosed females.

One-Month Intravenous Toxicity Study in Beagle Dogs: Dogs (3 M, 3 F/group) received sufentanil intravenously once a day, 6 days a week, during 1 month at doses of 0, 0.02, 0.16 and 1.25 mg/kg. The findings were: no mortality in any group; ataxia, hypoxia, mydriasis and sleep noted in all treated animals; symptoms disappeared after 1 hour in the low-dosed group, after 2 hours in the mid-dosed group and after 2-3 hours in the high-dosed group; decreased appetite and body weight loss in all treated animals; salivation (mid and high-dosed); emesis (high-dosed); increased heart rate (high-dosed); mild hypertension (mid and high-dosed); higher leucocyte values in all treated animals but still within normal limits; slightly high coagulation time values in all treated groups; high SGPT values in all treated groups; more dilated sinusoids and smaller hepatocytes in some treated animals (not dose-related); thymic involution in many dosed animals; atrophic effect on uterus along with thin-layered vaginal epithelium.

Epidural Toxicity: Subacute administration of epidural sufentanil was investigated in Wistar rats (0.63 or 320 mcg/rat x 5 days), Beagle dogs (10, 50 or 100 mcg/day x 15 days) and guinea pigs (2.5 mcg/day x 28 days). No signs of sufentanil-related pathological changes were observed except a dilated urinary bladder in the rat study at 320 mcg/rat. In all 3 studies inflammation with fibrous tissue around the catheter, independent of the use of sufentanil, was noted on histopathological examination. No neurological adverse effects were observed. The reported behavioural changes were typical for the administration of high doses of an opiate analgesic.

Chronic Toxicity

Six-Month Subcutaneous Toxicity Study in Wistar Rats: Male and female Wistar rats (20 M, 20 F/group) were administered daily subcutaneous doses of 0, 0.16, 0.63 or 2.5 mg/kg sufentanil for 6 months. Mortality due to suffocation occurred at all doses but was slightly elevated in males in the 2.5 mg/kg group. Dose-dependent and opiate-related changes included: loss of righting reflex, pinna and corneal reflex blockade, muscle rigidity and decrease in food consumption and body weight gain. Hematological changes included: decreased thrombocytes in males (WNL), increased segmented neutrophils and decreased lymphocytes in males and females. On urinalysis, decreased creatinine and specific gravity were seen in males, and increased pH, volume and incidence of bacteria and triphosphate crystals were noted in males and females. However, there was no clear evidence of specific nephrotoxicity. Organ weights were generally decreased; however, increased adrenal weight was noted in all dosed groups. Histopathological examination revealed changes to the adrenals, male and female genital tracts, mammary glands and thymus. Chronic inflammation and foamy cells were observed in the lungs of rats in the 0.16 and 0.63 mg/kg dose groups.

Reproduction and Teratology Studies

Male and Female Fertility Study in Wistar Rats: Eighty dosed males were coupled with nondosed females, and nondosed males were coupled with 80 dosed females. The doses used were: 0, 0.005 mg/kg, 0.02 mg/kg and 0.08 mg/kg. Dosed females received a single intravenous injection/day, 7 days a week for a minimum of 14 days and throughout gestation. Dosed males received the drug 5 days a week for a minimum of 56 days and further until mating. Pregnancy rate was comparable between groups; litter size was normal at low and mid-dose but significantly decreased at high-dose due to maternal toxicity; an increase in fetal resorptions was also noted at high dose. No evidence of teratogenicity was seen, and there were no adverse effects on male or female fertility.

Intravenous Embryotoxicity and Teratogenicity Study in Wistar Rats: Sufentanil was administered intravenously from day 6 through day 15 of gestation at doses of 0, 0.005, 0.02 and 0.08 mg/kg. Mortality was higher in the dams of the mid and high-dosed groups, and there was a decrease in pregnancy rates in the same groups. There was no difference between groups with regard to litter size and number of live, dead or resorbed fetuses. Decreased birth weight, attributed to maternal toxicity, was observed at 0.02 and 0.08 mg/kg. No drug-related abnormality was noted in the fetus.

Intravenous Embryotoxicity and Teratogenicity in New Zealand White Rabbits: Sufentanil was administered intravenously to female rabbits from days 6 through day 18 of pregnancy at doses of 0, 0.005, 0.02 and 0.08 mg/kg. Mortality increased in the mid and high-dosed group adult animals. There was a decrease in pregnancy rate at high-dose, but no effect on mean litter

size and number of live, dead and resorbed fetuses. Twenty-four hour survival rate decreased significantly at mid and high-doses. No abnormalities were found in the fetuses.

Intravenous Embryotoxicity and Teratogenicity Study in Wistar Rats

Peri- and Postnatal Toxicity Study: Sufentanil was administered intravenously to female rats at doses of 0.005, 0.02 and 0.08 mg/kg from day 16 of pregnancy through a 3-week lactation period. There was no difference noted between groups on mortality, pregnancy rate or gestation period. Litters were comparable between groups. There was a slightly lower weight gain during a 3-week neonatal period at 0.02 mg/kg. Almost no pups survived from the 0.08 mg/kg dose group. Survival rate decreased in all treated groups. These effects were thought to be related to anoxia or death of fostering mothers during the lactation period. No abnormalities were observed.

Mutagenicity: The micronucleus test in 30 female rats revealed that single intravenous doses of sufentanil as high as 80 mcg/kg produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

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PART III: CONSUMER INFORMATION

^NSUFENTANIL CITRATE INJECTION USP
Sufentanil Citrate Injection

This leaflet is part III of a three-part "Product Monograph" published when Sufentanil Citrate Injection USP was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about Sufentanil Citrate Injection USP. Contact your doctor if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Sufentanil Citrate Injection USP is indicated for the following uses:

- When injected in a vein, to induce and maintain unconsciousness during a major surgery;
- When injected in the spine, to relieve pain after surgery, and during labour and vaginal delivery.

What it does:

Sufentanil Citrate Injection USP, when injected in a vein, induces and maintains unconsciousness during a major surgery. When injected in the spine, it provides pain relief.

When it should not be used:

- Sufentanil Citrate Injection USP should not be used in patients with a known history of allergic reactions or sensitivity to this drug or other agents in the same drug family.
- To prevent breathing problems in the newborn baby, sufentanil should not be injected into a vein (intravenous use) during labour or cesarean section before the umbilical cord has been cut. Injection around the spinal cord (epidural use), however, is permitted.
- Sufentanil should not be injected around the spinal cord (epidural use) if there is shock, severe bleeding, systemic infection, or infection around the injection site. This use should also be avoided if you bleed easily or you are taking a blood-thinner.

What the medicinal ingredient is:

Sufentanil citrate.

What the important nonmedicinal ingredients are:

Citric acid, sodium chloride, sodium hydroxide, water for injection.

What dosage forms it comes in:

Sufentanil Citrate Injection USP is available in 1 mL ampoules, boxes of 10, and in 5 mL single use vials, boxes of 10. **For single use.**

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Sufentanil Citrate Injection USP should only be administered by persons with the appropriate training and experience with this kind of drug.**
- **Complete resuscitation (life-saving) equipment and an antidote to rapidly counteract the effects of the drug should always be available.**

BEFORE being given Sufentanil Citrate Injection USP, talk to your doctor if:

- You plan on operating a car or heavy machinery after receiving the drug.
- You are an elderly.
- You have a condition with any part of your body, such as your heart, lung, liver, or thyroid.
- You are taking any medication, such as blood thinners, pain killers.
- You have heavy alcohol use.
- You use any drugs not given you by a doctor.
- You are pregnant or breast feeding.
- You have a known allergic reaction to this drug or any other pain medications or any other general anesthetics.
- You have had a head injury, or if you experience difficulties breathing.

INTERACTIONS WITH THIS MEDICATION

Your doctor should tell you what medication you may or may not use after your surgery or childbirth.

Before taking Sufentanil Citrate Injection USP, tell your doctor about any other medications that you are using including certain antidepressants (selective serotonin reuptake inhibitors (SSRI) and serotonin/norepinephrine reuptake inhibitors (SNRI).

Drugs that may interact with Sufentanil Citrate Injection USP include: antifungals (ketoconazole, itraconazole), antivirals (ritonavir), sleeping pills (barbiturates), tranquilizers, pain medication (opioids), general anesthetics, or other depressants of the central nervous system, antidepressants (MAO inhibitors), and medicines for high blood pressure (beta-blockers). Other agents that may also interact are grapefruit juice and alcohol.

Grapefruit juice and alcohol may also change the effect of Sufentanil Citrate Injection USP.

PROPER USE OF THIS MEDICATION

Sufentanil Citrate Injection USP can only be used by a doctor in a facility with life-saving equipment.

Usual dose:

The dose given to you by your doctor will depend on such factors as how much you weigh, your current health status, any diseases you may currently have, and the kind of surgical procedure you will be undergoing.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

During or after the use of Sufentanil Citrate Injection USP, talk to your doctor or nurse if you feel anything unusual or bothering (see the following table).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Common			
Injection in a vein			
Low (fainting) or high blood pressure (headaches/dizziness)		✓	
Difficulty breathing		✓	
Slow heartbeat		✓	
Injection in the spine			
Sleepiness	✓		
Itching	✓		
Nausea/Vomiting	✓		
Difficulty urinating		✓	
Uncommon			
Injection in a vein			
Rapid/Irregular heartbeat		✓	
Nausea/Vomiting	✓		
Itching	✓		
Chills	✓		
Injection in the spine			
Slow heartbeat		✓	
Decreased breathing		✓	
Rash	✓		
Headache	✓		
Confusion	✓		

In rare cases, muscle stiffness and swollen face have been reported. Call your doctor if you have these conditions.

This is not a complete list of side effects. For any unexpected effects following the administration of Sufentanil Citrate Injection USP, contact your doctor or pharmacist.

HOW TO STORE IT

Sufentanil Citrate Injection USP should be stored between 15 and 30°C and protected from light.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document, plus the full product monograph prepared for health professionals, can be obtained by contacting the sponsor, Sandoz Canada Inc., at: 1-800-361-3062

or

by written request at:

145, Jules-Léger
Boucherville, (QC), Canada
J4B 7K8

or by e-mail at :
medinfo@sandoz.com

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