

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

^NSUFENTANIL CITRATE INJECTION USP

Sufentanil Citrate Injection

50 mcg/mL

USP

Opioid Analgesic

SteriMax Inc.
2770 Portland Drive
Oakville ON
L6H 6R4

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SUFENTANIL CITRATE INJECTION USP

Sufentanil Citrate Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intravenous or epidural injection	Injection/ 50 mcg/mL	sufentanil citrate equivalent to 50 mcg of sufentanil base, sodium chloride, citric acid, 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)

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Pediatrics (< 18 years of age)

The safety and efficacy 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 the active substance sufentanil or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- 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

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

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

Addiction, Abuse, and Misuse

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

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of Sufentanil Citrate Injection USP. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of Sufentanil Citrate Injection USP or following a dose increase. Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure

Accidental ingestion of even one dose of Sufentanil Citrate Injection USP, especially by children, can result in a fatal overdose of sufentanil (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of Sufentanil Citrate Injection USP during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol

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

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma,

and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

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

General

Patients should be instructed not to give Sufentanil Citrate Injection USP (sufentanil) to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. Sufentanil Citrate Injection USP should be stored securely to avoid theft or misuse.

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

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.

Patients should be cautioned not to consume alcohol while taking Sufentanil Citrate Injection USP as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of Sufentanil Citrate Injection USP can occur at particularly high doses. A sufentanil dose reduction or change in opioid may be required.

Abuse and Misuse

Like all opioids, Sufentanil Citrate Injection USP is a potential drug of abuse and misuse, which can lead to overdose and death, Therefore, Sufentanil Citrate Injection USP should be prescribed and handled with caution.

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

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

Carcinogenesis and Mutagenesis

See TOXICOLOGY section.

Cardiovascular

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.

Sufentanil administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Sufentanil Citrate Injection USP.

The use of Sufentanil Citrate Injection USP in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression and should be avoided (see DOSAGE AND ADMINISTRATION).

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of Sufentanil Citrate Injection USP and there is a potential for development of psychological dependence.

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

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

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

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 Effects

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

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.

Neonatal Opioid Withdrawal Syndrome (NOWS)

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

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Sufentanil Citrate Injection USP is not recommended to be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the risks. If Sufentanil Citrate Injection USP was used during pregnancy, special attention to NOWS is warranted.

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Sufentanil should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see DRUG INTERACTIONS). If the decision is made to prescribe a benzodiazepine or other CNS

depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Sufentanil Citrate Injection USP is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see DRUG INTERACTIONS).

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

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

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

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.

Peri-operative Considerations

Sufentanil Citrate Injection USP is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

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

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

be addressed as clinically indicated.

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

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

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

Psychomotor Impairment

Sufentanil Citrate Injection USP may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of sufentanil with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

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 $\frac{1}{4}$ of the full paralyzing dose of a non-depolarizing 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.

Respiratory

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

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

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. To reduce the risk of respiratory depression, proper dosing and titration of Sufentanil Citrate Injection USP are essential. Overestimating the Sufentanil Citrate Injection USP dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups, and DOSAGE AND ADMINISTRATION). **Use in Patients with Chronic Pulmonary Disease:** Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with Sufentanil Citrate Injection, as in these patients, even usual therapeutic doses of Sufentanil Citrate Injection may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of Sufentanil Citrate Injection USP is contraindicated in Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see CONTRAINDICATIONS).

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.

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

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

Pregnant Women: Studies in humans have not been conducted. Sufentanil Citrate Injection USP crosses the placental barrier and is not recommended to be administered to pregnant women unless, in the judgement of the physician, potential benefits outweigh the risks.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome, ADVERSE REACTIONS, Post-marketing Experience).

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

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 (> 65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Patients with Hepatic Impairment: 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.

Patients with Renal Impairment: 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.

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.

Opioid Adverse Events

Adverse effects of Sufentanil Citrate Injection USP (sufentanil) injection are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

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

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

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

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

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 Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

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

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

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression.

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.

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

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

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 \geq 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.

Physical Dependence

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Sufentanil Citrate Injection USP. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

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

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

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

OVERDOSAGE

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

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 overdose 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 overdose, 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.

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.

Central Nervous System: Sufentanil produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO₂ tension and to electrical stimulation.

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

Sufentanil causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone overdose.

Gastrointestinal Tract and Other Smooth Muscle: Sufentanil causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System: Sufentanil may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Endocrine System: Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may manifest from these hormonal changes.

Immune System: *In vitro* and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

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°C 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°C and 30°C and used within 48 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 ampoules, boxes of 10. **For single use.**

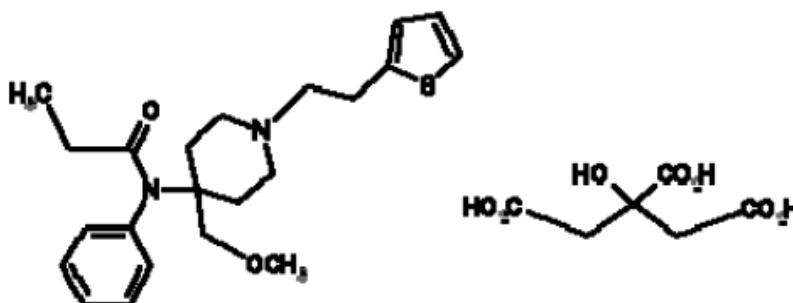
Sufentanil Citrate Injection USP is a preservative free, sterile aqueous solution. Each mL contains sufentanil citrate equivalent to 50 mcg of sufentanil base, sodium chloride for isotonicity, citric acid to adjust pH and water for injection.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

- Proper name: Sufentanil citrate
- Chemical name: Propanamide, N-[4-(methoxymethyl)-1-[2-(thienyl)-ethyl]-4-piperidiny]-N-phenyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)
- Molecular formula: $C_{22}H_{30}N_2O_2S \cdot C_6H_8O_7$
- Molecular mass: 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 pKa of 8.01. It is soluble in water; sparingly soluble in ethanol, acetone and chloroform; freely soluble in methanol.

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 pre-existing 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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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

NSUFENTANIL CITRATE INJECTION USP **Sufentanil Citrate Injection**

Read this carefully before you start taking Sufentanil Citrate Injection USP and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Sufentanil Citrate Injection USP.

Serious Warnings and Precautions

- **Even if you take Sufentanil Citrate Injection USP as prescribed you are at risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **You may get life-threatening breathing problems while taking Sufentanil Citrate Injection USP. This is less likely to happen if you take it as prescribed by your doctor.**
- **You should never give anyone your Sufentanil Citrate Injection USP. They could die from taking it. If a person has not been prescribed Sufentanil Citrate Injection USP, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took Sufentanil Citrate Injection USP while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
 - **has changes in their breathing (such as weak, difficult or fast breathing)**
 - **is unusually difficult to comfort**
 - **has tremors (shakiness)**
 - **has increased stools, sneezing, yawning, vomiting, or fever****Seek immediate medical help for your baby.**
- **Taking Sufentanil Citrate Injection USP with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**
- **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.**

What is Sufentanil Citrate Injection USP 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.

How does Sufentanil Citrate Injection USP used for?

Sufentanil Citrate Injection USP is a fast acting pain relief medication and belongs to a class of medicines known as opioids. It provides pain relief for a short period of time. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in Sufentanil Citrate Injection USP?

Medicinal ingredients: Sufentanil citrate.

Non-medicinal ingredients: Citric acid, sodium chloride, water for injection.

Sufentanil Citrate Injection USP comes in the following dosage forms:

Sufentanil Citrate Injection USP is available in 1 mL ampoules, boxes of 10, and in 5 mL ampoules, boxes of 10.

For single use.

Do not use Sufentanil Citrate Injection USP if:

- you are allergic to sufentanil or any of the other ingredients in Sufentanil Citrate Injection USP
- you can control your pain by the occasional use of other pain medications. This includes those available without prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOI) (such as phenelzine sulphate, tranylecypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sufentanil Citrate Injection USP. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your thyroid, adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- suffer from migraines
- are planning to become pregnant
- plan on operating a car or heavy machinery after receiving the drug
- are an elderly
- are taking any medication, such as blood thinners, pain killers
- have heavy alcohol use
- use any drugs not given you by a doctor
- are pregnant or breast feeding
- have a known allergic reaction to this drug or any other pain medications or any other general anesthetics
- have had a head injury, or if you experience difficulties breathing

Other warnings you should know about:

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

Pregnancy, nursing, labour and delivery: Opioids can be transferred to your baby through breast milk, or while still in the womb. Sufentanil Citrate Injection USP can then cause life-threatening breathing problems in your unborn baby or nursing infant. Your doctor will determine if the benefits of using Sufentanil Citrate Injection USP outweigh the risks to your unborn baby or nursing infant.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to Sufentanil Citrate Injection USP. Sufentanil Citrate Injection USP can cause:

- drowsiness
- dizziness or
- lightheadedness

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

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

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

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

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

Serotonin Syndrome symptoms include:

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

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

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

The following may interact with Sufentanil Citrate Injection USP:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol.
Do not drink alcohol while you are taking Sufentanil Citrate Injection USP. It can lead to:
 - drowsiness

- unusually slow or weak breathing
- serious side effects or
- a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by Sufentanil Citrate Injection USP
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take Sufentanil Citrate Injection, USP with MAO inhibitors (MAOI) or if you have taken MAOI in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- warfarin (such as coumadin) and other anticoagulants (used for prevention or treatment of blood clots)
- anti-retroviral drugs (used to treat viral infections)
- anti-fungal drugs (used to treat fungal infections)
- antibiotic drugs (used to treat bacterial infections)
- some heart medication (such as beta blockers)
- grapefruit juice
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take Sufentanil Citrate Injection USP:

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

Sufentanil Citrate Injection USP is given via an injection.

You should be given it:

- only in a hospital or a clinic that has the proper monitoring and support equipment in place.
- by a healthcare professional that has been specifically trained in the use of intravenous anesthetics.

Usual dose: Your doctor will decide the best dose for you. It will depend on your age, weight, your health, medications you are currently taking and the type of surgery you are having.

Overdose:

If you think you have taken too much Sufentanil Citrate Injection USP, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:

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

What are possible side effects from using Sufentanil Citrate Injection USP?

These are not all the possible side effects you may feel when taking Sufentanil Citrate Injection USP. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Light Headedness
- Sweating
- Constipation
- High or low blood pressure
- Excessive sweating
- Feeling of intense happiness or excitement (euphoria)
- Feeling agitated
- Crying
- Headache
- Trouble with your vision
- Sleep apnea (a sleep disorder where your breathing is interrupted during sleep)
- Pain at injection site
- Feeling tired
- Chills
- Low sex drive, impotence (erectile dysfunction), infertility

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing		✓	
Drowsiness, dizziness		✓	
Fast, slow, or uneven heartbeat		✓	
Severe nausea or vomiting	✓		
Stiffness in the muscles of your neck, chest, hands, or legs			
Trouble breathing, or chest tightness			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Mild skin rash or itching	✓		
Twitching or muscle movements you cannot control	✓		
Pain, itching, burning, swelling, or lump under your skin where the needle is placed	✓		
RARE			
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone cold and clammy skin			✓
Respiratory Depression: slow, shallow or weak breathing			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating		✓	
Fast, Slow or Irregular Heartbeat: heart palpitations		✓	
Low Blood Pressure: dizziness, fainting, light-headedness	✓		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓

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

Reporting Side Effects

We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.

3 ways to report:

- Online at MedEffect; (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>)
- By calling 1-866-234-2345 (toll-free)
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 1908C
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect. (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>)

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.

Storage:

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

Disposal:

Sufentanil Citrate Injection USP should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about Sufentanil Citrate Injection USP:

- Talk to your healthcare professional
- Find the full prescribing information that is prepared for healthcare professionals and includes this consumer medication information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.sterimaxinc.com, or by calling 1-800-881-3550.

This leaflet was prepared by SteriMax Inc.

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