DISCLAIMER

All labeling reflected on this website is for informational and promotional purposes only. It is not intended to be used by healthcare professionals or patients for the purpose of prescribing or administering these products. Questions regarding the current content of product labeling should be directed to Akorn's Customer Service department at 800.932.5676.

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use SUFENTANIL CITRATE INJECTION, safely and effectively. See full prescribing information for SUFENTANIL CITRATE INJECTION.**

**Sufentanil Citrate Injection, for intravenous and epidural use, CII**
**Initial U.S. Approval: 1984**

**WARNING: ADDICTION, ABUSE, AND MISUSE**

***See full prescribing information for complete boxed warning.***

- **Sufentanil citrate injection exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**

**RECENT MAJOR CHANGES**

| | |
|---|---|
| Boxed Warning | 12/2016 |
| Indications and Usage (1) | 12/2016 |
| Dosage and Administration (2) | 12/2016 |
| Contraindications (4) | 12/2016 |
| Warnings and Precautions (5) | 12/2016 |

**INDICATIONS AND USAGE**

Sufentanil Citrate Injection is an opioid agonist indicated: (1)

- as an analgesic adjunct in the maintenance of balanced general anesthesia in patients who are intubated and ventilated.
- as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, in patients who are intubated and ventilated, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.
- for epidural administration as an analgesic combined with low dose (usually 12.5 mg per administration) bupivacaine usually during labor and vaginal delivery.

**DOSAGE AND ADMINISTRATION**

- Sufentanil Citrate Injection should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.
- Ensure that an opioid antagonist, resuscitative and intubation equipment, and oxygen are readily available (2.1).
- Individualize dosing based on factors such as age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved. (2.1)
- Initiate analgesic treatment with 1 to 2 mcg/kg intravenously. (2.2)
- Initiate epidural injection for labor and delivery at 10 to 15 mcg of sufentanil administered with 10 mL bupivacaine 0.125% with or without epinephrine (2.3)

**DOSAGE FORMS AND STRENGTHS**

Solution for injection (sterile): eq. to 50 mcg/mL sufentanil base; 1 mL, 2 mL and 5 mL ampules (3)

**CONTRAINDICATIONS**

- Hypersensitivity to sufentanil. (4)

**WARNINGS AND PRECAUTIONS**

- Risks of Skeletal Muscle Rigidity and Skeletal Muscle Movement: Manage with neuromuscular blocking agent. See full prescribing information for more detail on managing these risks. (5.4)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.2)
- Severe Cardiovascular Depression: Monitor during dosage initiation and titration. (5.6)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue Sufentanil Citrate Injection if serotonin syndrome is suspected. (5.7)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, or Head Injury: Monitor for sedation and respiratory depression. (5.9)

**ADVERSE REACTIONS**

Most common adverse reactions were apnea, rigidity, and bradycardia. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Akorn, Inc. at 1-800-932-5676 or FDA at 1-800-FDA-1088 or www.fda.gov.medwatch.**

**DRUG INTERACTIONS**

- Concomitant Use of CNS Depressants: May decrease pulmonary arterial pressure and may cause hypotension. See FPI for management instructions. For post-operative pain, start with the lowest effective dosage and monitor for potentiation of CNS depressant effects. (5.5, 7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with Sufentanil Citrate Injection because they may reduce analgesic effect of Sufentanil Citrate Injection or precipitate withdrawal symptoms. (7)

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Infants exposed to Sufentanil Citrate Injection through breast milk should be monitored for excess sedation and respiratory depression. (8.2)

Rev. 12/2016

**FULL PRESCRIBING INFORMATION: CONTENTS***



* Sections or subsections omitted from the full prescribing information are not listed.

**FULL PRESCRIBING INFORMATION**

**WARNING: ADDICTION, ABUSE, AND MISUSE**

***See full prescribing information for complete boxed warning.***

- **Sufentanil citrate injection exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**

## 1 INDICATIONS AND USAGE

Sufentanil Citrate Injection is indicated for intravenous administration in adults and pediatric patients:

- as an analgesic adjunct in the maintenance of balanced general anesthesia in patients who are intubated and ventilated.
- as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, in patients who are intubated and ventilated, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

Sufentanil Citrate Injection is indicated for epidural administration:

- as an analgesic combined with low dose (usually 12.5 mg per administration) bupivacaine usually during labor and vaginal delivery.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Important Dosage and Administration Instructions

Sufentanil Citrate Injection should be administered only by persons specifically trained in the use of intravenous or epidural anesthetics and management of the respiratory effects of potent opioids.

In patients administered high doses of Sufentanil Citrate Injection, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

For purposes of administering small volumes of Sufentanil Citrate Injection accurately, the use of a tuberculin syringe or equivalent is recommended.

- Ensure that an opioid antagonist, resuscitative and intubation equipment, and oxygen are readily available.
- Individualize dosage based on factors such as age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.
- Monitor vital signs regularly.
- The selection of preanesthetic medications should be based upon the needs of the individual patient.
- The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required.

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

If Sufentanil Citrate Injection is administered with a CNS depressant, become familiar with the properties of each drug, particularly each product's duration of action. In addition, when such a combination is used, fluids and other countermeasures to manage hypotension should be available *[see Warnings and Precautions (5.5)]*.

Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

### 2.2 Intravenous use

Sufentanil Citrate may be administered intravenously by slow injection or infusion.

Adjunct to general anesthesia:

- Doses of up to 8 mcg/kg (see Table 1)
- Total Dosage Requirements Of 1 Mcg/Kg/Hr Or Less Are Recommended
- Dosage should be individualized and adjusted to remaining operative time anticipated.

**Table 1: Adult Dosage Range Chart, Analgesic Component To General Anesthesia, Intravenous Use**

| Total dosage | Maintenance dosage |
|---|---|
| **Duration of anesthesia 1 to 2 hours** | |
| **Incremental or Infusion: 1 to 2 mcg/kg** Approximately 75% or more of total sufentanil dosage may be administered prior to intubation by either slow injection or infusion titrated to individual patient response.<br>Dosages in this range are generally administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required. | **Incremental: 10 to 25 mcg (0.2 to 0.5 mL)** may be administered in increments as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to remaining operative time anticipated.<br>**Infusion:** Intermittent or continuous infusion as needed in response to signs of lightening of analgesia.<br>In absence of signs of lightening of analgesia, infusion rates should always be adjusted downward until there is some response to surgical stimulation.<br>Maintenance infusion rates should be adjusted based upon the induction dose of sufentanil so that the total dose does not exceed 1 mcg/kg/hr of expected surgical time. |
| **Duration of anesthesia 2 to 8 hours** | |
| **Incremental or Infusion: 2 to 8 mcg/kg** Approximately 75% or less of the total calculated sufentanil dosage may be administered by slow injection or infusion prior to intubation, titrated to individual patient response.<br>Dosages in this range are generally administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures in which endotracheal intubation and mechanical ventilation are required.<br>At dosages in this range, sufentanil has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery. | **Incremental: 10 to 50 mcg (0.2 to 1 mL)** may be administered in increments as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated.<br>**Infusion:** Intermittent or continuous infusion as needed in response to signs of lightening of analgesia.<br>In the absence of signs of lightening of analgesia, infusion rates should always be adjusted downward until there is some response to surgical stimulation.<br>Maintenance infusion rates should be adjusted based upon the induction dose of sufentanil so that the total dose does not exceed 1 mcg/kg/hr of expected surgical time. |

Induction And Maintenance Of Anesthesia

- As the primary anesthetic agent: doses ≥8 mcg/kg (see Dosage Range Chart, Table 2).
- Dosage should be titrated to individual patient response
- In children less than 12 years of age undergoing cardiovascular surgery: 10 to 25 mcg/kg administered with 100% oxygen
  - Supplemental dosages of up to 25 to 50 mcg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

**Table 2: Dosage Range Chart, Induction and Maintenance of Anesthesia, Intravenous Use**

| | |
|---|---|
| **Incremental or Infusion: 8 to 30 mcg/kg**<br>Generally administered as a slow injection, as an infusion, or as an injection followed by an infusion.<br>Sufentanil with 100% oxygen and a muscle relaxant has been found to produce sleep at dosages ≥8 mcg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. The addition of $N_2O$ to these dosages will reduce systolic blood pressure. At dosages in this range of up to 25 mcg/kg, catecholamine release is attenuated.<br>Dosages of 25 to 30 mcg/kg have been shown to block sympathetic response including catecholamine release.<br>High doses are indicated in patients undergoing major surgical procedures, in which endotracheal intubation and mechanical ventilation are required, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance.<br>Postoperative observation is essential and postoperative mechanical ventilation may be required at the higher dosage range due to extended postoperative respiratory depression. | **Incremental:** Depending on the initial dose, maintenance doses of 0.5 to 10 mcg/kg may be administered by slow injection in anticipation of surgical stress such as incision, sternotomy or cardiopulmonary bypass.<br>**Infusion:** Sufentanil citrate may be administered by continuous or intermittent infusion as needed in response to signs of lightening of anesthesia.<br>In the absence of lightening of anesthesia, infusion rates should always be adjusted downward until there is some response to surgical stimulation.<br>The maintenance infusion rate for sufentanil should be based upon the induction dose so that the total dose for the procedure does not exceed 30 mcg/kg. |

### 2.3 Epidural Use in Labor and Delivery

Proper placement of the needle or catheter in the epidural space should be verified before sufentanil citrate is injected to assure that unintentional intravascular or intrathecal administration does not occur. Unintentional intravascular injection of sufentanil could result in a potentially serious overdose, including acute truncal muscular rigidity and apnea. Unintentional intrathecal injection of the full sufentanil, bupivacaine epidural doses and volume could produce effects of high spinal anesthesia including prolonged paralysis and delayed recovery.

- Sufentanil should be administered by slow injection. Respiration should be closely monitored following each administration of an epidural injection of sufentanil.
- If analgesia is inadequate, the placement and integrity of the catheter should be verified prior to the administration of any additional epidural medications.

Dosage for Labor and Delivery

- 10 to 15 mcg administered with 10 mL bupivacaine 0.125% with or without epinephrine.
- Sufentanil and bupivacaine should be mixed together before administration.
- Doses can be repeated twice (for a total of three doses) at not less than one-hour intervals until delivery.

## 3 DOSAGE FORMS AND STRENGTHS

Sufentanil Citrate Injection, USP 50 mcg/mL (equivalent to 50 mcg/mL sufentanil base).

## 4 CONTRAINDICATIONS

Sufentanil Citrate Injection is contraindicated in patients with:

- Hypersensitivity to sufentanil (e.g., anaphylaxis) *[see Adverse Reactions (6.2)]*

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Addiction, Abuse, and Misuse

Sufentanil Citrate Injection contains sufentanil, a Schedule II controlled substance. As an opioid, Sufentanil Citrate Injection exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when handling Sufentanil Citrate Injection. Strategies to reduce these risks include proper product storage and control practices for a C-II drug. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

### 5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Sufentanil Citrate Injection should be administered only by persons specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, including respiration and cardiac resuscitation of patients in the age group being treated. Such training must include the establishment and maintenance of a patent airway and assisted ventilation. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of Sufentanil Citrate Injection. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide ($CO_2$) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

As with other potent opioids, the respiratory depressant effect of Sufentanil Citrate Injection may persist longer than the measured analgesic effect. The total dose of all opioid agonists administered should be considered by the practitioner before ordering opioid analgesics during recovery from anesthesia.

Certain forms of conduction anesthesia, such as spinal anesthesia and some epidural anesthetics, can alter respiration by blocking intercostal nerves *[see Clinical Pharmacology (12.2)]* Sufentanil Citrate Injection can also alter respiration. Therefore, when Sufentanil Citrate Injection is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

Patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of Sufentanil Citrate Injection. Elderly, cachectic, or debilitated patients may have altered pharmacokinetics or altered clearance compared to younger, healthier patients resulting in greater risk for respiratory depression.

Monitor such patients closely including vital signs, particularly when initiating and titrating Sufentanil Citrate Injection and when Sufentanil Citrate Injection is given concomitantly with other drugs that depress respiration. To reduce the risk of respiratory depression, proper dosing and titration of Sufentanil Citrate Injection are essential *[see Dosage and Administration (2.1)]*.

### 5.3 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of Sufentanil Citrate Injection with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of sufentanil and prolong opioid adverse reactions, which may exacerbate fatal respiratory depression *[see Warnings and Precautions (5.2)]*, particularly when an inhibitor is added after a stable dose of Sufentanil Citrate Injection is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Sufentanil Citrate Injection-treated patients may increase sufentanil plasma concentrations and prolong opioid adverse reactions. When using Sufentanil Citrate Injection with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Sufentanil Citrate Injection-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Sufentanil Citrate Injection *[see Dosage and Administration (2.1), Drug Interactions (7)]*.

Concomitant use of Sufentanil Citrate Injection with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could result in lower than expected sufentanil plasma concentrations, and decrease efficacy. When using Sufentanil Citrate Injection with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the Sufentanil Citrate Injection dosage *[see Dosage and Administration (2.1), Drug Interactions (7)]*.

### 5.4 Risks of Muscle Rigidity and Skeletal Muscle Movement

Intravenous administration or unintentional intravascular injection during epidural administration of Sufentanil Citrate Injection may cause muscle rigidity, particularly involving the muscles of respiration. The incidence and severity of muscle rigidity is dose related. These effects are related to the dose and speed of injection. Administration of sufentanil may produce muscular rigidity with a more rapid onset of action than that seen with fentanyl. Skeletal muscle rigidity also has been reported to occur or recur infrequently in the extended postoperative period usually following high dose administration. In addition, skeletal muscle movements of various groups in the extremities, neck, and external eye have been reported during induction of anesthesia with Sufentanil Citrate Injection; these reported movements have, on rare occasions, been strong enough to pose patient management problems.

The incidence of skeletal muscle rigidity can be reduced by: 1) administration of up to 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, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when sufentanil is used in anesthetic dosages (above 8 mcg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of sufentanil and a full paralyzing dose of a neuromuscular blocking agent when sufentanil is used in rapidly administered anesthetic dosages (above 8 mcg/kg).

The neuromuscular blocking agents used should be compatible with the patient's cardiovascular status. The hemodynamic effects and degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during sufentanil-oxygen anesthesia. Bradycardia and hypotension have been reported with other muscle relaxants during sufentanil-oxygen anesthesia; this effect may be more pronounced in the presence of calcium channel and/or beta-blockers. Muscle relaxants with no clinically significant effect on heart rate (at recommended doses) would not counteract the vagotonic effect of sufentanil, therefore a lower heart rate would be expected. Rare reports of bradycardia associated with the concomitant use of succinylcholine and sufentanil have been reported.

### 5.5 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

When benzodiazepines or other CNS depressants are used with Sufentanil Citrate Injection, pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of Sufentanil Citrate Injection are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

When Sufentanil Citrate Injection is used with CNS depressants, hypotension can occur. If it occurs, consider the possibility of hypovolemia and manage with appropriate parenteral fluid therapy. When operative conditions permit, consider repositioning the patient to improve venous return to the heart. Exercise care in moving and repositioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, consider administration of pressor agents other than epinephrine. Epinephrine may paradoxically decrease blood pressure in patients treated with a neuroleptic that blocks alpha adrenergic activity.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Sufentanil Citrate Injection with benzodiazepines or other CNS depressants (e.g., nonbenzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol).

If the decision is made to manage postoperative pain with Sufentanil Citrate Injection concomitantly with a benzodiazepine or other CNS depressant, start dosing with the lowest effective dosage and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression, sedation, and hypotension. Fluids or other measures to counter hypotension should be available. *[see Drug Interactions (7)]*

### 5.6 Severe Cardiovascular Depression

Sufentanil Citrate Injection may cause severe bradycardia, severe hypotension including orthostatic hypotension, and syncope. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. In patients with circulatory shock, Sufentanil Citrate Injection may cause vasodilation that can further reduce cardiac output and blood pressure. Monitor these patients for signs of hypotension after initiating or titrating the dosage of Sufentanil Citrate Injection.

### 5.7 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of Sufentanil Citrate Injection with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *[see Drug Interactions (7)]*. This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Sufentanil Citrate Injection if serotonin syndrome is suspected.

### 5.8 Risks due to Improper Epidural Injection

Proper placement of the needle or catheter in the epidural space should be verified before sufentanil is injected to assure that unintentional intravascular or intrathecal administration does not occur. Unintentional intravascular injection of sufentanil could result in a potentially serious overdose, including acute truncal muscular rigidity and apnea. Unintentional intrathecal injection of the full sufentanil/bupivacaine epidural doses and volume could produce effects of high spinal anesthesia including prolonged paralysis and delayed recovery. If analgesia is inadequate, the placement and integrity of the catheter should be verified prior to the administration of any additional epidural medications. Sufentanil should be administered epidurally by slow injection.

### 5.9 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, or Head Injury

In patients who may be susceptible to the intracranial effects of $CO_2$ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Sufentanil Citrate Injection may reduce respiratory drive, and the resultant $CO_2$ retention can further increase intracranial pressure. Monitor such patients for signs of increasing intracranial pressure.

### 5.10 Risks of Use in Patients with Gastrointestinal Conditions

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

### 5.11 Increased Risk of Seizures in Patients with Seizure Disorders

Sufentanil may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Sufentanil Citrate Injection therapy.

### 5.12 Risks of Driving and Operating Machinery

Sufentanil Citrate Injection may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery after Sufentanil Citrate Injection administration.

## 6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Skeletal Muscle Rigidity and Skeletal Muscle Movement *[see Warnings and Precautions (5.4)]*
- Interactions with Benzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.5)*
- Severe Cardiovascular Depression *[see Warnings and Precautions (5.6)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.7)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Epidural Use in Labor and Delivery

Epidural sufentanil was tested in 340 patients in two (one single-center and one multicenter) double-blind, parallel studies. Doses ranged from 10 to 15 mcg sufentanil and were delivered in a 10 mL volume of 0.125% bupivacaine with and without epinephrine 1:200,000. In all cases sufentanil was administered following a dose of local anesthetic to test proper catheter placement. Since epidural opioids and local anesthetics potentiate each other, these results may not reflect the dose or efficacy of epidural sufentanil by itself.

Individual doses of 10 to 15 mcg sufentanil plus bupivacaine 0.125% with epinephrine provided analgesia during the first stage of labor with a duration of 1 to 2 hours. Onset was rapid (within 10 minutes). Subsequent doses (equal dose) tended to have shorter duration. Analgesia was profound (complete pain relief) in 80% to 100% of patients and a 25% incidence of pruritus was observed. The duration of initial doses of sufentanil plus bupivacaine with epinephrine is approximately 95 minutes, and of subsequent doses, 70 minutes.

There are insufficient data to critically evaluate neonatal neuromuscular and adaptive capacity following recommended doses of maternally administered epidural sufentanil with bupivacaine. However, if larger than recommended doses are used for combined local and systemic analgesia, e.g. after administration of a single dose of 50 mcg epidural sufentanil during delivery, then impaired neonatal adaption to sound and light can be detected for 1 to 4 hours and if a dose of 80 mcg is used impaired neuromuscular coordination can be detected for more than 4 hours.

### 6.2 Postmarketing Experience

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

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

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

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in Sufentanil Citrate Injection.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

## 7 DRUG INTERACTIONS

Table 2 includes clinically significant drug interactions with Sufentanil Citrate Injection.

**Table 2: Clinically Significant Drug Interactions with Sufentanil Citrate Injection**

| | |
|---|---|
| **Inhibitors of CYP3A4** | |
| *Clinical Impact:* | The concomitant use of Sufentanil Citrate Injection and CYP3A4 inhibitors can increase the plasma concentration of sufentanil, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of Sufentanil Citrate Injection is achieved *[see Warnings and Precautions (5.4)]*.<br>After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the sufentanil plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to sufentanil. |
| *Intervention:* | If concomitant use is necessary, consider dosage reduction of Sufentanil Citrate Injection until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals.<br>If a CYP3A4 inhibitor is discontinued, consider increasing the Sufentanil Citrate Injection dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. |
| *Examples:* | Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice |
| **CYP3A4 Inducers** | |
| *Clinical Impact:* | The concomitant use of Sufentanil Citrate Injection and CYP3A4 inducers can decrease the plasma concentration of sufentanil *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to sufentanil *[see Warnings and Precautions (5.4)]*.<br>After stopping a CYP3A4 inducer, as the effects of the inducer decline, the sufentanil plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression. |
| *Intervention:* | If concomitant use is necessary, consider increasing the Sufentanil Citrate Injection dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider Sufentanil Citrate Injection dosage reduction and monitor for signs of respiratory depression. |
| *Examples:* | Rifampin, carbamazepine, phenytoin |
| **Benzodiazepines and Other Central Nervous System (CNS) Depressants** | |
| *Clinical Impact:* | The concomitant use of Sufentanil Citrate Injection with CNS depressants my result in decreased pulmonary artery pressure and may cause hypotension. Even small dosages of diazepam may cause cardiovascular depression when added to high dose or anesthetic dosages of Sufentanil Citrate Injection. As postoperative analgesia, concomitant use of Sufentanil Citrate Injection can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death. |
| *Intervention:* | As postoperative analgesia, start with a lower dose of Sufentanil Citrate Injection and monitor patients for signs of respiratory depression, sedation, and hypotension. Fluids or other measures to counter hypotension should be available. *[see Warnings and Precautions (5.5)]*. |
| *Examples:* | Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol. |
| **Serotonergic Drugs** | |
| *Clinical Impact:* | The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions 5.5]*. |
| *Intervention:* | If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Sufentanil Citrate Injection if serotonin syndrome is suspected. |
| *Examples:* | Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). |
| **Monoamine Oxidase Inhibitors** | |
| *Clinical Impact:* | MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.2)]*. |
| *Intervention:* | The use of Sufentanil Citrate Injection is not recommended for patients taking MAOIs or within 14 days of stopping such treatment. |
| *Examples:* | phenelzine, tranylcypromine, linezolid |
| **Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics** | |
| *Clinical Impact:* | May reduce the analgesic effect of Sufentanil Citrate Injection and/or precipitate withdrawal symptoms. |
| *Intervention:* | Avoid concomitant use. |
| *Examples:* | butorphanol, nalbuphine, pentazocine, buprenorphine |
| **Muscle Relaxants** | |
| *Clinical Impact:* | Sufentanil may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. |
| *Intervention:* | Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Sufentanil Citrate Injection and/or the muscle relaxant as necessary. |
| **Diuretics** | |
| *Clinical Impact:* | Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. |
| *Intervention:* | Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed. |
| **Anticholinergic Drugs** | |
| *Clinical Impact:* | The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. |
| *Intervention:* | Monitor patients for signs of urinary retention or reduced gastric motility when Sufentanil Citrate Injection is used concomitantly with anticholinergic drugs. |
| **Nitrous oxide** | |
| *Clinical Impact:* | Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of Sufentanil Citrate Injection. |
| *Intervention:* | Monitor patients for signs of cardiovascular depression that may be greater than otherwise expected. |

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with Sufentanil Citrate Injection in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, embryolethality and maternal toxicity were noted in rabbits when sufentanil was administered intravenously at 0.9 times the human procedural dose of 30 mcg/kg during organogenesis. Decreased live fetuses and pup survival were noted in rats treated with sufentanil late in gestation and throughout lactation at doses below the human procedural dose. No malformations were observed in either rats or rabbits at doses below the human procedural dose *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

*Fetal/Neonatal Adverse Reactions*

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.3)]*.

*Labor or Delivery*

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

The use of epidurally administered sufentanil in combination with bupivacaine 0.125% with or without epinephrine is indicated for labor and delivery. Sufentanil is not recommended for intravenous use or for use of larger epidural doses during labor and delivery because of potential risks to the newborn infant after delivery. In clinical trials, one case of severe fetal bradycardia associated with maternal hypotension was reported within 8 minutes of maternal administration of sufentanil 15 mcg plus bupivacaine 0.125% (10 mL total volume).

Data

*Animal Data*

Pregnant rats were treated with intravenous sufentanil doses of 0.005, 0.02, or 0.08 mg/kg/day (0.03, 0.1, or 0.4 times the human total procedural dose of 30 mcg/kg based on body surface area, respectively). No malformations or embryotoxic effects were noted despite maternal toxicity (increased mortality in the mid- and high-dose group).

Pregnant rabbits were treated with intravenous sufentanil doses of 0.005, 0.02, or 0.08 mg/kg/day (0.05, 0.2, or 0.9 times the human total procedural dose of 30 mcg/kg based on body surface area, respectively). Decreased live fetuses per litter and decreased litter size in the high dose group were noted in the presence of maternal toxicity (decreased body weight gain and mortality in the high-dose group).

No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered 10, 50, or 100 mcg/kg/day sufentanil (0.05, 0.27, or 0.54 times the human procedural dose of 30 mcg/kg/day based on body surface area) continuously from Gestation Day 5 through Gestation Day 20 via subcutaneously implanted osmotic minipumps.

Pregnant rats were treated intravenously with sufentanil 0.005, 0.02, or 0.08 mg/kg/day (0.03, 0.1, or 0.4 times the human total procedural dose of 30 mcg/day based on body surface area, respectively) from Gestation Day 16 through Lactation Day 21. Sufentanil reduced birth weights in the mid- and high-dose groups, decreased live fetuses in the high-dose group, and decreased pup survival in all groups in the presence of maternal toxicity (decreased weight gain and increased mortality in all groups).

### 8.2 Lactation

Risk Summary

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Sufentanil Citrate Injection and any potential adverse effects on the breastfed infant from Sufentanil Citrate Injection or from the underlying maternal condition.

Clinical Considerations

Infants exposed to Sufentanil Citrate Injection through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

### 8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2)]*.

### 8.4 Pediatric Use

The safety and efficacy of intravenous sufentanil in pediatric patients as young as 1 day old undergoing cardiovascular surgery have been documented in a limited number of cases. The clearance of sufentanil in healthy neonates is approximately one-half that in adults and children. The clearance rate of sufentanil can be further reduced by up to a third in neonates with cardiovascular disease, resulting in an increase in the elimination half-life of the drug.

### 8.5 Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to sufentanil. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of Sufentanil Citrate Injection slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.6)]*.

### 8.6 Hepatic Impairment

Sufentanil Citrate Injection should be administered with caution to patients with liver dysfunction because of the extensive hepatic metabolism. Reduce the dosage as needed and monitor closely for signs of respiratory depression, sedation, and hypotension.

### 8.7 Renal Impairment

Sufentanil Citrate Injection should be administered with caution to patients with kidney dysfunction because of the renal excretion of sufentanil citrate and its metabolites. Reduce the dosage as needed and monitor for signs of respiratory depression, sedation, and hypotension.

## 9 DRUG ABUSE AND DEPENDENCE

### 9.1 Controlled Substance

Sufentanil Citrate Injection contains sufentanil, a Schedule II controlled substance.

### 9.2 Abuse

Sufentanil Citrate Injection contains sufentanil, a substance with a high potential for abuse similar to other opioids including hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Sufentanil Citrate Injection can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

Sufentanil Citrate Injection, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Risks Specific to Abuse of Sufentanil Citrate Injection

Abuse of Sufentanil Citrate Injection poses a risk of overdose and death. The risk is increased with concurrent use of Sufentanil Citrate Injection with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

### 9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

## 10 OVERDOSAGE

Clinical Presentation

Acute overdose with Sufentanil Citrate Injection can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

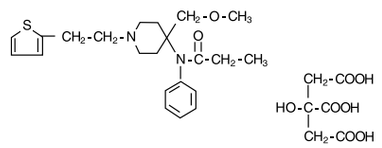
The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to sufentanil overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to sufentanil overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of sufentanil in Sufentanil Citrate Injection, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

## 11 DESCRIPTION

Sufentanil Citrate Injection, is an opioid agonist, available as a solution containing 50 mcg/mL eq. of sufentanil base, adjusted to pH 3.5 to 6.0. The chemical name is N-[4-(methyoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide: 2-hydroxy-1,2,3-propanetricarboxylate (1:1). The molecular weight is 578.68. It has the following chemical structure.




Sufentanil Citrate Injection, is a sterile, non-pyrogenic, preservative free aqueous solution for intravenous or epidural injection.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Sufentanil is an opioid agonist. When used in balanced general anesthesia, sufentanil has been reported to be as much as 10 times as potent as fentanyl. When administered intravenously as a primary anesthetic agent with 100% oxygen, sufentanil is approximately 5 to 7 times as potent as fentanyl.

### 12.2 Pharmacodynamics

Effects on the Central Nervous System

Sufentanil produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

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 origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the 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 biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Sufentanil produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon *[see Adverse Reactions (6.2)]*.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids *[see Dosage and Administration (2.1, 2.2)]*. The minimum effective analgesic concentration of sufentanil for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration–Adverse Reaction Relationships

There is a relationship between increasing sufentanil plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

### 12.3 Pharmacokinetics

Sufentanil Citrate Injection is administered by the intravenous or epidural route. The pharmacokinetics of intravenous sufentanil can be described as a three-compartment model.

Absorption

After epidural administration of incremental doses totaling 5 to 40 mcg sufentanil during labor and delivery, maternal and neonatal sufentanil plasma concentrations were at or near the 0.05 to 0.1 ng/mL limit of detection, and were slightly higher in mothers than in their infants.

Distribution

Plasma protein binding of sufentanil, related to the alpha acid glycoprotein concentration, was approximately 93% in healthy males, 91% in mothers and 79% in neonates. Sufentanil has a distribution time of 1.4 minutes and redistribution time of 17.1 minutes.

Elimination

The elimination half-life is 164 minutes in adults. The elimination half-life of sufentanil is shorter (e.g. 97 +/- 42 minutes) in infants and children, and longer in neonates (e.g. 434 +/- 160 minutes) compared to that of adolescents and adults.

*Metabolism*

The liver and small intestine are the major sites of biotransformation.

*Excretion*

Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of sufentanil have not been conducted.

Mutagenesis

Sufentanil was not genotoxic in the *in vitro* bacterial reverse mutation assay (Ames assay) or in the *in vivo* rat bone marrow micronucleous assay.

Impairment of Fertility

Fertility and early embryonic development studies were conducted in male and female rats treated with 0.005, 0.02 or 0.08 mg/kg sufentanil IV for 56 days and 14 days prior to mating through gestation respectively. Increased mortality was noted in all treatment groups. Lower pregnancy rated were noted following treatment of males at doses of 0.02 and 0.08 mg/kg (0.1 and 0.4 times the maximum human total procedural dose of 30 mcg/kg IV, based on a body surface area comparison), suggesting the potential for an adverse effect on fertility in males. Increased resorption of fetuses and reduced litter size was noted in the high dose females (0.4 times the maximum human total procedural dose of 30 mcg/kg IV, based on a body surface area comparison) suggesting the potential for fetotoxicity, likely due to maternal toxicity.

## 14 CLINICAL STUDIES

Epidural Use in Labor and Delivery

Epidural sufentanil was tested in 340 patients in two (one single-center and one multicenter) double-blind, parallel studies. Doses ranged from 10 to 15 mcg sufentanil and were delivered in a 10 mL volume of 0.125% bupivacaine with and without epinephrine 1:200,000. In all cases sufentanil was administered following a dose of local anesthetic to test proper catheter placement. Since epidural opioids and local anesthetics potentiate each other, these results may not reflect the dose or efficacy of epidural sufentanil by itself.

Individual doses of 10 to 15 mcg sufentanil plus bupivacaine 0.125% with epinephrine provided analgesia during the first stage of labor with a duration of 1 to 2 hours. Onset was rapid (within 10 minutes). Subsequent doses (equal dose) tended to have shorter duration. Analgesia was profound (complete pain relief) in 80% to 100% of patients and a 25% incidence of pruritus was observed. The duration of initial doses of sufentanil plus bupivacaine with epinephrine is approximately 95 minutes, and of subsequent doses, 70 minutes.

There are insufficient data to critically evaluate neonatal neuromuscular and adaptive capacity following recommended doses of maternally administered epidural sufentanil with bupivacaine. However, if larger than recommended doses are used for combined local and systemic analgesia, e.g. after administration of a single dose of 50 mcg epidural sufentanil during delivery, then impaired neonatal adaption to sound and light can be detected for 1 to 4 hours and if a dose of 80 mcg is used impaired neuromuscular coordination can be detected for more than 4 hours.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Sufentanil Citrate Injection, USP is a sterile aqueous, preservative-free solution, containing 50 mcg/mL eq. of sufentanil base, for intravenous and epidural use, supplied as:

| | |
|---|---|
| NDC 17478-050-01 | 1 mL ampules in packages of 10 |
| NDC 17478-050-02 | 2 mL ampules in packages of 10 |
| NDC 17478-050-05 | 5 mL ampules in packages of 10 |

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from light.

U.S. Patent No. 3,998,834
MAY 1995, SEPTEMBER 1995

AKORN

Manufactured by: **Akorn, Inc.**
Lake Forest, IL 60045

SFAON Rev. 12/16